Astrocytic Adrenoceptors: A Major Drug Target in Neurological and Psychiatric Disorders?

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Abstract: Considerable attention has recently been paid to astrocyte functions, which are briefly summarized. A large amount of data is available about adrenoceptor expression and function in astrocytes, some of it dating back to the 1970's and some of it very recent. This material is reviewed in the present paper. The brain is innervated by noradrenergic fibers extending from locus coeruleus in the brain stem, which in turn is connected to a network of adrenergic and noradrenergic nuclei in the medulla and pons, contributing to the control of (nor)adrenergic, serotonergic, dopaminergic and cholinergic function, both in the central nervous system (CNS) and in the periphery. In the CNS astrocytes constitute a major target for noradrenergic innervation, which regulates morphological plasticity, energy metabolism, membrane transport, gap junction permeability and immunological responses in these cells. Noradrenergic effects on astrocytes are essential during consolidation of episodal, long-term memory, which is reinforced by β-adrenergic activation. Glycogenolysis and synthesis of glutamate and glutamine from glucose, both of which are metabolic processes restricted to astrocytes, occurs at several time-specific stages during the consolidation. Astrocytic abnormalities are almost certainly important in the pathogenesis of multiple sclerosis and in all probability contribute essentially to inflammation and malfunction in Alzheimer's disease and to mood disturbances in affective disorders. Noradrenergic function in astrocytes is severely disturbed by chronic exposure to cocaine, which also changes astrocyte morphology. Development of drugs modifying noradrenergic receptor activity and/or down-stream signaling is advocated for treatment of several neurological/psychiatric disorders and for neuroprotection. Astrocytic preparations are suggested for study of mechanism(s) of action of antidepressant drugs and pathophysiology of mood disorders.

Keywords: Alzheimer's disease, astrocytes, cocaine, memory, mood disorders, multiple sclerosis, neuroprotection, noradrenergic receptors.

I. INTRODUCTION: ASTROCYTIC FUNCTIONS

Astrocytes constitute one of the two groups of macroglial cells (astrocytes and oligodendrocytes) that in the brain cortex by far outnumber neurons [1-2]. Astrocytes extend a large number of processes and filopodia and they cover most of the perimeter of microvessels [2-5]. They are coupled to each other by gap junctions, allowing passage of low-molecular constituents (ions, metabolites) from cell to cell [6-7]. In contrast to neurons, astrocytes are non-excitable cells [8], meaning that they do not generate action potentials. They were previously regarded as only structurally supportive cells, but within the last decades it has become obvious that they exert a number of functions of key importance for the function of the central nervous system (CNS). They surround synapses and accumulate released transmitter glutamate much more efficiently than neurons [9]. In addition glutamate stimulates not only postsynaptic receptors but also glutamate receptors on astrocytes [10-11]. One response to this stimulation is an increase in free cytosolic calcium concentration ($[Ca^{2+}]_i$), which often is oscillating. Among the effects of a rise in astrocytic $[Ca^{2+}]_i$ is a vasodilation [12], which may play a major role for the increase in blood flow occurring during brain activation.

An increase in $[Ca^{2+}]_i$ in one cell can spread through gap junction-coupled astrocytes and even reach astrocytic networks that are not coupled to the initially activated cells [11, 13-14]. Astrocytic gap-junctional communication is regulated by neurotransmitters, cytokines, and growth factors, providing the basis for functional networks that could constitute sophisticated and plastic pathways between defined groups of astrocytes. Several transmitters, including noradrenaline [15-16], can elicit intra- and/or inter-cellular calcium waves, but a calcium wave can also originate spontaneously in astrocytes [17]. Neurons that are encountered by the wave of increased astrocytic $[Ca^{2+}]_i$ react with either a stimulation or an inhibition [18-20], occurring in spite of the fact that these neurons are not synaptically coupled to the initially excited neuron.

Astrocytes also make a substantial contribution to the immediate clearance of neuronally released potassium ions (K^+), mainly by stimulation of two transporters: i) a Na^+,K^+-ATPase, which in contrast to neuronal Na^+,K^+-ATPase is stimulated by an increased K^+ concentration at its extracellular K^+-activated site [21-22], and ii) a cotransporter of K^+ together with one sodium ion (Na^+) and two chloride

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ions (Cl^-), which likewise is activated by above-normal K^+ concentrations [23]. In addition a local increase in K^+ can be re-distributed within the extracellular space by a current-mediated re-distribution through the astrocytic network ("the spatial buffer"), but this mechanism can only operate efficiently over short distances [24]. It is of functional importance in the retina and in simpler central nervous systems like the frog tectum, where it contributes to information processing [25].

Both K^+ and glutamate uptake occur by active transport, and it is consistent with the ability of astrocytes to carry out energy-requiring processes that their rate of oxygen uptake and glycolysis (formation of pyruvate or lactate from glucose) per volume unit are comparable to those in neurons (although glycolysis may be faster in astrocytes), both in cultured cells and in the brain *in vivo* [27-30]. Virtually all glycogen in the brain is found in astrocytes [31], where it is present in even the thinnest and most distal astrocytic processes and filopodia, which are too slender to contain mitochondria [32-33]. These cell extensions form a specific functional compartment, which accounts for 80% of the total cell surface [2-4]. An enhanced glycogenolysis (formation of pyruvate or lactate from glycogen) occurs during stimulation of brain activity [34-35]. It has been suggested that the immediate response to a requirement for energy in the peripheral processes, e.g., to accumulate an extracellular load of K^+, primarily may be covered by glycolysis or glycogenolysis. Adenosine triphosphate (ATP) and phosphocreatine formed in large amounts by oxidative metabolism of the generated pyruvate more centrally in the astrocytes may only secondarily take over to support the energy-requiring process and to provide the energy required for re-synthesis of glycogen from glucose [36-38]. Part of this energy is retained in the glycogen molecule, for which reason glycogenolysis in contrast to glycolysis from glucose does not require an initial oxygen-dependent [37, 39] 'priming' to produce a phosphorylated metabolite.

Glycolysis, glycogenolysis, and oxidative metabolism of pyruvate and glutamate in primary cultures of astrocytes are stimulated by adrenergic agonists [37,40]. Since both glutamate uptake [41-44] and Na^+,K^+-ATPase activity are increased [19], this stimulation could partly reflect an increase in energy-requiring processes. In addition adrenergic agonists exert a powerful direct effect on oxidative metabolism [45], probably to a large extent mediated by the evoked increase in $[Ca^{2+}]_i$, and on glycogenolysis, mediated by protein kinase A (PKA) stimulation and/or the $[Ca^{2+}]_i$ effect [37, 40]. Conversely, adrenergic antagonists or noradrenergic denervation decrease glucose utilization and oxidation in the brain [46], at least in most of its regions [47].

Recently it has been demonstrated that adrenergic stimulation has an inhibitory effect on immune reactions in the CNS. This effect may play a major role in multiple sclerosis (MS), where a disappearance of astrocytic β_2-adrenergic receptors in white matter has been observed [48]. Alzheimer's disease is associated with pronounced cell death of adrenergic neurons in locus coeruleus, the nucleus of origin for adrenergic innervation of the entire cerebral cortex and subcortical nuclei. It is therefore an exciting possibility that an impairment of adrenergic function in astrocytes may contribute to inflammatory reactions and CNS malfunction in this devastating disorder [49-50].

A detailed understanding of the role of astrocytic adrenoceptors in CNS function and dysfunction requires thorough knowledge of noradrenergic innervation of the nervous system, of receptor expression on astrocytes, and of the functional activities which are stimulated or inhibited by adrenergic agonists. In this review we will initially briefly discuss adrenergic and noradrenergic cell groups in the central nervous system (CNS), including locus coeruleus, with their afferent connections and ascending and descending efferent fibers to the brain and the spinal cord. In addition a brief summary of adrenoceptor transduction pathways will be provided. Subsequently we will describe in more detail adrenoceptor expression on cultured and dissociated astrocytes and especially on astrocytes within the mammalian CNS. This will be followed by a description of adrenergic effects at the cellular level and in the functioning CNS and of disease states where astrocytic adrenoceptor function may be impaired. Towards the end astrocytic adrenoceptors will be discussed as potential drug target(s).

II. THE NORADRENERGIC AND ADRENERGIC SYSTEMS IN BRAIN

A. CNS Nuclei and Pathways

1. A Medullo-Pontine Noradrenergic/Adrenergic Network

Compared to glutamatergic and GABAergic neurons the CNS contains very few noradrenergic and even fewer adrenergic neurons. Their cell bodies are located in the brain stem within medulla and pons. One can distinguish between two groups of adrenergic and noradrenergic neurons [51-52]. One group primarily functions in the supraspinal regulation of the entire autonomic nervous system. It consists of both noradrenergic and adrenergic neurons, extending fibers which reach caudally into the spinal cord and rostrally to the limbic system. The second group consists of a single nucleus, the locus coeruleus, and it provides virtually the entire noradrenergic innervation of the cerebral hemispheres (cerebral cortex, hippocampus and cerebellum) from its rostral and medium parts and part of the noradrenergic innervation of the spinal cord from its caudal part. Developmental differences are found between these two groups, with the development of neurons in the rostral part of locus coeruleus being independent of the gene *Rnx*, required for the development of all other noradrenergic neurons in pons and medulla [53]. Pharmacological differences also exist, since locus coeruleus is more sensitive to systemic administration of the neurotoxin DSP-4 (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine) than the other noradrenergic cell groups, probably reflecting differences in the affinity of uptake carriers for both this drug and noradrenaline itself [54-55].

Adrenergic cell bodies are restricted to the cell groups C1-C3, with the C1 and C2 groups found close to the ventral and dorsal surface of the medulla, respectively. These cell groups project descending bulbospinal fibers regulating autonomic activity in the periphery as well as ascending fibers, which constitute a subset of a ventral catecholaminergic bundle arising in the medulla. This bundle also carries fibers from all noradrenergic groups in

medulla and pons with the exception of nucleus coeruleus. The ventral catecholaminergic bundle innervates locus coeruleus and the pericoerulear region [56-58], and it provides the major (nor)adrenergic innervation of the dorsal pons, containing the raphe nuclei [52, 59], the origin for serotonergic fibers innervating the cerebral hemispheres, of the hypothalamus [60], and of the mesencephalic tegmentum [61]. It also sends fibers to nucleus basalis [62-63], the origin of cholinergic fibers to the cerebral hemispheres, and to nucleus accumbens, a dopaminergic centre [64-65]. Accordingly there are functional connections both between noradrenergic activity in the cerebral hemispheres and systemic noradrenergic activity [66], and between noradrenergic, serotonergic, dopaminergic, and cholinergic signaling to the brain hemispheres.

2. Locus coeruleus

The largest and most thoroughly studied noradrenergic cell group is locus coeruleus, which is located in the dorsal part of pons at the lateral edges of the fourth ventricle. This nucleus plays a major role in attention, behavioral flexibility, and cognitive processes [67-69]. In the normal human brain the right and left nuclei combined contain at most 50,000 noradrenergic neurons [70-71], and the number is decreased in Alzheimer's disease [72-73]. Ascending fibers from locus coeruleus constitute the dorsal noradrenergic bundle, which contains noradrenergic fibers but no adrenergic fibers and supplies the cerebral cortex with virtually its entire source of noradrenaline [74-75]. Most transmitter release in these fibers occurs from varicosities, and only a relatively low proportion of noradrenergic varicosities make synaptic contacts, predominantly with small or medium-size dendrites [76-78]. Noradrenergic axons often form perivascular loops [79], and in the immediate vicinity of the microvessels, astrocytic processes represent their major target [77]. Locus coeruleus also innervates cerebellum, and it sends descending fibers to the spinal cord [80-81]. The fibers to the different areas of the CNS originate in morphologically and topographically distinct neurons within locus coeruleus [82-84], with the fibers to the spinal cord emanating from its caudal part [85]. Neonatally the locus coeruleus neurons are electrotonically coupled [86]. This does not seem to be the case in adults, where changes in tonic and stimulus-induced activity are tightly correlated with fluctuations in behavioral performance [69, 87]. Although most attention has been paid to the role of locus coeruleus in the innervation of the brain cortex, there are also afferent connections from the dorsal prefrontal cortex to locus coeruleus as well as to the raphe nuclei [88-89]. Accordingly the dorsal prefrontal cortex has direct influence on the activity of locus coeruleus and can thereby influence noradrenergic innervation of large areas of the cerebral cortex.

B. Transduction Mechanisms

1. Adenylyl Cyclase-Mediated Transduction

After stimulation of a G_s-coupled receptor and exchange of bound guanosine diphosphate (GDP) for guanosine triphosphate (GTP) the activated a subunit of the G protein stimulates one of several subtypes of adenylyl cyclase [90-91]. Differences in the characteristics of the individual subtypes can explain variability in tissue response to adrenergic receptor agonists [91]. For example, in primary cultures of cerebral rat astrocytes a_1-adrenergic receptor stimulation decreases the cAMP response to b-adrenergic stimulation [92], whereas this response is enhanced by a_1-adrenergic stimulation in striatal cultures of mouse astrocytes [93].

The generated cAMP binds to the regulatory subunits of inactive protein kinase A (PKA), releasing its free catalytic subunits, which are then able to phosphorylate and activate their target proteins in phosphorylation-dephosphorylation cascades. Protein kinase A can also phosphorylate and inactivate adenylyl cyclase, providing the possibility of feed-back inhibition [94]. The free catalytic subunits of PKA enter the cell nucleus, where they phosphorylate the transcription factor CREB (CRE-binding protein), leading to the activation of cAMP-inducible genes containing the regulatory sequence CRE (cAMP responsive element) and thus to synthesis of specific proteins. In addition cAMP is able to exert some actions that are independent of protein kinase A activation, e.g., on ion channels.

The stimulated adenylyl cyclase can be inhibited by transmitters, including α_2-adrenergic agonists, acting on receptor-coupled G_i-, or G_o-proteins and exerting a direct effect on the adenylyl cyclase [95-96]. Inhibition of β-adrenergic stimulation by activation of α_2-adrenergic receptors probably explains the reduction of β-adrenoceptor-mediated stimulation in astrocytes reported by Northam *et al*. [97]. This mechanism is different from presynaptic inhibition, exerted by stimulation of presynaptic α_2-adrenergic receptors, which reduces the release of noradrenaline from presynaptic nerve endings, secondary to opening of inwardly rectifying potassium channels [98] or reduction of presynaptic calcium influx [99].

2. Phospholipase C-Mediated Transduction

Following stimulation of an α_1-adrenergic receptor the dissociated and GTP-bound α subunit of the G_q protein interacts with specific regions of one of the isoenzymes of the PLC-β family, leading to the formation of diacylglycerol (DAG) and inositoltrisphosphate (IP_3) from phosphatidylinositide-4,5-bisphosphate (PIP_2). IP_3 is released to the cytosol, whereas DAG remains membrane-bound (Fig. **1**). IP_3 causes release of Ca^{2+} from intracellular stores on the endoplasmic reticulum, leading to an increase in $[Ca^{2+}]_i$, and DAG stimulates protein kinase C (PKC). Hydrolysis of PIP_2 and ensuing DAG formation and PKC activation can also be accomplished by stimulation of receptor tyrosine-kinases, e.g., by growth factors. These factors activate PLC-γ, triggering protein kinase cascades, which eventually lead to phosphorylation of extracellular signal-regulated kinases (ERK_1 and ERK_2). After phosphorylation ERK can enter the nucleus and activate transcription. Some of the PLC-β isoforms are also activated by binding of βγ subunits of G proteins. Therefore receptors activating different G proteins than the G_q protein, e.g., β-adrenergic receptors, can lead to IP_3- and DAG-mediated transduction including an increase in $[Ca^{2+}]_i$ [100]. Binding of βγ subunits to PLC-β is a major signaling pathway in the case of α_2-adrenergic activation of G_i or G_o proteins [101], which besides inhibition of adenylyl cyclase activity and of presynaptic release of noradrenaline also activate PLC-mediated transduction pathways, as indicated by increase in

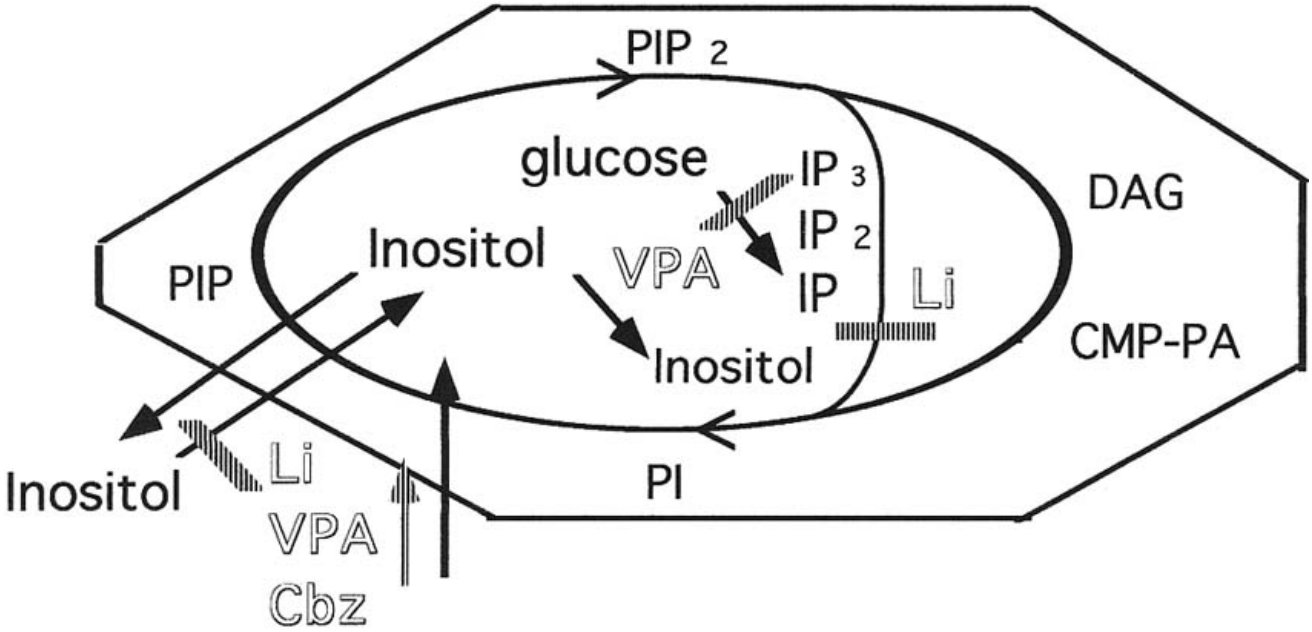

Fig. (1). Schematic illustration of conversion of phosphatidylinositide-4,5-bisphosphate (PIP_2), a cell membrane component, to the two second messengers inositoltrisphosphate (IP_3), which is released to the cytosol (within the oval), and diacylglycerol (DAG), which remains membrane-associated (between the oval and the octagonal). Subsequent metabolism of IP_3 produces inositol bisphosphate (IP_2), inositol monophoshate (IP) and inositol. The generated inositol condenses with cytidine monophosphoryl-phosphatidate (CMP-PA), a metabolite of DAG, to form phosphatidylinositol (PI), from which PIP_2 is regenerated *via* phosphatidylinositide- phosphate (PIP). Tear and wear of cycle constituents as well as cellular release of inositol are compensated for by de novo synthesis of inositol from glucose and by uptake of inositol from the extracellular fluid, mediated by two different inositol transporters: a high-affinity Na^+-dependent myo-inositol transporter and a lower-affinity H^+-dependent myo-inositol transporter. Inhibition of inositol monophosphatase by lithium (Li), indicated by vertically striped bar, interferes with the formation of inositol from IP and thus with regeneration of PIP_2, and may thereby jeopardize formation of IP_3 and DAG upon renewed receptor stimulation. However, valproic acid (VPA) and carbamazepine (Cbz) do not inhibit inositol monophosphatase, but VPA inhibits inositol formation from glucose (vertically striped bar). Chronic (but not acute) treatment with either lithium, VPA, or Cbz inhibits one astrocytic inositol transporter (vertically striped bar) but stimulates the second astrocytic inositol transporter (vertically striped arrow), which may account for effects of lithium treatment on inositol pool size in brain. From [102].

$[Ca^{2+}]_i$ and in IP_3. This mechanism may be of considerable importance in astrocytes.

Maintenance of phospholipase C-mediated signaling over time is contingent upon re-synthesis of PIP_2 from IP_3 and DAG (Fig. **1**). IP_3 is hydrolyzed *via* cytosolic IP_2 and inositol phosphate (IP) to free inositol, and DAG is converted to cytidine monophosphoryl-phosphatidate (CMP-PA), which remains membrane-bound. Subsequently CMP-PA condenses with inositol to form phosphatidylinositol (PI) from which PIP_2 is resynthesized *via* phosphatidyl monophosphate (PIP). Since inositol is rapidly transported across cell membranes, an equilibrium between intra- and extracellular inositol is established, and the efficacy of inositol uptake across the cell membrane may also influence the availability of intracellular inositol and thus the re-synthesis of precursor for DAG and IP_3. Inhibition of astrocytic uptake of inositol may be a major mechanism of action for anti-bipolar drugs (102).

4. Nitric Oxide (NO)/Cyclic GMP-Mediated Transduction

Production of NO by nitric oxide synthase (NOS) can be stimulated by activation of G protein-coupled receptors (GPCRs) [103], including β_1-, β_2- and β_3-receptors [104-105]. A NO-sensitive guanylyl cyclase, sGC, functions as a major receptor for NO and its activation leads to the formation of cyclic guanosine monophosphate (cGMP) [106]. In turn, cGMP targets protein kinase G (PKG) and cGMP-regulated ion channels. In astrocytes the NO/cyclic GMP/PKG pathway has been implicated in the generation of Ca^{2+} waves [107].

5. Transactivation

Transactivation of mitogenic growth factor receptors by GPCRs represents a recently established signaling pathway through which GPCRs are capable of regulating cell proliferation, differentiation and survival. Two types of receptors for growth factors can be stimulated by GPCR-induced transactivation: i) Trk receptor tyrosine kinases, which are receptors for the nerve growth factor (NGF) family (NGF, brain-derived neurotrophic factor [BDNF] and neurotrophin-3 [NT-3]); and ii) epithelial growth factor (EGF) receptors (EGFR) [108-109]. Trk receptor transactivation is characterized by its slow onset (~1 hr) and the absence of any growth factor release. Although β_2-receptor agonists and agents increasing cAMP or directly stimulating PKA can cause transactivation of NGF receptors in other cell types [110-113], noradrenergic transactivation of NGF receptors in brain cells has not been explored. However, the content of NGF in astrocytes is increased by activation of β-adrenergic receptors [114].

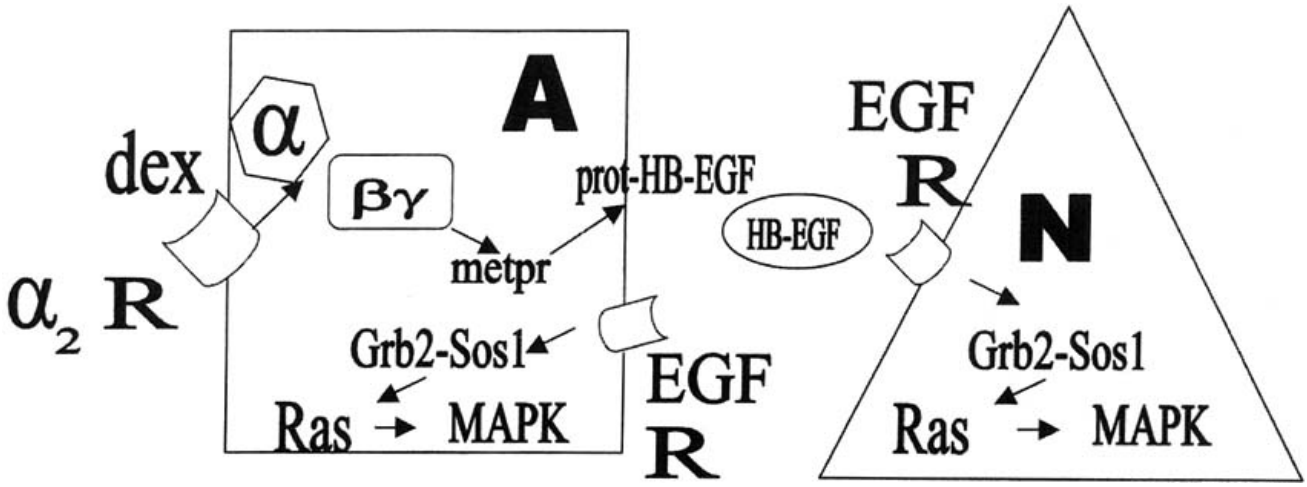

Fig. (2). Schematic representation of key signaling mechanisms presumably involved in transactivation by exposure of astrocytes (A) to the α_2-adrenergic agonist dexmedetomidine. The β,γ subunits of the activated, heterotrimeric G_i protein lead to shedding of HB-EGF from its extracellular transmembrane-spanning protein-HB-EGF precursor, catalyzed by a metalloprotease (metpr). The shedded HB-EGF transactivates EGF receptors (EGFR) in the same (A) and adjacent cells, presumably including neurons (N), in conventional manners, i.e., the EGFR is phosphorylated by a receptor-tyrosine kinase and internalized. This leads to the recruitment of Grb2-Sos1 complexes to the activated receptor-tyrosine kinase and the exchange of GDP for GTP on the low molecular weight G protein, Ras. Activation of Ras, in turn, initiates the phosphorylation cascade consisting of Raf, MEK, and the MAP kinases (MAPK) ERK. From [117].

The EGF family members (EGF, transforming growth factor-α [TGF-α] and heparin-binding EGF [HB-EGF]) are membrane-anchored proteins. Transactivation of EGFR by GPCRs occurs within a time period of minutes. Soluble mature EGFR ligand, e.g., HB-EGF, is proteolytically processed from its larger membrane-anchored precursor by a metalloproteinase. The signaling mechanisms have been studied in some detail in transfected COS-7 cells [115] and are illustrated in (Fig. **2**). HB-EGF is inactivated by the administration of heparin [116] and release of all the ligands can be prevented by metalloproteinase inhibition. α_2-Adrenergic agonists like dexmedetomidine are able to activate EGFR in astrocytes [117], where dexmedetomidine increases $[Ca^{2+}]_i$ [118] and stimulates ERK phosphorylation with similar concentration dependence. The phosphorylation of ERK can be inhibited by an EGFR inhibitor, and by heparin [119] as well as by a metalloproteinase inhibitor (V. Prevot, personal communication). It is likely that the released growth factor also transactivates EGFRs in surrounding neurons, which may provide neuroprotection under pathological conditions (Fig. **2**).

C. Termination of Transmitter Activity

1. Cellular Uptake

Transmitter activity is terminated by cellular uptake, followed by intracellular degradation. There are many reports that rat or mouse astrocytes in primary cultures or explant culture take up [^{3}H]noradrenaline [120-124]. However, the uptake mechanism is disputed. The Kimelberg group [121, 123] has repeatedly observed a high-affinity, sodium-dependent, concentrative uptake of noradrenaline, which is blocked by tricyclic antidepressants. The other investigators have found only modest accumulation of noradrenaline by facilitated diffusion and little evidence that the uptake should be saturable. A histochemical study has shown a specially marked expression of the extraneuronal transporter in area postrema [125].

2. Monoamine Oxidase (MAO) Activity

Two different MAOs exist, MAO A and MAO B, which show different substrate selectivity and different selectivity to inhibitors. MAO deaminates serotonin and noradrenaline much better than the trace amine phenethylamine, which is the preferred substrate for MAO B. Deprenyl is a specific inhibitor of MAO B, whereas inhibitors that preferentially affect MAO A have antidepressant effects. Brain cortex of newborn mice express mainly MAO A but during development the activity of MAO A is doubled, whereas that of MAO B is increased almost 15-fold. A similar development occurs in primary cultures of astrocytes, where MAO activity increases slightly between day 14 and day 85, whereas MAO B activity increases 5-6-fold [126]. The activity of the enzyme is much higher than the rate of noradrenaline uptake, indicating that the rate of the diffusional uptake is greatly increased when uninhibited MAO activity continuously establishes a concentration gradient of non-metabolized noradrenaline.

The presence of both species of MAO in primary cultures of astrocytes has repeatedly been confirmed [127-129], whereas C-6 glioma cells show almost exclusively MAO A activity [130]. Immunocytochemical determination of brain tissue has shown that MAO B is preferentially expressed in astrocytes and in serotonergic neurons [130-132], whereas MAO A activity is mainly found in noradrenergic neurons, although it is also expressed in non-neuronal cells [132].

3. Catecholamine O-methyl Transferase (COMT) Activity

Noradrenaline is also metabolized by catecholamine O-methyl transferase (COMT). This enzyme is found in non-neural tissue, and it is also expressed in astrocytes [133], oligodendrocytes and in neuronal perikarya [134]. In brain

cortex COMT expression has been demonstrated immunocytochemically both in astrocytes and in neuronal processes [135].

III. ADRENOCEPTOR EXPRESSION ON ASTROCYTES

A. β-Adrenergic Receptors

1. Cultured and Dissociated Cells

The first indication that β-adrenergic receptors are present in any astrocytic preparation was the simultaneous observations by Gilman and Nirenberg [136] and Clark and Perkins [137] that the concentration of cAMP in rat glioma cells and human astrocytoma cells is increased by catecholamines. Slightly later, similar effects were reported also in non-transformed, primary cultures of mouse and rat astrocytes [92, 138] and, to less extent, in glial cells obtained from intact brains after cell dissociation and centrifugation [139]. During the following years these findings were corroborated and expanded by a multitude of authors [140] most recently in 1992 [141]. Both β_1- and β_2-adrenergic receptors are involved [142].

Demonstration of β-adrenergic binding lagged behind, because the ligands used, including noradrenaline itself, bound not only to genuine receptor sites, but also showed a much larger cellular retention that was not receptor-related. Eventually, Maguire *et al*. [143] succeeded in determining a K_D of 250 pM and a Bmax of 100-150 fmol/mg protein for specific binding of [^{125}I]iodohydroxybenzylpindolol to a homogenate of rat C-6 glioma cells. A large part of this binding was stereospecifically inhibited by L-propranolol. From these values they concluded that 4000 receptors were present on each cell. Since similar cells were found to generate 500 pmol cAMP per min per mg protein, the turnover rate of the adenylyl cyclase is about 80 per sec. Values between 4,400 and 10,000 β-adrenergic receptors per C-6 glial cell have been confirmed by other investigators [144-146].

An approximately similar density of β-adrenergic receptors was observed in primary cultures of chick astrocytes by Maderspach and Fajczi [147]. Binding to both β_1- and β_2-adrenergic receptors was found in primary cultures of mouse and rat astrocytes [142, 148]. An autoradiographic study showed that all individual cells in these cultures expressed β-adrenergic receptors [149]. In homogenates of our own highly purified mouse astrocytes, which contain ~300 pg of protein per cell [150], the specific binding of dihydroalprenolol amounts to 35 femtomol/mg protein or 2.1×10^{10} molecules/mg protein [151], suggesting a binding density of ~6,500 β-adrenergic receptors per cell. The same cells produce ~150 pmol cAMP per min per mg protein [152], indicating a turnover of the adenylyl cyclase of 70/sec, i.e., the same value as calculated for glioma cells by Maguire *et al*. [143]. This turnover rate is high compared to a turnover rate of 15, which can be calculated for isolated cardiomyocytes [153].

A potential problem with purified astrocyte cultures is that the cells normally are grown in the absence of neurons, and that the presence of neurons might alter receptor expression. It is therefore of importance that Lerea and McCarthy [154] found a higher density of β-adrenergic receptors in astrocytes in neuronal-astrocytic co-cultures, that Hösli and Hösli [155] observed β-adrenergic binding sites on astrocytes in explant cultures, and that β_1- and β_2-adrenergic receptor expression on both astrocytes and neurons have been shown in freshly isolated cells from the rat brain [156-158]. In the forebrain, cerebral cortex and cerebellum β-adrenergic receptors were more concentrated on astrocytes than on neurons [158].

Recently expression of β-adrenergic receptors in chick astrocytes has been determined by reverse transcription polymerase chain reaction (RT-PCR). The expression of β_2-receptors exceeded that of β_1-receptors, and for the first time expression of β_3-receptors was established [159]. This receptor subtype was expressed at the same level as β_2-receptors.

2. Intact CNS

β-Adrenergic receptor expression in the intact CNS has been studied by aid of mono- or polyclonal antibodies directed against the β-adrenergic receptor molecule or specific loops or tail of this molecule and by binding of [^{125}I]iodohydroxybenzylpindolol, [^{125}I]iodocyanopindolol or [^{125}I]iodopindolol, occasionally in combination with subtype-specific displacers. Differences exist between the expression of β-adrenergic receptors labeled by the receptor ligands and those labeled with antibodies towards specific loops or tails, perhaps reflecting different ability to recognize both membrane-associated receptors and receptors that are undergoing desensitization or are in the process of being synthesized or degraded [160]. Using an antibody towards the β-receptor, immunoreactive profiles were initially described not only on postsynaptic densities, but also in endoplasmic reticulum and pinocytic vesicles in dendrites and on glial processes [161]. Later studies, using an antibody specifically to the C-terminal tail of the β_2-adrenergic receptor (but recognizing both β_1- and β_2-adrenergic receptors) showed in visual cortex a predominant localization of the receptor on small astrocytic processes contacting catecholaminergic axon terminals [162-163]. Pronounced expression of β-adrenergic receptors has also been demonstrated by aid of the receptor ligand [^{125}I]iodocyanopindolol in both cerebral cortex, striatum and cerebellum, with the highest receptor density on cerebellar astrocytes [164]. In the kitten visual cortex close to one half of all β-adrenergic receptors were found on astrocytes [165]. The astrocytic localization of the β-adrenergic receptor develops gradually in the rat during the first postnatal weeks [160]. As can be seen from Table **1**, in a surveyed tissue volume of ~10,000 μm^3, the total immunoreactive sites increase from 6 to 13 μm^3 between the age of 2 and 3 weeks, and the relative amount on astrocytes increases from 29% to 65% of the total. According to Aoki *et al*. [166] and Nakadate *et al*. [167] monocular deprivation during the sensitive period of ocular dominance modifies β-adrenergic receptor expression on astrocytes in the visual cortex, whereas Wilkinson *et al*. [168] found no effect.

Within the nucleus tractus solitarius in the medulla immunoreactive astrocyte processes form multiple thin lamellae about both adrenergic/noradrenergic and non-adrenergic neuronal cell bodies and dendrites, and they surround groups of axon terminals [169]. A high density of

β-adrenergic receptors has also been demonstrated in the trigeminal motor nucleus, where β_2-adrenergic receptors dominate [170]. After neuronal damage there is an increase in β-adrenergic receptor expression on astrocytes, with the greater proportional increase occurring in β_1-adrenergic receptors. Analogously optic nerve crush or transection increases the expression of its constituent β_2-adrenergic receptors [171]. β_2-Adrenergic receptors also exist in white matter of normal brain (Fig. **3**), and they are prominently expressed in the boundary of cerebral infarctions [48].

Table 1. Areal Density of β-Adrenoceptor Immunoreactive Profiles in Layer 1 of Developing Rat Visual Cortex (Modified from [160])

Immunoreactive Site*	2-Week-Old	3-Week-Old
Total Immuno-reactive Sites	**0.06%**	**0.13%**
Dendritic Postsynaptic	0.42/100 μm^2 0.32/100 μm^2	0.37/100 μm^2 0.37/100 μm^2
Axonal Presynaptic	0.22/100 μm^2 0.07/100 μm^2	0.10/100 μm^2 0.37/100 μm^2
Glial	1.85/100 μm^2	8.46/100 μm^2

*At both ages ~10,000 μm^2 were surveyed. The density of profiles exhibiting immunoreactive sites is expressed as labeled structure encountered per 100 μm^2 surveyed.

β_3-Adrenergic receptor expression is dense in cerebral cortex and in hippocampus [172], but the cellular localization has not been established in the brain in situ.

B. α_1-Adrenergic Receptors

1. Cultured and Dissociated Cells

Accumulation of ^{3}H-inositol phosphates in cultured astrocytes after exposure to labeled inositol is dose-dependently increased by noradrenaline, and this stimulation is blocked by a low concentration of an α_1-adrenergic antagonist [173-175]. An increase in $[Ca^{2+}]_i$ by α_1-adrenergic agonists has been described both in cultured astrocytes [176-178], in freshly isolated cells [179] and in brain slices, where calcium waves can be evoked by stimulation of α_1-adrenergic receptors [180].

Mouse brain astrocytes in primary cultures express α_1-adrenergic receptors [181-182], although the binding density is less than that found for β-adrenergic receptors, and α_1-adrenergic receptors are not present on all individual astrocytes [183]. α_1-Adrenergic receptors have also been described on freshly isolated astrocytes [157, 164] from different brain areas as well as from the trigeminal motor nucleus, where they decrease following neuronal injury [170].

2. Intact CNS

The α_1-adrenoceptor has been divided into the subtypes $\alpha_{1a/c}$, α_{1b}, and α_{1d} [184]. Inhibition of a subgroup of α_{1b}-adrenoceptors decreases motor activity in otherwise exploratory situations and appears to be activated by adrenaline rather than noradrenaline [185-186]. The detailed localization of such 'motoric' α_1-adrenergic receptors has been identified by the ability of microinjections of the specific α_1-adrenergic agonist terazosin in discrete regions of the mouse brain to induce immobility during exposure to a novel surroundings [186-187]. Five injection sites have given definite positive responses (i.e., inactivity after the injection): i) the dorsal pons in or near the locus coeruleus; ii) the dorsal raphe; iii) the nucleus accumbens; iv) the cerebellar lobules dorsal to the fourth ventricle; and v) the fourth ventricle itself. These locations suggest that the 'motoric' α_1-adrenergic recptors may regulate noradrenergic, serotonergic and dopaminergic receptor activation in locus coeruleus, the raphe nuclei and nucleus accumbens.

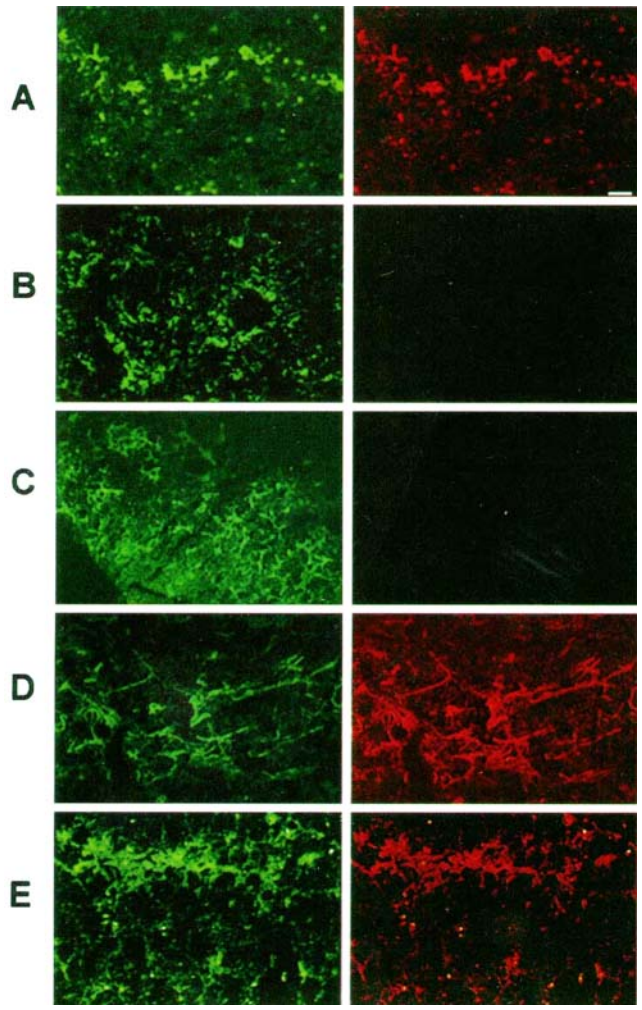

Fig. (3). Immunofluorescent double-labeling for GFAP (green) and β_2-adrenergic receptor (red). (A) astrocytes in white matter of a control; (B) astrocytes in normal-appearing white matter in MS; (C) reactive astrocytes in a chronic active MS plaque; and (D) reactive astrocytes at the boundary of a cerebral infarction. From [48].

C. α_2-Adrenergic Receptors

1. Cultured and Dissociated Cells

α_2-Adrenoceptors are classified as $\alpha_{2A/D}$, α_{2B}, and α_{2C}-adrenoceptors [184], and they are found both presynaptically and on target cells. Cultured astrocytes express α_2-adrenergic receptors, which exist as two forms: high affinity sites, which are identical to the high affinity sites found in rat brain, and low affinity binding sites, which were not fully characterized [181]. They also express mRNA for α_2-adrenergic receptors [188]. The expression of α_2-adrenergic

receptors and their mRNA is greatly increased in astrocyte cultures treated with dibutyryl cyclic AMP (dBcAMP), and these receptors are almost exclusively of the α_{2A} subtype [189]. The α_2-adrenergic agonist dexmedetomidine inhibits forskolin-induced increases in cyclic AMP and stimulates accumulation of IP_3. Both dexmedetomidine and clonidine increase $[Ca^{2+}]_i$ in cultured astrocytes treated with dBcAMP [40, 118, 176-178].

2. Intact CNS

The distribution of α_2-adrenergic receptors in the adult rat central nervous system is widespread, with moderate labeling in cortex and intense labeling of the basal forebrain and locus coeruleus and labeling of both perikarya and neuropil at most locations [190]. In the adult monkey prefrontal cortex the α_{2A}-adrenergic receptor is by far the most prominent subtype. It is frequently found along the plasma membrane of proximal dendrites, dendritic spines, within terminals, in the perikaryal cytoplasm, and in astrocytic processes. The areal density of immunoreactivity at morphologically identifiable synapses is low presynaptically but higher postsynaptically, where it reaches ~50%. This observation confirms a previous conclusion that only a minor fraction of α_2-adrenergic receptors are presynaptic [191]. Moreover, there is a robust expression of α_2-adrenergic receptors prior to synaptogenesis [192]. Thus, in spite of the ability of α_2-adrenergic activity to drastically reduce the release of noradrenaline [193], most identifiable synapses are postsynaptic, and a large fraction of the noradrenergic axons do not form synapses but interact with other postjunctional structures, including astrocytic processes. A somewhat larger presynaptic expression of α_2-adrenergic receptors has been found in hippocampus, but even here the majority of these receptors is either postsynaptic or astrocytic [194]. In the bird brain, most α_2-adrenergic receptors are postsynaptic [195].

Autonomic (e.g., cardiovascular and gastrointestinal) reactions to aversive emotional events can be modulated by α_{2A}-adrenergic agonists [196]. Labeling of α_2-adrenergic receptors in the central nucleus of amygdala, which projects descending fibers to the dorsal vagal complex nucleus, was therefore performed in rats receiving microinjection of fluorogold, a retrograde tracer, into the dorsal vagal complex [197]. Of all immunolabeled dendrites one quarter also showed label by fluorogold, suggesting their participation in afferent vagal input, and more than one half of the labeled neuronal perikarya were also labeled by the retrograde tracer. Glial processes accounted for 13% of all α_{2A}-adrenergic receptors, and they were in numerous instances apposed to the labeled neurons. In nucleus tractus solitarius, which includes some of the cell aggregates in the adrenergic-noradrenergic network in the brain stem, an even larger fraction of α_{2A}-adrenoceptors is found on glia (30-50%, depending on the level of the nucleus) (Fig. **4**). At the caudal level of this nucleus more α_{2A}-adrenergic receptors are located on glia than on dendrites [198]. The labeled glial cells appose both unlabeled dendrites and terminals, and dendrites expressing tyrosine hydroxylase immunoreactivity. They are also frequently located close to dendrites or axon terminals expressing μ opioid receptors [199].

Since α_2-adrenergic agonists potently inhibit noradrenergic neurons projecting from locus coeruleus to the brain hemispheres, the ultrastructural localization of α_2-adrenergic receptors in this nucleus is of special interest. α_{2A}-Adrenoceptors are predominantly found on dendrites (~50%) and on glial cells (~30%) with only a minor fraction (~15%) on axons [200]. The astrocytic processes exhibiting α_{2A}-adrenergic receptor immunoreactivity are closely apposed to axons labeled for tyrosine hydroxylase. Some dendrites also express α_{2C}-adrenergic receptors in astrocytic processes apposed to tyrosine hydroxylase expressing dendrites [201].

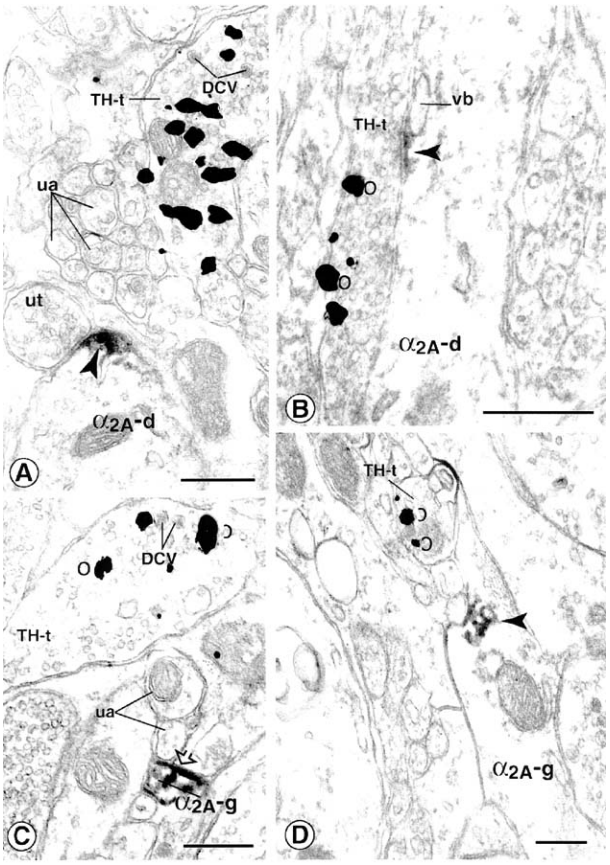

Fig. (4). **A:** A tyrosine hydroxylase-labeled terminal (TH-t) and an α_{2A}-adrenoceptor-positive dendrite (α_{2A}-d) are segregated by a patch of unlabeled neuropil. Gold particles (arrows) for tyrosine hydroxylase can be seen throughout TH-t. This terminal is contacted by numerous unlabeled axons (ua) separating it from the α_{2A}- positive (arrowhead) α_{2A}-d, apposed to an unlabeled terminal (ut). **B:** A tyrosine hydroxylase-labeled terminal (TH-t) is apposed to a longitudinally sectioned α_{2A}-adrenoceptor-positive dendrite (α_{2A}-d). The receptor labeling (arrowhead) is seen on only a discrete portion of the plasma membrane near a membranous saccule resembling smooth endoplasmic reticulum (vb). **C:** An α_{2A}-adrenoceptor-positive astrocyte (α_{2A}-g) is labeled mainly on the plasma membrane. This glia forms an apparent gap junction (open arrow) with an unlabeled astrocytic profile. A large tyrosine hydroxylase-containing terminal (TH-t), which exhibits gold particles (solid arrows) abutting small synaptic vesicles and large dense core vesicles (DCV), can be seen nearby. **D:** A small tyrosine hydroxylase-labeled terminal (TH-t) is apposed to an α_{2A}-adrenoceptor-positive glia (α_{2A}-g). The α_{2A}-labeling is associated with the plasma membrane and nearby cytosolic space of this glia. Scale bars 0.5 mm. From [198].

Whether or not astrocytes in the dorsal horn of the spinal cord express α_2-adrenergic receptors is disputed. Ridet *et al*. [202] noted that noradrenergic descending fibers to the spinal cord mainly established non-synaptic contacts. Numerous astrocytic profiles apposed noradrenergic varicosities, and the proportion of astroglia was higher around noradrenergic varicosities devoid of synaptic contacts than around synapses. On the other hand an immunocytochemical study by Stone *et al*. [203] did not show any α_2-adrenergic receptor expression on glia. This suggests that astrocytes are not engaged in spinal antinociception, a concept that is further supported by the observation that the dexmedetomidine-induced spinal analgesia is mediated by α_{2C}, not α_{2A} receptors [204], whereas astrocytic α_2-adrenergic receptors are of the α_{2A} subtype, at least at the cortical level.

IV. EFFECTS OF ASTROCYTIC ADRENOCEPTOR STIMULATION AT THE CELLULAR LEVEL

A. Introduction

Adrenoceptors influence a multitude of parameters in astrocytes, ranging from morphological plasticity, through energy metabolism, transport across the cell membrane, gap junction permeability and membrane potential to immunity and scar formation. Different subtypes are involved and some processes are stimulated by more than one subtype, as summarized in Table **2**.

B. Morphological Plasticity

One of the first demonstrated effects of noradrenaline on astrocytes was its ability to transform polygonal, flat astrocytes in primary cultures to a stellate morphology, much more similar to protoplasmic astrocytes in the brain *in vivo* [205]. A similar effect can be evoked by addition of forskolin or dibutyryl cyclic AMP to the cultures, indicating that this is a β-adrenergic effect [206-209]. The cAMP-mediated stellation is a result of coordinated changes in phosphorylation of the actin cytoskeleton and of extracellular matrix proteins [210] and at the same time mitosis is inhibited [211-212]. The morphological change is accompanied by a multitude of biochemical changes, perhaps most notably the development of L-type Ca^{2+} channels [213-214], enhanced expression of α_{2A}-adrenergic receptors [189], and changes in protein phosphorylation [208]. Besides the developmental importance of this effect [215-216], analogous morphological changes of astrocytes and of the astrocyte-like pituicytes play a major role in the hypothalamo-hypophyseal system, facilitating the release of vasopressin (AVP) and oxytocin [217-218]. These changes in cell shape are probably also a result of activation of β-adrenergic receptors [219-220].

C. Energy Metabolism

1. Glucose Uptake and Glycolysis

Both glucose uptake in cultured chick astrocytes and formation of pyruvate/lactate from glucose in primary

Table 2. Adrenergic Subtypes Involved in Different Responses of Astrocytes at the Cellular Level

Parameter	α_1	α_2	β_1 and/or β_2	β_3
Glycose Uptake				X
Glycolysis	X			
Glycogenolysis		X	X	
Glycogen Synthesis		X	X	
Pyruvate Dehydrogenation		X		
α-Ketoglutarate Dehydrogenation	X	X		
Glutamine Hydrolysis		X		
Glutamate Uptake	X			
GABA Uptake			X	
Taurine Uptake			X	
Taurine Release			X	
Na^+,K^+-ATPase Activity	?		X	
Decrease in Gap Junction Permeability			X	
Decrease in Gap Junction Permeability↓	X			
Depolarization	X	X		
Hyperpolarization			X	
Inhibition of Inflammation			X	
Reactivity and Scar Formation			X	
Glucose Uptake				X

*Indirect evidence from learning experiments

cultures of mouse astrocytes are stimulated by noradrenaline. However the effect on glucose uptake is exerted on β_3-adrenoceptors [159] and that on glycolysis on α_1-adrenoceptors [221-222].

2. Glycogenolysis and Glycogen Synthesis

Formation of pyruvate/lactate from glycogen in brain and retina has long been known to be stimulated by noradrenaline [223-227], and since virtually all glycogen and its metabolizing enzyme in brain and retina are located in astrocytes, and the astrocyte-like retinal Müller cells [31, 228-230], it must be an astrocytic effect. It is in keeping with this conclusion that glycogenolysis is stimulated by noradrenaline in cultured C-6 astrocytoma cells [231-232] and in primary cultures of rodent and chick astrocytes [233-237]. In cultured astrocytes both the β-adrenergic agonist isoproterenol and the α_2-adrenergic agonist clonidine induce glycogenolysis, whereas the α_1-adrenergic agonist phenylephrine has no glycogenolytic effect [234].

It is often believed that glycogen storage serves the purpose of providing the brain, especially neurons, with glucose equivalents for use during failure of glucose delivery [33, 238]. However, glycogen metabolism is much more dynamic than would be expected from a compound serving only as an emergency store. Thus, both glycogenolysis and glycogen resynthesis are stimulated during and immediately after brain activation [34-35]. Concomitant glycogenolysis and glycogen synthesis may at first seem counterintuitive, since glycogen synthesis requires a supply of energy, which is only partly recovered during glycogenolysis. However, as discussed in section I, glycogenolysis provides the advantage over glycolysis that no ATP is required to "prime" glucose equivalents in glycogen for further metabolism, and that glycogen is present in even the thinnest astrocytic processes. This means that glycogenolysis rapidly can provide energy even at locations where oxidatively generated energy is not immediately available. Subsequently oxidatively derived energy may contribute to the resynthesis of glycogen.

Since glycogen is not only rapidly degraded but also re-synthesized during and after brain activation and at specific stages of learning [239-240], it becomes of importance to establish whether noradrenaline also enhances glycogen synthesis. Magistretti and coworkers have demonstrated that it leads to a large, but delayed protein synthesis-dependent induction of glycogen synthase and increase in glycogen, an effect which is mediated by protein kinase A and its phosphorylation of CREB [241-242]. However, such a long-term effect is unable to explain re-synthesis of glycogen concurrently with or soon after glycogenolysis. The first hint that noradrenaline can cause an immediate increase in glycogen synthesis was the observation by Pearce *et al*. [243] that deoxyglucose incorporation into glycogen is stimulated by noradrenaline. Experiments by ourselves have confirmed an acute stimulatory effect of noradrenaline on glycogen synthesis and suggested that this is an α_2-adrenergic effect [37].

3. Oxidative Metabolism

By far the largest yield of energy (ATP) during degradation of glucose is obtained when pyruvate, formed during glycolysis or glycogenolysis is oxidatively degraded in the mitochondria (Fig. **5**). For this purpose pyruvate is converted to acetyl coenzyme A (reaction 1 in Fig. **5**) and introduced into the tricarboxylic acid (TCA) cycle, where it condenses with the TCA cycle intermediate oxaloacetate to form citrate. During each turn of the cycle a substantial amount of ATP molecules is formed, and oxaloacetate is regenerated, ready to combine with another molecule of pyruvate. Since one molecule of oxaloacetate is consumed and one molecule of oxaloacetate is produced during each turn of the TCA cycle, this reaction cannot give rise to any net synthesis of TCA cycle intermediates or their derivatives glutamate, glutamine and GABA. In the CNS there is a need for resynthesis, especially of glutamate and glutamine. This is brought about by combining pyruvate metabolism to acetyl coenzyme A with carboxylation of another molecule of acetyl coenzyme A to form a new molecule of oxaloacetate (reaction 2 in Fig. **5**) and condensing the two to form a molecule of citrate. This 'new' molecule of citrate can then undergo further metabolism in the TCA cycle, e.g., to α-ketoglutarate, a direct precursor of glutamate (reaction 4 in Fig. **5**). Since neurons in contrast to most other cell types (including astrocytes) do not express pyruvate carboxylase activity and therefore are unable to carry out pyruvate carboxylation, this process must occur in astrocytes [245-247].

In contrast to 'conventional wisdom' but in agreement with decades-old observations in cultured astrocytes [26, 27], solid evidence has recently been obtained that astrocytes in the brain *in vivo* show a substantial rate of oxidative metabolism [28-29, 248-249], so that their respiratory rate per unit volume is comparable with that in neurons [28, 37]. Moreover, during the last 10-15 years, studies in tissues other than brain [250-252] have shown that an increase in free intramitochondrial Ca^{2+}, secondary to a transmitter-induced rise in $[Ca^{2+}]_i$, within seconds causes a direct stimulation of the mitochondrial dehydrogenases, pyruvate dehydrogenase (the enzyme carrying pyruvate generated during glycolysis into the TCA cycle), isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase (enzymes functioning during the operation of the TCA cycle). Moreover, there are Ca^{2+}-mediated increases of glutaminase activity [253] and a direct enhancement of oxidative phosphorylation [252, 254]. A similar response occurs in astrocytes, where noradrenaline and α_2-adrenergic agonists stimulate pyruvate dehydrogenation [40, 118, 178], α-ketoglutarate dehydrogenation [221] and hydrolysis of glutamine to glutamate [255] (Table **2**). No corresponding effect on α-ketoglutarate dehydrogenation was observed in cultured neurons [256]. ATP, another transmitter acting on phospholipase C, depolarizes the mitochondrial membrane potential in astrocytes in primary cultures, which may reflect entry of Ca^{2+} into the mitochondria [257].

Unlike pyruvate dehydrogenase activity and glutamine hydrolysis, α-ketoglutarate dehydrogenase activity is also stimulated by the ·1-adrenergic agonist phenylephrine [221]. Thus, there is no simple correlation beween an increase in astrocytic $[Ca^{2+}]_i$ and stimulation of oxidative metabolism, as also indicated by the ability of other transmitters (e.g. serotonin and vasopressin) to increase $[Ca^{2+}]_i$ without stimulating pyruvate dehydrogenation [258-259]. It is a further indication of the complexity that noradrenaline stimulates α-ketoglutarate dehydrogenation considerably less

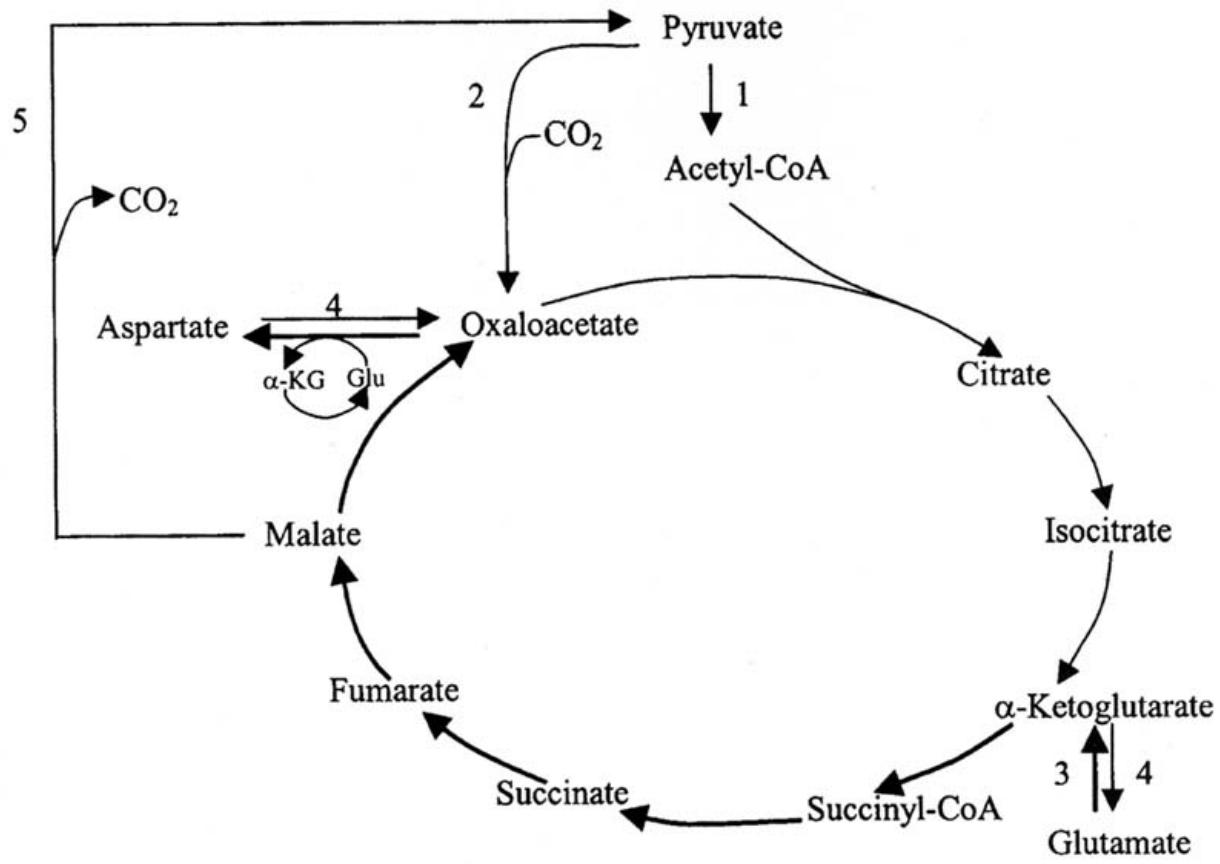

Fig. **(5)**. Schematic representation of the tricarboxylic acid (TCA) cycle and closely connected reactions i.e., formation of acetyl-CoA from pyruvate (1), pyruvate carboxylation (2), glutamate conversion to α-ketoglutarate (3), α-ketoglutarate conversion to glutamate (4) and pyruvate formation from malate (5). From [244].

potently that it stimulates glycogenolysis and pyruvate dehydrogenation [178, 221, 234].

2. Glutamate and Glutamine Oxidation

Glutamate and glutamine are oxidatively metabolized in the brain *in vivo* [260-261], probably primarily in astrocytes, where glutamate and glutamine are avidly degraded [262-265]. Glutamate is initially converted to α-ketoglutarate (reaction 3 in Fig. **5**), which is metabolized in the TCA cycle to malate, which can be decarboxylated to pyruvate (reaction 5 in Fig. **5**). It is therefore a parallel to the effect of noradrenaline on mitochondrial dehydrogenases that both noradrenaline and dexmedetomidine stimulate glutamine hydrolysis to glutamate as well as the further oxidation of glutamate in the TCA cycle [255, 266-267]. The dose-response curve for dexmedetomidine-induced increase in glutamine metabolism is identical to that for the increase in $[Ca^{2+}]_i$ [118].

D. Membrane Effects

1. Uptake and Release of Amino Acids

In the brain *in vivo* glutamate released from neurons is mainly accumulated by the powerful astrocytic glutamate transporters GLT-1 and GLAST [9]. It is therefore of major functional importance for the regulation of glutamatergic activity in the CNS that glutamate uptake in astrocytes is stimulated by noradrenaline. This effect was first shown in cultured astrocytes where glutamate uptake is increased by the α_1-adrenergic agonist phenylephrine but decreased by stimulation of β-adrenergic receptors and unaffected by α_2-adrenergic receptor activation [41-42]. Subtype-specific inactivation of the α_1-adrenergic receptor has shown that the stimulatory effect is mediated by α_{1b}-adrenoceptor[43]. A phenylephrine-activated increase in clearance of glutamate from the extracellular space in rat brain has been confirmed in a microdialysis study [44]. Glutamine uptake in astrocytes is also enhanced by noradrenergic stimulation as indicated by an increase in the contents of both labeled glutamine and in its metabolites glutamate and aspartate after 30 min of exposure to [U-^{14}C]glutamine [255].

GABA uptake in the brain *in vivo* occurs mainly by neuronal re-uptake, and GABA uptake in astrocytes is much less intense than glutamate uptake [244, 268]. The astrocytic uptake of both GABA and taurine, another amino acid which is generally regarded as purely inhibitory, is stimulated by β-adrenergic receptor activation, but unaffected by α_1 or α_2 receptor agonists [42]. However, also the release of taurine is enhanced by activation of β-adrenergic receptors, both in bulk-prepared astrocytes [269] and in primary astrocyte cultures [270-272]. In the hypothalamo-hypohysial system the basal release of vasopressin and oxytocin from a

perifused explant of the anterior lobe of the pituitary is enhanced by taurine [273]. Accordingly a noradrenaline-mediated taurine release may operate in concert with the noradrenaline-induced morphological changes in astrocytic processes to stimulate vasopressin release. However, in purified neurohypophysial nerve endings, activation of strychnine-sensitive glycine receptors by taurine inhibits the rise in $[Ca^{2+}]_i$ and subsequent release of vasopressin evoked by K^+-mediated depolarization [274].

2. Ion Carriers and Ion Channels

A stimulation of Na^+,K^+-ATPase activity in brain tissue by noradrenaline [275-279] and by β- or α_1-adrenergic agonists [280-281] has repeatedly been demonstrated. In homogenates of primary cultures of cortical and spinal cord astrocytes Na^+,K^+-ATPase activity is significantly increased by both noradrenaline and the β-adrenergic agonist isoproterenol, whereas there is no effect by clonidine and an apparent effect by phenylephrine failed to reach significance [22] (Table **2**). In contrast, channel-mediated K^+ influx into astrocytes is not affected by noradrenaline, although it is drastically decreased by an active phorbolester [282], mimicking the effect of DAG.

3. Gap Junction Permeability

Gap junction permeability is reduced by an α_1-adrenergic agonist whereas it is increased by β-adrenergic activation [283] (Table **2**). Cell coupling in cultured astrocytes and in hippocampal brain slices is reduced if the cells have been treated with either an active phorbolester or a synthetic diacylglycerol that activates protein kinase C [284-286]. Such a modulation of gap junctional conductance by noradrenaline and/or other transmitters could transiently isolate or promote specific pathways within the astrocytic syncytium to form an extraneuronal information transfer network in brain.

4. Membrane Potential

A large decrease in membrane potential has been found both in primary cultures of rat astrocytes and in astrocytes in organotypic cultures from the spinal cord or the brain stem during exposure to noradrenaline acting on α_1-adrenergic receptors [287-288]. The astrocytes in the organotypic cultures showed a similar decrease during exposure to clonidine, whereas they hyperpolarized in the presence of isoproterenol (Table **2**). The effect of noradrenaline could be due to a reduction of K^+ conductance in astrocytes, as reflected by an inhibition of Kir currents [8]. Isoproterenol exerted a similar inhibition suggesting that this was a β-adrenergic effect. However, activation of β-adrenergic receptors has also been found to open calcium-activated K^+ channels [289]. Accordingly the correlation between noradrenergic effects on membrane potential and ion conductance is complex.

E. Immune Reactions

1. The Innate Immune System

The innate system is a non-specific immune system present since birth that does not require previous exposure to pathogens to become operational and acts within minutes of an infection. Macrophages and polymorphonuclear neutrophilic leukocytes (neutrophils) recognize pathogens by aid of cell-surface receptors, including receptors for complement and CD14, a receptor for bacterial lipopolysaccharide (LPS). LPS binding to a specific receptor triggers a transduction pathway, which culminates in the phosphorylation of IκB, a cytosolic protein, which binds to the transcription factor NFκB and thereby retains it in the cytoplasm. After the phosphorylation IκB dissociates from the complex, allowing NFκB to enter the nucleus where it activates genes involved in host defense by aid of cytokines, chemokines, NOS2 induction, and activation of a complement cascade [290].

Noradrenaline and isoproterenol suppress LPS-mediated inflammatory reactions [291-292]. cAMP-mediated changes in NOS2 expression are the result of changes in promoter activation [293], and one possible reason for the reduced activation of NOS2 expression is that the PKA-mediated phosphorylation of CREB leads to binding of CREB binding protein (CBP) to CREB rather than to the NFκB component p65, which is a necessary co-activator for NFκB-mediated transcription of the NOS2 gene. A second mechanism by which noradrenaline could reduce inflammatory gene expression is by inhibiting phosphorylation of IκB [294-295]. Moreover, a noradrenaline induced inhibition of arginine uptake in astrocytes [296] could contribute to the decrease in NO, since arginine is a NO precursor. In astrocyte cultures transfected with tumor necrosis factor (TNF) and interleukin-6 (IL-6), noradrenaline and isoproterenol also inhibit expression of TNF and IL-6 genes, induction of the adhesion molecule ICAM-1 in response to LPS, and expression of NOS2 in response to cytokines [297]. The inhibitory effect can be blocked in the presence of a β_2-adrenoceptor antagonist but not in the presence of a β_1-adrenoceptor antagonist. LPS-induced transcription of IL-1β is also inhibited by other agents that increase intracellular cAMP [298]. In addition to noradrenaline itself dopamine is capable of stimulating β-adrenergic receptors on astrocytes and thereby inhibit LPS-mediated TNF-a production and NOS2 activity [299].

Recently the importance of peroxisome proliferator-activated receptor γ (PPARγ) for noradrenaline-mediated suppression of inflammatory responses has been emphasized [295, 300]. PPARγ is one of 3 PPARs isoforms (PPARα, β/δ and γ), which are ligand-activated transcription factors belonging to the nuclear receptor superfamily. They contain several different functional domains, including one determining the specificity of promoter DNA sequence recognition and another determining ligand recognition [301-302]. The genes expressing DNA sequences recognized by PPARs include many that are involved in inflammatory responses, e.g., NFκB, and the ligands include fatty acids and eicosanoids as natural ligands and non-steroidal anti-inflammatory drugs like ibuprofen among the many pharmacologically relevant agonists [303]. In the rat brain *in vivo* PPARs have been demonstrated in both neurons and glial cells, with PPARγ being mainly expressed in frontal cortex, basal ganglia and the reticular formation [304]. All 3 PPARs are also expressed and operating in rat and human cortical and cerebellar astrocytes [305-306]. Incubation of murine cortical astrocytes with noradrenaline results in an increase of both mRNA and protein level of PPARγ, which can be blocked by propranolol, but not by the α-adrenergic

antagonist phentolamine [300]. These results suggest that the anti-inflammatory effects of noradrenaline on brain cells at least partly may be mediated by an increase in PPARγ.

2. The Adaptive Immune System:

The adaptive immune system develops in response to previous exposure to pathogens or their constituents (by infection or vaccination), and it is pathogen-specific. It is also the system which is responsible for auto-immune diseases. Its operation is triggered by antigen presenting cells (APCs). Professional APCs, e.g., B lymphocytes, macrophages and dendritic cells constitutively express major histocompatibility complex (MHC) class I and class II molecules. The MHC class II present peptides derived from pathogens or other antigens to $CD4^+$ T lymphocytes, called T_H cells, mediated by ICAM-1 on the APCs and an integrin on the T cell. The interaction between an APC and a $CD4^+$ lymphocyte initiates T_H cell activation towards the antigen presented by the MHC II complex and production of the cytokines Il-2, TNF and interferon- γ (INF-γ). In addition, the interaction induces the APCs to produce the proteins CD 40 and B7 that provide a second, co-stimulatory signal to the T_H cell. In the presence of both the antigen-specific signal and the co-stimulatory signal the stimulated T_H cells undergo clonal expansion, greatly promoting their activities, whereas interaction of T_H cells with the antigen-specific signal in the absence of the co-stimulatory factors leads to a state of non-responsiveness (clonal anergy). However re-activation of previously activated T_H cells (memory cells) can occur even in the absence of the co-stimulatory signal [290, 307].

The role of astrocytes as APCs is disputed. ICAM-1 is constitutively expressed in astrocytes, but they do not constitutively express class II MHC molecules. However, Wong *et al*. [308] showed that astrocytes in primary cultures can be induced by IFN-γ to express these molecules, a finding that has been repeatedly confirmed. Also, intrathecal injection of IFN-γ induces class II MHC expression in astrocytes *in vivo* [309] and this effect is enhanced by the simultaneous presence of TNF-α, an observation confirmed by Benveniste and co-workers [307]. However, most studies indicate that human astrocytes normally do not express the co-stimulatory molecules B7 and CD 40. In rodent astrocytes these cofactors may be induced by stimulation with INF-γ. [310-311]. Accordingly, untreated murine astrocytes are able to re-activate previously activated T_H cells, but not naïve T cells [311]. After treatment with IFN-γ these cells expressed B7 and were now able to also stimulate the proliferation of naïve T cells. Recently Zeinstra *et al*. [312] have observed that reactive astrocytes in chronic active plaques of multiple sclerosis express B7, and hence may have the necessary attributes to act as antigen-presenting cells.

Noradrenaline can inhibit immune reactions by interactions with MHC class II expression in response to INF-γ. A dose-dependent inhibition of the ability of INF-γ to induce MHC class II expression on cultured astrocytes was first demonstrated by Frohman *et al*. [310]. Noradrenaline, isoproterenol, cAMP analogs and forskolin also counteract an enhancement of the expression of ICAM-1 in astrocytes by IL-1β, TNF-α and INF-γ [313]. Moreover, a major role of the adaptive immune system is to enhance function in the innate immune system, and the inhibitory effects of noradrenaline on that system will also diminish the immune response.

3. Response to Cell Injury

Neuronal injury, including that evoked by seizure activity, neurotrauma, exposure to radiation, or excitotoxicity induces IL-1 expression, primarily in microglia, which subsequently release IL-1 [314-317]. The released IL acts on astrocytes, which in normal brain express few, if any IL receptors, although they do express IL-1 receptor mRNA [318-319]. However, after local injury of the CNS astrocytes become reactive and show IL-1 binding [320-321]. Exposure to IL-1 activates NFκB in astrocytes, an effect which can be counteracted by an increase in cAMP evoked by forskolin or cAMP analogs [322], similar to what was described for noradrenaline-mediated suppression of LPS-induced NFκB activation. IL-1 also stimulates astrocytic production of TNF-α [323], of IL-1β itself [324], and of IL-6 [325], and it induces the expression of NOS2 *via* an NFκB-dependent mechanism [322, 326].

In contrast to the inhibitory effect by noradrenergic activation of the inflammatory response the formation of a glial scar is faciliated. This is shown by the observation that the expression of GFAP in response to cell injury in the dorsal horn of the spinal cord is decreased by one third when the injured tissue is depleted for noradrenaline, whereas it is increased by ~50% if the tissue is hyperinnervated by experimentally induced neuronal sprouting [327-328]. The increased formation of reactive astrocytes is reduced by β-adrenergic receptor blockade [329].

V. ROLES OF ASTROCYTIC ADRENOCEPTORS IN BRAIN FUNCTION AND DYSFUNCTION

A. Brain Function

1. Establishment of Memory

As already discussed, locus coeruleus nucleus plays a major role in attention, behavioral flexibility, and cognitive processes [67-69, 87]. Its role during learning is illustrated by the observations that destruction of locus coeruleus neurons by DSP-4 treatment results in amnesia in day-old chicks [330] and impairment of memory for at least some tasks in rats [331-333]. A large amount of experimental evidence exists that administration of noradrenaline or β-adrenergic agonists enhances memory formation, whereas β-adrenergic receptor antagonists impair the acquisition of memory in a variety of tasks in both rats and chickens [rewieved in 334]. Also, the memory impairment after DSP-4-induced cell death in locus coeruleus in day-old chicks can be prevented by noradrenaline or the β_2-adrenergic agonist salbutamol [330]. In contrast to the repeated observations that β-adrenergic agonists enhance memory, there is only little evidence that α_1-adrenergic stimulation is necessary for the establishment of memory and considerable evidence that it can inhibit learning [334-336].

Noradrenergic agonists and antagonists exert different actions in modulation of memory formation in different brain regions and at different times in the sequence of memory processing. Region-, time- and subtype-specificity have been especially thoroughly studied during one trial

aversive learning in the day-old chick as recently reviewed by Gibbs and Summers [334]. In this model day-old chicks are trained by being offered two artificial beads of different colors, one of which is tainted by the aversively tasting drug methylanthranilate (MeA), whereas the other is untainted [337]. The chickens subsequently refuse to peck at any bead of the color previously associated with aversive taste, unless memory is impaired by training with a weakened stimulus (use of 20% MeA, rather than 100%), in which case a labile memory is expressed only during the first 30 min, or unless memory is extinguished by use of specific drugs. Labile memory can be consolidated into permanent memory by administration of noradrenaline or a β_2-adrenergic agonist at any time during the first 30 min after learning into the intermediate hyperstriatum ventrale (IMHV), a multimodal association centre corresponding to the mammalian cerebral cortex. β_1-Adrenergic receptor agonists are unable to consolidate labile memory and α_2-adrenergic agonists are only able to consolidate labile memory if injected during the first 30 min into a different region, lobus parolfactorius (LPO), corresponding to mammalian basal ganglia.

Propranolol, an inhibitor of β_1- and β_2-adrenergic receptors inhibits strongly reinforced learning when injected into IMHV between 5 and 25 min post-training, with memory loss after 30 min. However, if propranolol is given into the LPO, rather than into the IMHV, it is effective between 5 min before learning and 2.5 min after learning, but not at later times, indicating a different target. This is probably β_1-adrenergic receptors, since a subtype specific β_1-antagonist has a similar effect [334]. A β_3-adrenergic antagonist is only effective when given at 5 min after learning, and memory is extinguished already after 20 min [338]. The α_2-adrenergic receptor antagonist yohimbine also has to be given into LPO between 10 and 15 min but memory loss is after 30 min [339].

The main conclusion from both agonist and antagonist experiments is that there are two important periods during establishment of memory, when release of noradrenaline in the brain and thus locus coeruleus activity play a decisive role: i) within the first min after acquisition, when attentional or arousal factors are crucial for initiating the

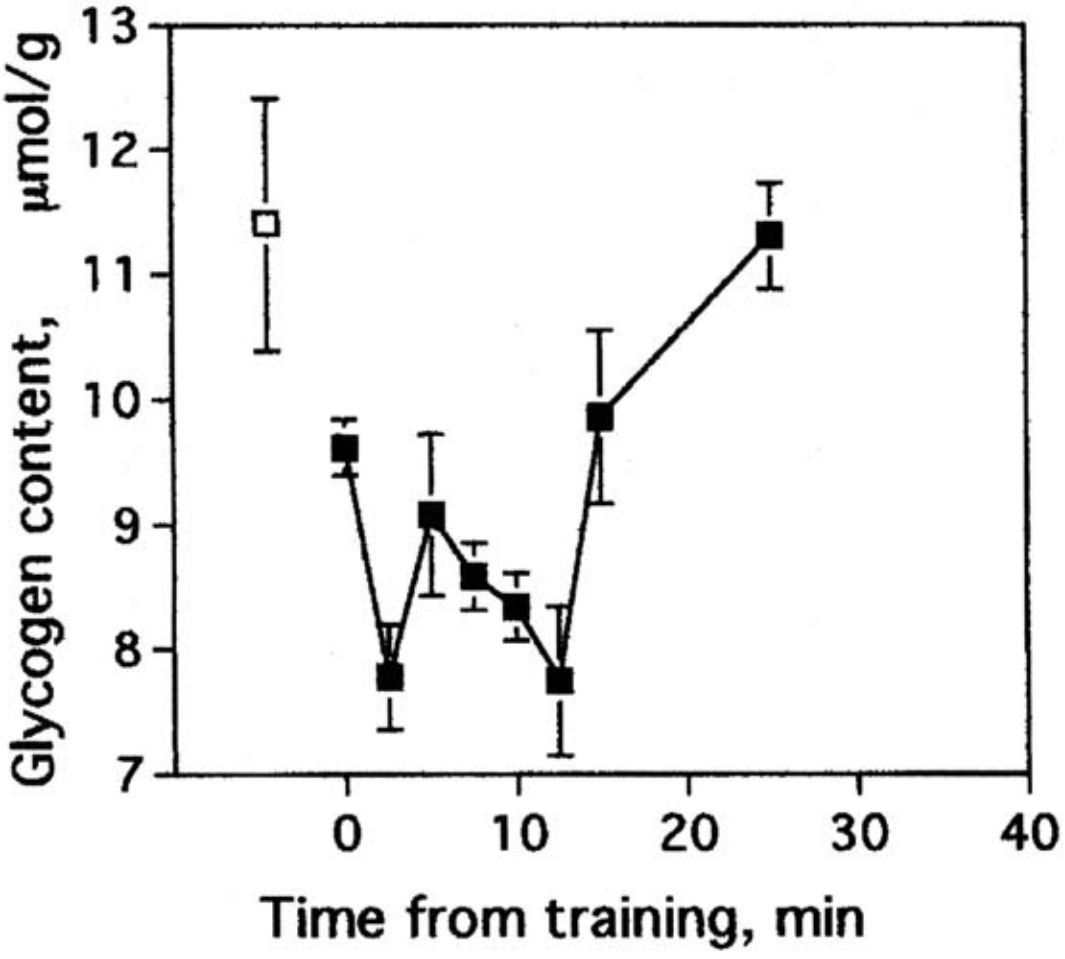

Fig. (6). Content of glycogen in the forebrain of day-old chicks after pretraining, involving pecking at a water-coated bead (open square) and representative of the non-aversively-trained animal, and after one-trial aversive training, involving pecking at a red aversively tasting bead and a blue neutral bead (filled-in squares, with the training performed seconds before the first point). The aversive training induces a rapid decline in glycogen content (~4 µmol/g wet wt within 2.5 min), which is statistically significant (<0.05 or better) between 0 and 2.5 min, followed by a maintained reduction in glycogen level between 2.5 and 12.5 min (possibly with some oscillation of the level) and complete restoration of aversive-training level of glycogen between 12.5 and 25 min. From [37].

process of memory formation, an effect which is localized in the LPO and probably exerted on β_1-adrenergic receptors; and ii) the time of consolidation when a labile memory trace is consolidated into permanent memory, an effect occurring in IMHV and probably mainly exerted on β_2-adrenergic receptors. β_3-Adrenergic receptor activation is also important for memory consolidation, but the early extinction of memory contrasts with the maintenace of memory until 30 min post-training, when a β_2-adrenergic receptor antagonist is administered. LPO also plays a role in consolidation, since injection of an α_2-adrenergic agonist in this structure can consolidate labile memory, whereas the α_2-adrenergic antagonist extinguishes memory, an effect that becomes apparent after 30 min [334].

Neuronal-astrocytic interactions have previously been established during learning in the day-old chick [340-341], and it is an important question to what extent the receptor activation involves adrenergic receptors on astrocytes. The most direct indication may be the occurrence of glycogenolysis, an astrocyte-specific process, which has been demonstrated not only during one-trial aversive learning in day-old chicks [242-243] but also during odor learning in rats pups [342]. However, glycogenolysis in brain tissue and in cultured astrocytes can be evoked not only by β- or α_2-adrenergic stimulation but also by an elevation of the extracellular concentration of K^+ [343-345].

Glycogen contents are transiently reduced and rapidly built up again during at least two stages of one-trial aversive learning in the day-old chick [239-240]. The first period of glycogenolysis occurs immediately after the training (Fig. **6**). Iodoacetate, an inhibitor of glycolysis both during breakdown of glucose and of glycogen inhibits learning if injected immediately before the reduction of glycogen content [346]. That this effect mainly may be due to inhibition of breakdown of glucose equivalents originating from glycogen is suggested by the recent observation that a specific inhibitor of glycogenolysis (but not of glycolysis) also inhibits learning from 30 min and onwards, if it is injected into the IMHV immediately before learning (M.E. Gibbs and L. Hertz, unpublished observation). However, it is unknown if the glycogenolysis is activated by noradrenergic activation, since propranolol at this time only inhibited memory formation if it was injected into the LPO, and all effects of α_2-adrenergic stimulation also were restricted to LPO. This suggests that the effect of β_1-adrenergic stimulation during the first few min after learning is not exerted on astrocytes. Perhaps glycogenolysis at this time is mediated by K^+-induced depolarization, since the extracellular K^+ concentration is elevated by the aversive stimulus [347].

At least a fraction of the generated pyruvate may serve as a precursor for glutamate and glutamine, which in the left hemisphere reaches a higher level in the tissue than at any other time during the first 30 min after training [240]. The increase in glutamate and glutamine co-incides with release of glutamate, which likewise is restricted to the left hemisphere [348]. Since both glutamate and glutamine are increased there must be net synthesis from glucose *via* the TCA cycle constituent α-ketoglutarate. Because this process requires pyruvate carboxylase activity it must take place in astrocytes. A second increase in glutamate and glutamine contents occurs 30 min after the aversive experience, i.e., at the time at memory consolidation. This increase is found in the right hemisphere [240], and it co-incides with a bilateral release of glutamate [349]. At this time at most a small decrease in glycogen content has been observed [239], suggesting either that the main precursor for the generated glutamate and glutamine may be glucose or that glycogen synthesis from glucose keeps pace with glycogen breakdown. It is consistent with the latter possibility that the specific inhibitor of glycogenolysis also inhibits learning, if it is administered at this time (M.E. Gibbs and L. Hertz, unpublished experiments). It is also likely that stimulation of astrocytic glycogenolysis may be a major, and perhaps the only, reason for the dependence of consolidation of labile memory on administration of noradrenaline or a β_2-adrenergic agonist at the very latest 30 min after learning into the intermediate hyperstriatum ventrale (IMHV), and for the ability of propranolol to inhibit memory when injected into IMVH during approximately the same time period. On the other hand, it is consistent with utilization of glucose that memory retention is abolished by administration before 25 min post-training of deoxyglucose, which competes with glucose for phosphorylation and thereby reduces glucose metabolism [350]. In muscle cells [351-353] and cultured chick astrocytes [159] stimulation of β_3-adrenergic receptors leads to increased uptake of glucose from the extracellular fluid into the cell. Deoxyglucose is transported into the cells by the same transporter as glucose, and β_3-receptor activation can therefore be expected to increase deoxyglucose uptake, if a similar mechanism operates in the brain. This does, indeed, seem to be the case, since a concentration of glucose that is too low to interfere with learning by itself, causes disruption of memory (Fig. **7**), if a β_3- adrenergic agonist is co-administered [350]. The increase in uptake of glucose in astrocytes by stimulation of β_3-adrenergic receptors [159] suggests that this may primarily or exclusively be an astrocytic effect, although it cannot be excluded that neurons also express β_3-adrenergic receptors.

The mechanism by which injection of the α_2-adrenergic antagonist yohimbine into the LPO inhibits expression of memory whereas the α_2-adrenergic agonist clonidine consolidates labile memory is unknown. It is probably not by abrogation or stimulation of the effect of presynaptic inhibitory autoreceptors, since injection of yohimbine into locus coeruleus enhances memory consolidation, whereas injection of the α_2-adrenergic agonist clonidine inhibits (M.E. Gibbs, unpublished experiments). It is therefore likely α_2-adrenergic ligands have a post-junctional target in either neurons or astrocytes. It is consistent with this conclusion that most α_2-adrenergic receptors in the chicken brain are postsynaptic [195].

In contrast to the enhancement of episodal long-term memory by activation of β-adrenergic receptors, systemic administration of a β-adrenergic agonist can inhibit working memory in primates [354]. Working memory, which is dependent on frontal cortex function, is a short-term memory guiding attentional focus, inhibiting inappropriate responses and organizing strategy for future actions by enabling the individual to flexibly react to an ever changing environment during the execution of his or her activities [355-356]. Working memory is also inhibited by α_1-adrenergic agonists

[357-358] and by stress and anxiogenic drugs which increase noradrenaline release [359-360]. However, α_2-adrenergic agonists have convincingly been shown to improve working memory even in young monkeys without memory impairment [361-362]. This effect, which is exerted on α_{2A}-adrenergic receptors [363], is postjunctional, as indicated by the observation that the α_2-adrenergic agonist clonidine becomes more, not less effective at producing cognitive improvement in animals after noradrenergic destruction by 6-OHDA or depletion of noradrenaline by reserpine [364-366]. The beneficial effect of α_{2A}-adrenergic stimulation could be due to a G_i-mediated antagonism of c-AMP- and PKA-mediated effects, but it could also be due to activation of postjunctional α_{2A}-adrenergic receptors on either astrocytes or neurons. The only hint of a possible participation of astrocytes is that regional blood flow in prefrontal cortex in monkeys performing a working memory test is enhanced by the α_{2A}-adrenergic agonist guanfacin [367]. This reaction is likely to involve astrocytes, since a glutamate-mediated increase in astrocytic $[Ca^{2+}]_i$ signaling seems to be a crucial component of activity-induced vasodilation in brain [12].

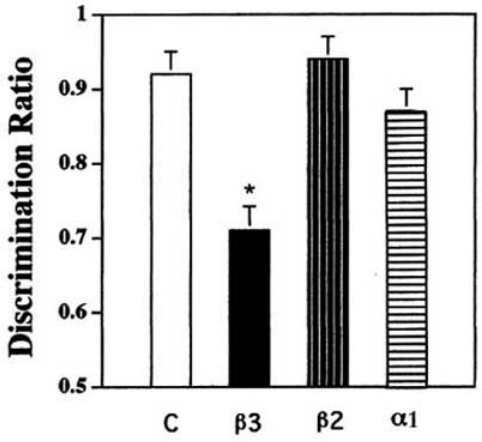

Fig. (7). Effect of a β_3-adrenergic agonist (β_3), a β_2-adrenergic agonist (β_2) and an α_1-adrenergic antagonist (α_1) on memory retention 120 min after one-trial aversive training of day-old chicks given a dose of deoxyglucose that by itself did not impair memory consolidation (C). Normal learning is indicated by a discrimination ratio of ~0.9, and the significant reduction of this ratio, shown by an asterisk ($P<0.05$), during exposure to the β_3-adrenergic agonist indicates impairment of learning. From [350].

2. Cytoprotection

It has been suggested that the α_2-adrenergic agonist dexmedetomidine might reduce extracellular glutamate concentration by a post-junctional effects on astrocytes, where it enhances oxidative metabolism of glutamine, thus reducing the amount available for resynthesis of transmitter glutamate [266]. However, no dexmedetomidine-mediated decrease in extracellular glutamate concentration was observed during *in vivo* ischemia by Engelhard *et al*. [368]. Nor did dexmedetomidine decrease the concentration of noradrenaline, but nevertheless it had a neuroprotective effect. These observations have focused the interest on a 'transactivation' process in astrocytes, leading to 'shedding' of growth factor(s), which cause $ERK_{1/2}$ phosphorylation [117, 119]. Transduction pathways down-stream of ERK phosphorylation have not been established, but dexmedetomidine may alter the balance between pro- and anti-apoptotic genes in brain by ultrarapid gene induction and transcription [369]. $ERK_{1/2}$ activation seems to protect astrocytes in primary cultures against ischemia [370]. It has also recently been found that hypoxia-induced ischemic tolerance in neonatal rat brain is correlated with enhanced $ERK_{1/2}$ signaling, and that inhibition of the activation of $ERK_{1/2}$ significantly attenuates the neuroprotection [371]. Immunofluorescence staining showed that hypoxia-induced $ERK_{1/2}$ phosphorylation was found mainly in microvessels and astrocytes..

B. Dysfunction

1. Multiple Sclerosis, Canine Distemper and EAE

In order to initiate the inflammatory cascade leading to demyelination in multiple sclerosis, invading T_H cells must recognize their specific myelin antigen, presented as a class II MHC molecule by antigen presenting cells in the CNS. Double-labeling histochemistry in postmortem samples originating from patients suffering from multiple sclerosis, cerebral infarctions or no neurological disorder have shown that astrocytes in the control samples, in normal-looking white matter from the multiple sclerosis samples and at the boundary of cerebral infarctions are MHC class II negative. However, a subset of astrocytes in active chronic multiple sclerosis plaques show positive MHC class II staining, indicating their ability to present antigen [372]. For astrocytes to function as complete immunocompetent cells triggering clonal expansion of TH cells they must also express the co-stimulatory molecules B7 and CD 40. It is therefore of major importance that Zeinstra *et al*. [312] recently have reported that reactive astrocytes in chronic active lesions of multiple sclerosis express B7. The astrocytic expression of MHC class II molecules in multiple sclerosis may be a result of failure of noradrenergic suppression. This concept is consistent with the finding by the same group [48, 373-374] that white matter astrocytes in multiple sclerosis lack expression of β-adrenergic receptors (Fig. **3**) and that by Frohman *et al*. [310] that noradrenaline inhibits immune reactions by interfering with the effect of INF-γ on MHC class II expression. Other subtypes of noradrenergic receptors are not deficient [373], and β-adrenergic receptor expression is unaltered in neurons [48].

The etiology of the abolishment of astrocytic β-adrenergic receptor expression in multiple sclerosis is unknown, but it has been suggested that a viral infection might have taken place. It is in support of this hypothesis that a similar abrogation of β-adrenergic receptors on white matter astrocytes is seen in canine distemper encephalitis, a demyelinating disease in dogs that closely resembles multiple sclerosis and is caused by a virus, which primarily infects astrocytes [375]. Again, MHC class II expression could be identified in astrocytes of demyelinated lesions and, again, receptor expression on neurons was normal.

The situation appears to be very different in experimental autoimmune encephalomyelitis (EAE), since the ablation of locus ceruleus by electrolytically induced lesions or by administration of 6-OHDA completely inhibits the development of clinical signs of this disease [376-377]. In addition the occurrence and intensity of lesions in the central

nervous system is markedly diminished, and the production of antibody against rat brain myelin basic protein is reduced. These changes may mainly be related to changes in the periphery, possibly mediated by hypothalamically released steroids, since there is also a reduction of the size of the thymus and a depletion of $CD4^+$ lymphocytes in peripheral blood [378]. EAE may accordingly only reflect the immunological aspects of MS, whereas a primary impairment of astrocytic β-adrenoceptor function is lacking in this model.

2. Learning and Attention Impairment

There is a large amount of evidence that α_2-adrenergic agonists can remedy disturbances of attention and working memory. In animal experiments this includes reversal of aging-induced decline in memory and improvement of attention by neutralization of distracting drug effects and events, and in humans the α_2-adrenergic agonists guanfacine has been successfully used in the treatment of attention deficit hyperactivity disorder and Tourettes' syndrome [364, 366, 379-380]. In animal experiments medetomidine [381], the racemic form of the dexmedetomidine is also effective. It would be of great interest to investigate the detailed cellular localization of these effect as well as the molecular events involved.

3. Alzheimer's Disease

In Alzheimer's disease there is pronounced cell death of noradrenergic neurons in locus coeruleus, especially in those parts, which extend processes to the vulnerable parts of the brain [70-72, 382-386]. In contrast the caudal part of the nucleus sending projections to non-cortical regions is spared [387]. It is generally assumed that the cell injury is a retrograde consequence of AD changes in cerebral cortex and hippocampus, which is consistent with the observation that injection of synthetic β-amyloid into the rat hippocampus produces a 50% reduction of tyrosine hydroxylase activity of afferent neurons [388]. However, it has also been suggested that the disease initially might affect locus coeruleus, with the normally innervated cerebral cortex and hippocampus suffering the effects of deficient noradrenergic innervation [49]. A possible reason for a primary defect in locus coeruleus could be accumulation of 3,4-dihydroxyphenylglycolaldehyde, the toxic product generated, when noradrenaline is metabolized by MAO A. This compound is increased three-fold in locus coeruleus from AD patients [389]. The surviving locus coeruleus neurons may have a rapid turnover of noradrenaline, as suggested by the finding that dopamine β-hydroxylase is increased 10 times, and that the ratio in brain between noradrenaline and a methylated product of 3,4-dihydroxyphenylglycolaldehyde is increased in AD brain [390].

A decreased content of noradrenaline has repeatedly been reported in the Alzheimer brain [382, 391-393], but the interpretation of this finding in postmortem tissue is difficult, since it might equally well indicate decreased synthesis and enhanced degradation. Also, determination of noradrenaline content may lead to an overestimate of locus coeruleus function, because of sympathetic ingrowth, characterized by morphological changes in noradrenergic fibers. This ingrowth is caused by sprouting of sympathetic neurons along blood vessels into brain parenchyma [394]. The sympathetic ingrowth affects G-proteins and increases the expression of certain PKC isozymes, whereas other subtypes are decreased [395-396]. It may protect the denervated neurons from apoptosis, but nevertheless jeopardize consolidation of long-term memory and function of working memory by an α_1-adrenergic effect, rather than enhancing learning [397-398]. One may wonder whether the abnormal noradrenergic innervation is normally coupled to transduction pathways, since CREB level is normal in Alzheimer brains, whereas its phosphorylation, which is indispensable for CRE-mediated gene expression and thus for consolidation of long-term memory, is reduced [399]. A reduction of basal and isoproterenol-stimulated adenylyl cyclase activity and of binding of cAMP to protein kinase A has also been found in brain cortical samples from patients who had suffered from Alzheimer's disease [400-401].

α_2-Adrenergic receptors have been reported as either unaltered [402] or reduced [403-405] in frontal cortex of Alzheimer patients. However, the preservation or decrease of α_2-adrenergic receptors in brain tissue occurs in spite of a large increase in α_2-adrenergic receptors in cerebral microvessels [406]. Accordingly the density of parenchymal α_2-receptors must be decreased. Available evidence regarding other noradrenergic receptors is less consistent [402, 407-409]. MAO B increases during normal aging, but is overexpressed in Alzheimer's brains, compared to age-matched controls [410-412], at least partly reflecting that MAO B is associated with fibrillary astrocytes in and around amyloid plaques [413].

Deficient noradrenergic innervation of astrocytes might contribute to explain many metabolic alterations in Alzheimer's disease [49]. There is a progressive decrease in glucose phosphorylation, measured by aid of the 2-deoxyglucose technique [414-417], which partly might be secondary to impairment of the normal stimulatory effect of noradrenaline on glycolysis and TCA cycle activity in astrocytes. It is consistent with this concept that pyruvate dehydrogenase activity is compromised in Alzheimer brains [418-419]. A reduction of Na^+,K^+-ATPase activity [420] could also mainly be an astrocytic effect, since noradrenaline stimulates Na^+,K^+-ATPase activity in cultured astrocytes with little effect on cultured neurons [22].

Lesion of locus coeruleus has replicated several of the changes found in Alzheimer's brains, including a transient decrease in Na^+,K^+-ATPase activity and ouabain binding [421] and metabolic impairment indicated by a delayed re-reduction of respiratory co-enzymes after response to neuronal excitation [422-423]. This might reflect effects of noradrenaline on astrocytic TCA cycle enzymes, although the cellular localization of the response has not been determined. In these animals there is also a significant reduction of cAMP and of the lowering of glycogen content during excitation [45, 424]. That the responses are reduced, not abolished, and in some cases transient suggests the presence of redundant mechanisms, for example serotonin-mediated glycogenolysis and stimulation of Na^+,K^+-ATPase activity [258, 425]. However, in contrast to the decreased α_2-adrenergic binding in tissue from Alzheimer patients, α_2-adrenergic receptors are upregulated [426].

Given the correlation between neuronal injury and up-regulation of cytokines, increased expression of cytokines

can be expected in Alzheimer's disease, and there is a positive correlation between the number of microglia staining for IL-1 and those of tau immunoreactive neuritic plaques and neurofibrillary tangles [427-428]. Moreover, brains from Alzheimer's patients contain more IL-1-positive microglia cells than control brains [429]. These observations support the concept of a cytokine cycle in which neuronal injury stimulates microglia to release IL, which triggers astrocytes to become reactive and to release cytokines and other neurotrophic factors and neurons to process more β-amyloid precursor protein, favoring additional deposition of β-amyloid, and so on [430-432].

Heneka *et al*. [50] investigated whether loss of noradrenaline-mediated anti-inflammatory protection due to cell death in nucleus coeruleus could exacerbate inflammatory events. Adult rats were injected with the selective neurotoxin DSP-4 to induce cell death in locus coeruleus, and subsequently β-amyloid was injected into the cortex. The injection of β-amyloid increased IL-1 expression initially in microglia and at later times in GFAP-positive reactive astrocytes. The DSP-4-treated animals showed a higher number of GFAP-positive cells than did control rats (an indication of the formation of reactive astrocytes), IκBexpression was lower, NOS activity higher and IL-1 expression more intense in DSP-4-treated animals than in controls (Fig. **8**). In addition NOS2 expression was induced in neurons, known to become NOS2 positive in Alzheimer's disease [433-434], but not expressing NOS2 after injection of β-amyloid in animals that are not locus coeruleus-lesioned. It is not known whether the neuronal expression of NOS2 is evoked by the loss of a direct effect of noradrenaline on neurons or whether the neurons responded to a greater than normal expression of IL-1 and perhaps also other cytokines in astrocytes and microglia. The potentiating effects of DSP-4 treatment on NOS2 and IL-1 expression were attenuated by co-injection with noradrenaline or isoproterenol, and administration of PPAR agonists prevented inflammatory responses and restored IκB [50, 295]. These findings are consistent with the hypothesis that cortical and hippocampal damage in Alzheimer's disease could be a response to degeneration of adrenergic neurons in locus coeruleus. The importance of astrocytes in the inflammatory reaction and at least in some of the metabolic responses is in agreement with the suggestion that Alzheimer's disease might be an anterograde degeneration, originating in the brain stem, and disrupting metabolic and functional interactions between neurons and glial cells [49].

4. Mood Disorders

An aminergic hypothesis of major depression was first suggested by Schildkraut [435], based on the fact that virtually all antidepressants used at that time, i.e, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors, either acutely inhibit noradrenaline uptake in brain preparations (although most, if not all also inhibited serotonin uptake) or inhibit degradation of noradrenaline and therefore are likely to enhance the effect of released noradrenaline. However, antidepressant drugs require treatment for a couple of weeks before their therapeutic effect sets in, and subsequently it was found that chronic treatment of experimental animals for a comparable length of time with these drugs lead to a down-regulation of β-adrenergic receptors in rodent brain cortex [436], a repeatedly confirmed finding. Based on the downregulation of β-adrenergic receptor binding, Sulser and co-workers suggested that the therapeutic effect of chronic treatment with antidepressants is due to the down-regulation of adrenergic activity. Moreover,

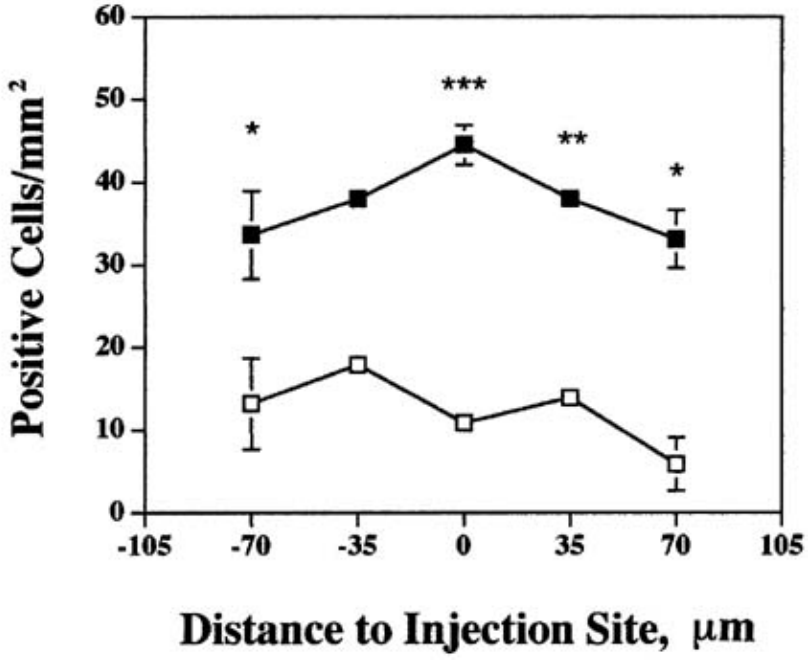

Fig. (8). Astrocytes in rat brain staining positive for IL-1β (indicated as immunopositive cells/mm^2) within a radius of 70 μm from the injection site of β-amyloid (0 μm). Two groups of rats were used, one of which had previously been injected with DSP-4 (DSP4) to destroy noradrenergic innervation of the brain (filled squares) and the second of which (control) had received saline (open squares). S.E.M. values are shown by vertical bars, and statistical significances between the two groups are indicated by 1, 2, or 3 asterisks, corresponding to P<0.05, <0.005, and <0.0005. From [50].

the opposite alteration, an increase in β-adrenergic receptor binding sites in brain cortex (Table **3**), is a rather consistent finding in brains of suicide victims [437-440].

Table 3. β-Adrenergic Receptor Density and Adenylyl Cyclase Coupling in Brain and in Cultured Astrocytes After Chronic Treatment with Antidepressant Drugs Compared to Changes in the Same Parameters in Brains from Suicide Victims

	β-Adrenergic Receptor Density*		Adenylyl Cyclase Coupling*	
	Brain	**Cells**	**Brain**	**Cells**
Antidepressants	Down	Down	Up	Up
Suicide Brain	Up		Down	

*for references, see text

Other evidence supports, however, the concept of an impairment in cortical noradrenergic receptor activation and/or in second messenger systems activated by PKA in major depression and a correction of this impairment by antidepressant drugs [441-442]. G protein, and especially G_s, may be a key target for chronic treatment with antidepressants, which facilitate the activation of adenylyl cyclase by $G_{s\alpha}$, assayed in the presence of a GTP analog (Table **3**). Acute exposure to these drugs has no effect, and there is no change in the total amount of G proteins [443-444]. Moreover, antidepressant treatment increases the number of active $G_{s\alpha}$/adenylyl cyclase complexes immunoprecipitated by an anti-$G_{s\alpha}$ antibody in brain tissue but not in other tissues [445]. In contrast the adenylyl cyclase activity in postmortem brains of suicide victims shows a reduced response to β-adrenergic stimulation [446-449].

Using the ability of antidepressants to counteract immobility during a modified swim test as a measure of their efficacy, it was found that discrete lesion of the ventral bundle (connecting the different adrenergic/noradrenergic cell groups in the brain stem) prevents the effect of reboxetine, an antidepressant, which is a specific inhibitor of the uptake of (nor)adrenaline. In contrast, lesions of the dorsal noradrenergic bundle augments its apparent anti-depressant effect [450]. The effect of interruption of the ventral bundle is consistent with the suggestion by Stone *et al.* [186] that adrenaline acts on a subgroup of 'motoric' α_{1b}-adrenergic receptors in the brain stem to regulate behavior by a parallel excitation of all three major monoaminergic (noradrenergic, serotonergic and dopaminergic) systems innervating the brain. This system appears to be impaired during stress and depression and may represent a major therapeutic target for antidepressants. This hypothesis seems to imply that the establishment of a normal balance between the monoaminergic transmitter systems may be a main goal of antidepressant therapy. This notion receives support from a study by Gross-Isseroff *et al*. [440] suggesting that the most important abnormality in receptor expression in brains from suicide victims is a disturbance of normal correlations both between different subtypes of individual monoamines and between receptors for the different monoamines.

Many of the effects of chronic treatment with antidepressants have been replicated in cultured astrocytes (Table **3**). Five days of treatment with 1 μM amytriptyline has no effect on isoproterenol-induced stimulation of cAMP formation but after at least two weeks of chronic treatment the stimulation is down-regulated by 25-30%, an effect that is shared by chronic treatment with the monoamine oxidase inhibitor tranylcypromine [152] but not with the anti-psychotic haloperidol or the anti-anxiety-drug clonazepam. A downregulation of stimulated cAMP accumulation after chronic antidepressant treatment has been confirmed in C-6 glioma cells treated with either amitriptyline or desipamine [451-453]. A reduction of β-adrenergic receptor binding has also been observed in chronically treated C-6 glioma cells [451, 454] and in freshly isolated astrocytes from rats treated chronically with desipramine [455]. However, a β-adrenergic down-regulation after chronic antidepressant treatment is not specific for astrocytes but has also been observed in freshly isolated neurons [455], and even in non-neural cells [456].

As in the brain *in vivo* [443], the ability of a GTP analog and/or forskolin to stimulate adenylyl cyclase activity in membrane preparations is increased in chronically treated C-6 glioma cells [452, 457]. This effect sets in later than the receptor down-regulation, and it is correlated with a clustering of $G_{s\alpha}$ of the glioma cells in the cell bodies combined with a decrease in the tips of the cells [458]. A similar redistribution is also seen after chronic treatment with fluoxetine, a specific inhibitor of serotonin re-uptake. Chlorpromazine has no such effect, and chronic treatment with antidepressants does not affect the distribution of the α subunit of the G_o protein under similar conditions.

Although chronic treatment with an antidepressant is required to obtain β-adrenergic downregulation and forskolin- and $G_{s\alpha}$-mediated enhancement of adenylyl cyclase stimulation, there are also acute interactions between antidepressants and β-adrenergic binding to astrocytes. Thus, a multitude of antidepressants have been found to displace β-adrenergic binding both from brain homogenates or membranes, although with relatively low potency [459-462]. A similar inhibition of β-adrenergic binding occurs in C-6 glioma cells [143, 454] and in primary culturesof astrocytes [151], in general with higher potency than in brain tissue (Table **4**). Conversely, acute administration of antidepressants (1-5 μM) inhibit dihydroalprenolol retention and isoproterenol-mediated cAMP accumulation in primary cultures of astrocytes [152, 463].

The other major mood disorder, bipolar (manic-depressive) disease is typically treated with either lithium salts ('lithium') or any of the two anti-epileptic drugs valproic acid or carbamazepine. Lithium exerts a multitude of drug effects, some of them connected with PKA and others with PLC-mediated signaling. The presently most widely accepted theory for its mechanism of action is that it inhibits resynthesis of PIP_2 and thus has a modulating effect on its availability for continued signaling (Fig. **1**). There is consensus that pharmacologically relevant concentrations of lithium inhibit the formation of inositol from IP, an effect that also has been established in glioma cells [464]. This effect is not shared by either valproic acid or carbamazepine [465], although valproic acid inhibits synthesis of inositol from glucose [466], a process that may be important in the long-term maintenance of the inositol pool. However, chronic but not acute treatment with either of these three

Table 4. K_i Values, in Micromolar, for the Inhibition by Antidepressant Drugs of β-Adrenergic Ligand Retention in Various Preparations

Drug [reference]	C-6 Glioma Homogenate [143, 454]	Rat Brain Membranes [459, 460]	Rat Brain Homogenate [462]	Calf Cortex Homogenate [461]	Intact Mouse Astrocytes [151]*
Amitriptyline	30		20	7	2
Imipramine		40	30	15	10
Desipramine	7, 30	100	15	15	5
Zimelidine			100	10	20
Tranylcypromine		50			25
Doxepin			20	20	5
Mianserin			100	10	20
Iprindole		50, 100		20	5

*Displacement of 1.8 nM [^{3}H]dihydroalprenolol

antibipolar drugs affects cellular uptake of inositol in primary cultures of astrocytes and in glioma cells [467]. Although it was initially believed that the effect is always inhibitory it has turned out that its direction depends upon the extracellular concentration of inositol during the uptake measurement: at relatively low inositol concentrations, inositol uptake is enhanced by chronic treatment with lithium, whereas it is reduced by this treatment if the ambient concentration of inositol is high [468]. Accordingly the pool size of inositol, which is exchangeable with extracellular inositol is increased by lithium treatment at low extracellular inositol concentrations, but it is reduced at high extracellular inositol concentrations. This effect may therefore tend to normalize the content of inositol available for cell signaling [102]. The physiological basis for such different effects by lithium may be the existence of two different inositol transporters with different affinity, and conditions are known (e.g., changes in pH) that affect the two uptake carriers in opposite directions [469].

Reduction of inositol availability by chronic treatment with lithium reduces the response of $[Ca^{2+}]_i$ to noradrenaline. Thus, (Fig. **9**) shows a large reduction of the increase of $[Ca^{2+}]_i$ in primary cultures of astrocytes in response to 1 μM noradrenaline [470]. In light of the far-reaching consequences of astrocytic $[Ca^{2+}]_i$ for neuronal irritability, such an effect may have major consequences for function in the intact CNS.

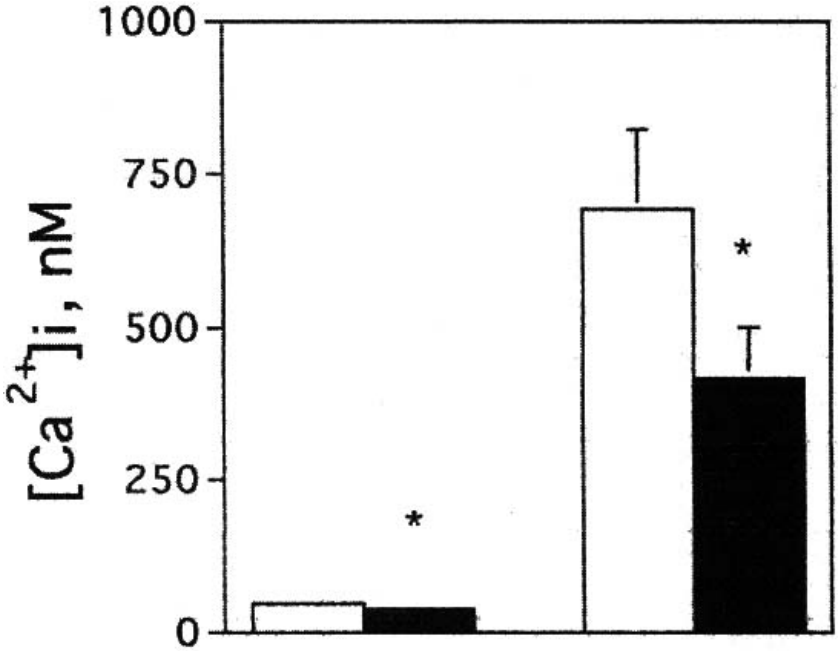

Fig. (9). Free cytosolic calcium concentration ($[Ca^{2+}]_i$) in primary cultures of mouse astrocytes during basal conditions (left part) and during exposure to 1 μM noradrenaline (right part) in untreated control cultures (open columns) and in sister cultures (filled columns) from the same batches, which were studied in parallel and had been treated with 1 mM lithium chloride (at 40 μM inositol) for 7-14 days before the experiment as well as during the measurements. S.E.M. values are shown by vertical bars, and statistical significant differences ($P<0.05$) between treated and untreated cultures are indicated by asterisks. From [470].

5. Drug Addiction

After 2 months of chronic exposure of young primary cultures of astrocytes to cocaine at toxicologically relevant level (1 or 3 μM) the rate of α-ketoglutarate dehydrogenation shows an increase of ~50% [471]. Moreover, in contrast to the distinct stimulation of α-ketoglutarate dehydrogenation when noradrenaline is added to drug-naive cultures of the same age, there is no effect of noradrenaline on cocaine-treated cultures. After exposure to cocaine for 21 days, both the enhanced basal activity and the abolishment of the normal response to noradrenaline persisted during 'withdrawal' (cessation of drug exposure) throughout the total period investigated, i.e., to an age in culture of 60 days, corresponding to a withdrawal period of 36 days. Based on a comparison between development in rats and humans the period during which the cultures were treated with cocaine corresponds to cocaine exposure during the third trimester of pregnancy. They may therefore have a bearing on the finding in the brain *in vivo* that prenatal cocaine administration delays astroglial maturation [472]. However, also in adult animals cocaine administration and cocaine withdrawal cause significant modifications in astrocyte numbers and cell size and a drastic alteration of cell process morphology [473-474]

Clonidine has been found to alleviate most somatic signs of opiate withdrawal in humans [475]. In addition, electrophysiological studies in rats have shown that naloxone-induced opioid withdrawal triggers intense hyperactivity of locus coeruleus neurons, and that this increase in firing rate can be prevented by clonidine. It was therefore assumed that the therapeutic action of clonidine resulted from its ability to reduce locus coeruleus firing *via* presynaptic stimulation of α_2-adrenoceptors [476-477]. However, studies in rats treated with 6-hydroxydopamine to almost completely (~94%) eliminate noradrenergic innervation have shown not only that clonidine retained its ability to alleviate withdrawal symptoms, but also that it became more potent [478], i.e., that it must act on post-junctional receptors. It is unknown whether this postjunctional effect is exerted on neurons or on astrocytes. Morphine does interact with noradrenaline effects on cultured astrocytes, as indicated by a morphine-induced enhancement of noradrenaline-induced incorporation of deoxyglucose into glycogen [243], although morphine alone has no effect on brain glycogen content [479].

VI. ASTROCYTIC ADRENOCEPTORS AS POTENTIAL DRUG TARGETS

A. Neuroprotection

1. Brain Ischemia

Dexmedetomidine and clonidine have a neuroprotective effect in animal models of focal cerebral ischemia [368-369, 480-481], transient global ischemia [482], and hypoxic-ischemic brain injury in neonates [483]. Since dexmedetomidine is effective as a neuroprotectant even when the extracellular concentrations of glutamate and noradrenaline are not reduced [368], and since it appears to cause transactivation in astrocytes [119], its neuroprotective effect might be due to a paracrine action of released growth factor on adjacent neurons [117] as suggested in (Fig. **2**). An ability to induce release of growth factor(s) inside the brain itself by administration of small molecules like dexmedetomidine, which easily crosses the blood-brain barrier, may become of major importance in the treatment of brain ischemia.

In the brain *in vivo*, the β_2-adrenergic agonist clenbuterol reduces infarct size after ischemia, and in mixed hippocampal cultures, β-adrenergic stimulation decreases glutamate-induced neuronal damage. At the same time morphological changes are induced in astrocytes, suggesting that astrocytic functions might also be involved in neuroprotection by β-adrenergic agonists [484]. This concept is strengthened by the observation that the neuroprotective effect is exerted *via* NGF [485-486], which could have been induced in astrocytes by transactivation [117]. β_2-Adrenergic stimulation also enhances expression of transforming growth factor-β1 (TGF-β1) after transient forebrain ischemia [487]. Formation of this cytokine cannot be a direct result of transactivation since it belongs to neither the NGF nor the EGF family. However, it may be an indirect result of transactivation, if astrocytes react like tanycytes (cells belonging to the ependymo-astroglial family). In the median eminence these cells respond to astrocytically generated TGF-α with EGFR receptor phosphorylation, release of prostaglandin E2 (PGE2) and and a prostaglandin-mediated release of TGF-β [488-489].

2. Glaucoma

Glaucoma is now regarded as a neurodegenerative disease [490-491], in which retinal neurons die by apoptosis [492-493]. It is generally but not invariably accompanied by increased intraocular pressure. α_2-Adrenergic agonists, acting on receptors located in the inner retina [494], have neuroprotective effects, which are unrelated to their effect on pressure [495], and with respect to some parameters can be better than those of pressure reduction alone [496]. These agents reduce retinal ganglion cell apoptosis by promoting synthesis of proteins of the Bcl family, which decrease mitochondrial membrane permeability [497]. They protect retinal neurons from optic nerve crush injury [495, 498-500], and ischemia [491, 501]. After transient retinal ischemia, the α_2-adrenergic agonist brimonidine also decreases the release of glutamate [502]. Up-regulation of growth factors, including BDNF [500], and basic fibroblast growth factor, FGF2 [501, 503] may play a major role in the neuroprotective effect of the α_2-adrenergic agonists. BDNF is a member of the NGF family, but FGF2 is neither a member of this family, nor of the EGF family.

The α_2-adrenergic agonists xylazine and clonidine induce an increase in ERK phosphorylation in the retina, which protects photoreceptor cells from light damage and is prevented by yohimbine. It has been shown immunocytochemically that the increase in ERK phosphorylation mainly occurs in Müller cells [504], an astrocyte-like cell type. The expression of basic fibroblast growth factor (FGF2) is increased in the inner segment region of the photoreceptors [503]. Like TGF-β1, FGF2 is not a direct product of transactivation, and it would be interesting to know if growth factor cascades similar to those occurring in astrocytes and tanycytes operate between Müller cells and photoreceptors.

B. Reduction of Neuroinflammation

1. Multiple Sclerosis

Given that adrenergic receptors are absent from white matter astrocytes in MS, treatment with β-adrenergic agonists is unlikely to be successful. However, phosphodiesterase inhibitors have been suggested as treatment of multiple sclerosis [505], and combination therapy with 3 different phosphodiesterase inhibitors has recently been shown in a small material to lead to a dramatic decrease in relapse rate [505]. It is a possibility that the inhibition of the phosphodiesterases may amplify the effect of other transmitters operating *via* cAMP. The phosphodiesterase inhibitors failed to ameliorate EAE [506], which is consistent with the previously made suggestion that this condition only reflects the immunological aspects of MS.

2. Alzheimer's Disease

In light of the massive reduction of noradrenergic input from locus coeruleus to the brain in Alzheimer's disease and the anti-inflammatory effects of noradrenaline it has been a logical approach to test the efficacy of deprenyl, a MAO B inhibitor, against symptoms of Alzheimer's disease. Based on a review of published trials it has been concluded that deprenyl for Alzheimer's disease has proved disappointing [507]. The α_2-adrenergic agonist guanfacine has also no therapeutic effect [508-509]. These negative results do not necessarily imply that deprenyl or guanfacine prophylaxis might not be effective in postponing the onset of the disease [510] or retarding its early course. It would be useful to establish conclusively if Alzheimer's disease is an ascending neurodegeneration secondary to an initial cell death in locus coeruleus, or if the degeneration begins in the cortex and hippocampus and secondarily affects their afferent connections. If Alzheimer's disease turns out to be a primary disease of locus coeruleus (with or without injury in nuclei of origin for other aminergic and cholinergic neurons), then prophylaxis and early treatment would in all likelihood include either amplification of adrenergic transmission and of its downstream transduction pathways or attempts to prevent further nucleus coeruleus damage (or both). Regardless of the pathogenesis enhanced noradrenergic activity would counteract inflammatory reactions.

Since one of the correlates of Alzheimer's disease is a progressive decline in glucose phosphorylation and deficits in long-term memory can be improved by administration of glucose and/or β_3-adrenergic agonists it might be worthwhile to test the effect of β_3-adrenergic agonists. The effect of these agents on brain function is virtually unknown, except for their facilitation of long-term memory consolidation, and it ought to be studied in more detail.

C. Enhancement of Cognitive Function

Guanfacine, an α_2-adrenergic agonist is effective in the treatment of ADHD [511]. It is a relatively safe drug, without the stimulatory side effects of amphetamine derivatives, the typical treatment for ADHD. Rather, the potential toxicities include drowsiness, bradycardia and hypotension [512], which are the somatic side effects to be expected from α_2-adrenergic agonists, modifying function both in the brain and in the autonomic nervous system. Guanfacine also improves working memory in aged monkeys [513]. There is presently no firm evidence indicating that part of its actions is exerted on astrocytes. However, this is not unlikely in light of the large fraction of postsynaptic α_2-adrenergic receptors found on astrocytes and of the evidence that the guanfacine-mediated improvement of working memory is exerted on postsynaptic receptors. Further study of the molecular mechanisms of working memory, similar to those carried out in the case of long-term memory, might well be fruitful.

The ability of noradrenaline to re-inforce 'weak' learning makes it likely that noradrenergic agonists capable of entering the brain may have therapeutic effect in some cases of cognitive impairment.

D. Mood Disorders

Mood disorders may be a category of major illnesses where we, albeit unwittingly, already are using drugs acting on astrocytic adrenoceptors. The similarities between the effects of chronic administration of antidepressants on receptors and downstream signaling in intact brain and in cultured astrocytes is remarkable (Table **3**). Accordingly, astrocyte cultures might be a preparation of choice for further studies of alterations in signal transduction by long-term treatment with different types of antidepressants. It will be important to follow the alterations sequentially in time, since the antidepressant fluoxetine (a serotonin- specific uptake inhibitor) exerts opposite effects on glycogenolysis in cultured astrocytes after 1- and 3-week treatment [514]. It is a further impetus for study of the effects of antidepressant drugs on astrocytes that morphological changes occur in astrocytes in major depression [515-516]. However, acute interactions between antidepressants and noradrenergic drugs might also provide a fruitful area of research since these interactions may provide the basis for those occurring after chronic treatment. It is remarkable that both antidepressant drugs and antibipolar drugs interact with astrocytes, although in very different manners. One may wonder whether this is co-incidence or whether astrocytes play a very major role in regulation of mood and thus in mood disorders.

E. Drugs of Abuse

There is little doubt that cocaine interferes with astrocytic function and development, perhaps especially at early developmental stages. Nevertheless, this is a virtually unexplored field.

VII. CONCLUDING REMARKS

A largely untapped potential may exist for the development of drugs modifying noradrenergic signaling against a multitude of neurological and psychiatric diseases, including multiple sclerosis, brain ischemia, mood and cognition disorders and early and perhaps even pre-clinical stages of Alzheimer's disease. Due to the intricate correlation between CNS effects and autonomic effects a major challenge will be to harness the therapeutic effects without unwanted side effects. The possibility that astrocytic receptors are targeted or at least co-targeted ranges from very high in multiple sclerosis and perhaps also in

neuroprotection, mood disorders, and withdrawal from addictive drugs, to likely in Alzheimer's disease and possible in cognitive disorders. However, this list is not comprehensive. Other conditions, like Parkinson's disease [517], AIDS-related dementia [518-519] and Prion diseases [520] are known to affect astrocytes and it is possible that drugs acting on astrocytic adrenoceptors might have therapeutic potential in many of these diseases.

Regardless whether the direct effect of noradrenergic drugs are exerted on neurons or astrocytes it should be kept in mind that astrocytes do not function alone but in collaboration with neurons, which secondarily will be affected when the primary target is astrocytic. However, the opposite is also true. The exciting novel findings of astrocytic calcium waves and their interaction with neuronal excitation has not only provided new understanding of cellular interactions, but also given added credibility to the functional importance of older studies of drug effects on astrocytes, including many reviewed in this article. By modifying astrocytic calcium dynamics, potassium homeostasis, provision and metabolism of amino acid transmitters and energy metabolism such drugs may profoundly affect CNS function.

ABBREVIATIONS

$[Ca^{2+}]_I$ = Free cytosolic calcium concentration
AC = Adenylyl cyclase
AD = Alzheimer's disease
ADHD = Attention deficit hyperactivity disorder
APC = Antigen-presenting cell
ATP = Adenosine triphosphate
AVP = Vasopressin
BDNF = Brain-derived neurotrophic factor
cAMP = Adenosine 3':5'-cyclic monophosphate
CBP = CREB binding protein
Cbz = Carbamazepine
cGMP = Guanosine 3':5'-cyclic monophosphate
Cl^- = Chloride ion
CNS = Central nervous system
COMT = Catecholamine O-methyl transferase
CRE = CAMP responsive element
CREB = CRE-binding protein
DAG = Diacylglycerol
DSP-4 = N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine
EAE = Experimental autoimmune encephalomyelitis
EGF = Epithelial growth factor
EGFR = Epithelial growth factor receptor
FGF2 = Basic fibroblast growth factor
GC = Guanylyl cyclase
GDP = Guanosine diphosphate
GFAP = Glial fibrillary acidic protein
GPCR = G protein-coupled receptor
GTP = Guanosine triphosphate
HB-EGF = Heparin-binding epithelial growth factor
IFN = Interferon
IL = Interleukin
IP = Inositol phosphate
IP_2 = Inositol bisphosphate
IP_3 = Inositol trisphosphate
K^+ = Potassium ion
LPS = Lipopolysaccharide
MAO = Monoamine oxidase
MHC = Major histocompatibility complex
MS = Multiple sclerosis
Na^+ = Sodium ion
NGF = Nerve growth factor
NO = Nitric oxide
NOS = Nitric oxide synthetase
NT-3 = Neurotrophin-3
PI = Phosphatidylinositol
PKA = Protein kinase A
PKC = Protein kinase C
PKG = Protein kinase G
PLC = Phospholipase
PPAR = Peroxisome proliferator-activated receptor
TGF = Transforming growth factor
TNF = Tumor necrosis factor
VPA = Valproic acid

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