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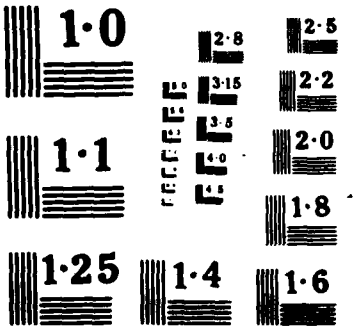
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19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The work described here is part of an ongoing set of studies aimed at characterizing the physiological actions and anatomical organization of the monoaminergic projection systems to the rat cerebral cortex, cerebellum and hypothalamus. The underlying theme of this work is that the endogenous monoamines, norepinephrine (NE) and serotonin (5-HT), serve to modulate central neuronal responsiveness to afferent synaptic inputs and by so doing participate in the cognitive process of selective attention. Specifically, individual studies describe: 1) the effects of NE and 5-HT on rat visual and somatosensory cortical neuron responses to afferent pathway stimulation, 2) topographic organization of the neocortical projection neurons in the serotonergic dorsal raphe nucleus, 3) pharmacological characterization of NE effects in rat lateral hypothalamus and 4) similarity between the modulatory actions of NE and stimulant drugs, cocaine and amphetamine. Overall, the data provide further support for the contention that the diffusely distributed monoamine systems of the mammalian brain may enhance the performance of target neuronal circuits as a function of changing behavioral conditions.

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ANNUAL TECHNICAL REPORT

AFOSR-85-0155
"The Role of Central Monoaminergic Systems
in Arousal and Selective Attention."
3-1-85 to 2-28-86

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1. Summary

The major goal of ongoing studies has been to evaluate the role of the endogenous monoamines, norepinephrine (NE) and serotonin (5-HT), in the transfer of sensory information through neuronal networks of mammalian brain. Previously demonstrated modulatory actions of NE and 5-HT on single cell responses to synaptic inputs in the rat cerebral cortex, cerebellum and hypothalamus have suggested that these monoaminergic systems might enhance neuronal circuit function and participate in the cognitive process of selective attention. Individual studies conducted during the past year have focused on further electrophysiological characterization of the parameters of cell responsiveness regulated by NE and 5-HT as well as identification of the receptor systems responsible for mediating these modulatory effects. Additional studies have revealed a functionally significant topographic organization within monoamine - containing nuclei as well as similarity between the physiological actions of NE and stimulant drugs, cocaine and amphetamine, which are known to produce alerting and enhanced performance effects in laboratory animals and man. Overall, the data collected during this first year of the project provide further support for the contention that the diffusely distributed monoamine systems of the mammalian brain may enhance the performance of target neuronal circuits as a function of changing behavioral conditions. Procedures and apparatus for microiontophoresis and recording in the awake, behaving rat have also been developed over the past year and are ready to be incorporated into the project. Such capabilities will permit more direct tests of monoamine actions in local circuits of behaving animals.

2. Research Objectives

The primary focus of the project has not deviated from the originally stated aims listed below.

Aim 1. Investigate the basic physiological actions of the noradrenergic and serotonergic projection systems in primary sensory areas of the mammalian brain.

Initial studies will employ iontophoretic methods of drug application to characterize the elemental effects of NE and 5-HT on somatosensory or visual cortical neuronal responses to peripheral stimulation of afferent synaptic pathways or to microiontophoresis of putative transmitter substances. In other studies, stimulation of the locus coeruleus or dorsal raphe nucleus will be employed to cause release of endogenous monoamines at anatomically relevant sites in target neuronal circuits and confirm results observed with iontophoretic application of NE and 5-HT. Similar studies will be carried out in other regions of the brain that relay sensory information and receive monoaminergic projections, e.g. lateral geniculate nucleus, superior colliculus. The goal here will be to further develop the concept that NE and 5-HT operate in a neuromodulatory mode as part of a signal "gating" or "filtering" mechanism in primary sensory neocortex and other sensory information relay circuits in the brain. While these initial studies will be carried out in anesthetized rats, a major effort will be mounted to examine these issues in awake, behaving animals using recently developed techniques for chronic unit recording and iontophoretic drug application (West and Woodward, 1985).

Aim 2. Analysis of the physiological actions of amphetamine and cocaine at the synaptic level in cerebrocortical and cerebellar circuits. The primary issues to be investigated here are whether these psychostimulant agents can mimic the facilitating actions of NE on neuronal responsiveness to synaptic inputs and putative transmitter substances and whether or not such effects correlate with the overt behavioral responses which have been reported for these drugs. The proposed experiments will employ the electrophysiological assays developed previously for study of the NE system to determine the effects of these drugs on synaptic mechanisms. The merit of this approach derives from the fact that a common set of experimental neurophysiological tests can be used to examine the function of the noradrenergic system (see Aim 1) as well as drugs which are known to interact with this system.

Aim 3. Examine the anatomical organization of monoamine-containing projection neurons with respect to sensory-specific target regions of the CNS. These investigations will employ single and double retrograde tracer techniques and computer-assisted image analysis to study the distribution of monoamine-containing projection neurons with respect to sensory-modality specific target regions in the CNS. Initial studies using retrograde transport of HRP suggest that the monoamine nuclei have an internal organization such that activity in subsets of dorsal raphe and locus coeruleus cells may independently influence separate populations of neurons within serotonergic and noradrenergic terminal fields of the neocortex. Moreover, double-labeling protocols have revealed single dorsal raphe neurons which project to both rat visual cortex and cerebellar paraflocculus, areas which are known to receive visual information. The emphasis of the proposed studies will be to explore the possibility that central monoaminergic projections are organized according to the sensory function of target neuronal circuits and whether such an organization would be consistent with a postulated role of these systems in attentional mechanisms.

3. Status of Research

A brief description of individual studies (see Publications Supported) is provided below.

#1 Waterhouse et al.

Distribution of Neocortical Projection Neurons in Rat Dorsal Raphe: Retrograde transport studies using HRP were conducted to examine the intranuclear distribution of dorsal raphe (DR) neurons that project to rostrocaudally aligned regions of rat cerebral cortex. Neocortical projection neurons were identified following HRP injections into either frontal, sensorimotor or occipital cortex. The locations of labeled cells were recorded relative to a three-dimensional biological coordinate system maintained by a computer linked to a light microscope. This analysis revealed a topographic ordering of cortical projection neurons in the DR which reflected the rostrocaudal alignment of injection sites. Specifically in the coronal plane, DR neurons projecting to the frontal and sensorimotor areas were concentrated in the dorsal and intermediate portions of the nucleus, respectively; whereas cells projecting to the occipital region were situated most ventrally, between the medial longitudinal fasiculi. In summary, these results raise the possibility that activity in subsets of DR neurons may independently influence distinct regions within serotonergic terminal fields of the cerebral cortex. These findings will aid the placement of stimulating electrodes in other

proposed studies where activation of serotonergic pathways will be interacted with synaptically-evoked responses of cortical neurons. Moreover, the topographic ordering of DR neurons revealed here, provides new insights into the functional anatomical organization of the raphe system.

#M2 Waterhouse et al.

Actions of Serotonin in Somatosensory Cortex: A previously initiated study where iontophoretically applied serotonin (5-HT) was interacted with somatosensory cortical unit responses to afferent synaptic inputs and putative transmitter substances has now been completed. In contrast to the previously demonstrated facilitating actions of norepinephrine (NE), 5-HT selectively depressed synaptically evoked excitatory responses or antagonized stimulus bound inhibitions relative to changes in background firing rate in a majority of neurons studied. 5-HT also reduced acetylcholine or glutamate-induced excitations and blocked GABA-mediated inhibitions. Taken together these results suggest that endogenous 5-HT exerts a physiological action opposed to that of NE in target neuronal circuits of the mammalian CNS.

#M2 Waterhouse et al.

Norepinephrine and Serotonin Actions in Rat Visual Cortex: The purpose of this study was to examine the effects of mic- iontophoretically applied norepinephrine (NE) or serotonin (5-HT) on extracellular responses of individual simple and complex cells (area 17, rat cortex) to moving visual stimuli. In 25 of 34 cells tested, NE enhanced visually evoked neuronal responses, whereas 5-HT in 17 of 21 cases tested suppressed single unit responses to visual inputs. In addition to changes in magnitude of response, administration of NE and 5-HT produced alterations in receptive field size and directional preference for visually responsive neurons. The opposing influences of NE and 5-HT on synaptically evoked responses suggests that the noradrenergic and serotonergic systems may operate in concert to up- or down-regulate the sensitivity of the visual cortical circuitry to afferent sensory information. A particularly interesting noradrenergic effect which should be noted was that in some cases iontophoretic application of NE revealed responses to visual stimuli which were not observed during the control condition. The implication of this finding is that potentially threshold synaptic inputs may normally arrive at visual cortical neurons but appear absent or extremely weak unless facilitated by NE. Overall, studies in the visual cortex are potentially the most exciting since they may distinguish the most subtle modulatory influences of the monoamines on sensory information transfer through neuronal networks.

#M3 Cheng and Waterhouse
#M4 Cheng et al.
#A4 Cheng et al.

In Vivo and In Vitro Effects of Norepinephrine in the Lateral Hypothalamus: A series of experiments aimed at characterizing norepinephrine actions in the rat lateral hypothalamus has been ongoing for the last two years. Essentially these studies indicate that norepinephrine augments inhibitory synaptic processes in the lateral hypothalamus, in vivo, in a manner identical to that observed in the cerebellum and cerebral cortex.

A longstanding challenge has been to identify the membrane changes and mechanisms associated with such phenomena. It is likely that the best way to address this issue is to use intracellular recording techniques in the in vitro slice preparation. However, the phenomena of norepinephrine augmentation of GABA-mediated inhibition had to first be characterized in the in vitro preparation in order to validate such an approach. Thus, many background studies were and still are necessary before the question of mechanism can be investigated.

In summary, the experiments conducted to date indicate that the commonly observed in vivo phenomenon of norepinephrine potentiation of GABA-induced inhibition can be demonstrated in the in vitro hypothalamic tissue slice preparation, but less frequently (i.e. 25% of cases tested) than in the whole animal (85% of cases tested).

The more frequently observed effects of NE on lateral hypothalamic neurons recorded in vitro are antagonism of GABA inhibition and increased spontaneous discharge. Pharmacological studies with adrenergic agonists and cyclic AMP analogs indicate that these latter actions result from activation of alpha type adrenoceptors whereas enhancement of GABA is mediated by beta receptor binding and subsequent increases in intracellular cAMP. The decreased ability of NE to augment GABA in hypothalamic tissue slices must, therefore, reflect a functional shift in favor of alpha adrenoceptor mechanisms. Thus, while the slice preparation will be useful for further intracellular studies of NE effects on neuronal responsiveness, some caution must be exercised in making direct comparisons of this data with findings in whole animals.

A major issue at this point is to determine the intracellular events that are brought about by increased cyclic AMP and lead to changes in GABA potency. A further question is to consider the factors (e.g. temperature) which result in the shift toward alpha mediated responses in the hypothalamic slice preparation. Overall, an investigation of these issues in vitro offers the best hope for elucidating the mechanisms responsible for NE-mediated enhancement of neuronal responsiveness.

#A1 Waterhouse et al.
#A2 Michael et al.

The Actions of Stimulant Compounds on Purkinje Cell Responses to GABA: The purpose of these studies was to determine the effects of amphetamine and cocaine, compounds known to interact with noradrenergic synapses, on neuronal circuit function. Using the cerebellar Purkinje cell as a model, we have observed that systemically or locally applied amphetamine and cocaine can augment inhibitory neuronal responses to microiontophoretically applied GABA. In some cases the effects of amphetamine were observed in awake, freely moving animals using the recently developed technique of chronic microiontophoresis.

Presumably, these drug effects on GABA responses result from the ability of amphetamine and cocaine to elevate synaptic levels of NE. Nevertheless, further studies are in progress to clarify the mode of interaction between exogenously applied compounds and the endogenous noradrenergic system. The importance of these studies is that amphetamine, cocaine and NE may share a common set of physiological actions in neuronal circuits which underlies the

behavioral alerting effects of the drugs and the functional role of the endogenous noradrenergic system.

#A3 Woodward et al.

2-DG Uptake Patterns Following Drug Administration: A series of pilot experiments have been completed where glucose metabolism was measured in anatomically identified brain regions of animals receiving bilateral forepaw stimulation and either cocaine, amphetamine or ethanol. The results indicate that these compounds differentially affect glucose uptake within the somatosensory pathway. Amphetamine in particular caused increased glucose metabolism relative to other drug treated and control animals in the forepaw area of the somatosensory cortex, sensory portion of the caudate nucleus and the cerebellar cortex.

The overall goal of these studies is to determine the effects of both stimulant and depressant compounds, on the transfer of signals through sensory pathways in the brain.

Comment on Progress:

During the current funding period, several previously initiated studies have been completed and the manuscripts detailing those results are being prepared for publication. For the most part, these studies have further clarified the lowest threshold actions of NE and 5-HT in cerebral cortex as well as further characterized the topography of projections from the dorsal raphe to the neocortex.

Other studies have focused on a characterization of NE modulatory actions in the lateral hypothalamus utilizing both in vivo and in vitro techniques. The in vitro tissue slice preparation provides the advantage of being able to study dose-response relationships associated with previously observed (in vivo) monoamine modulatory phenomena. Moreover, we are hopeful that tissue slice preparations will allow us to identify the membrane potential changes and intracellular events associated with NE activation of membrane receptors. Since the hypothalamic in vitro preparation is well documented, we decided to begin studies aimed at such mechanistic questions in tissue slices taken from this brain region. The goal of this effort is to establish general principles of monoamine action in hypothalamic tissue and subsequently confirm our findings using technically more demanding cerebellar and cerebrocortical tissue slice preparations. A number of successful in vitro experiments have already been carried out using cerebellar slices.

A pilot study employing the 2-deoxyglucose (2-DG) technique to investigate stimulant and depressant drug effects on somatosensory pathway transmission has also been initiated. Although not described in the original proposal, this study takes advantage of a recently developed computer image analysis system (Dr. D.J. Woodward, University of Texas Health Science Center) to examine amphetamine and cocaine-induced changes in glucose uptake patterns within the CNS of awake, behaving animals. The results of such experiments will compliment data collected from electrophysiological studies of stimulant drug actions in local neuronal circuits. As such this experimental approach represents a logical extension of the proposed work.

Considerable progress has also been made in assembling the core of equipment necessary for electrophysiological recording and iontophoretic drug application in the awake, unanesthetized animal. Although technically the most difficult, studies in the behaving animal using this equipment hold the promise of providing the most physiologically relevant information concerning monoamine effects on synaptic function. When this chronic unit recording apparatus is completed, we will have the capacity to examine monoamine actions in neuronal circuits of isolated tissue slices, intact anesthetized and intact awake animals.

4. Publications Supported by AFOSR-85-0155

Papers:

1. Waterhouse, B.D., Mihailoff, G.A., Baack, J.C. and Woodward, D.J. 1986. Topographical distribution of dorsal and median raphe neurons projecting to motor, sensorimotor and visual cortical areas in the rat. J. Comp. Neurol. (In Press).

Manuscripts:

M1. Waterhouse, B.D., Moises, H.C. and Woodward, D.J. Interaction of serotonin with somatosensory cortical neuronal responses to afferent synaptic inputs and putative neurotransmitters. In preparation.

M2. Waterhouse, B.D., Azizi, S.A., Burne, R.A. and Woodward, D.J. Modulation of area 17 simple and complex cell responses to moving visual stimuli during norepinephrine and serotonin microiontophoresis. In preparation.

M3. Cheng, J.-T. and Waterhouse, B.D. Noradrenergic enhancement of lateral hypothalamic neuron response to inhibitory synaptic inputs and GABA iontophoresis. In preparation.

M4. Cheng, J.-T., Azizi, S.A., Chapin, J.K. and Waterhouse, B.D. In vitro pharmacological characterization of norepinephrine interactions with lateral hypothalamic neuron responses to GABA iontophoresis.

Abstracts:

A1. Waterhouse, B.D., Stowe, Z.N., Cheng, J.-T., Michael, A.J. and Woodward, D.J. 1985. Physiology of abuse potential substances in central neuronal circuits: effects of cocaine on spontaneous discharge and GABA responsiveness of cerebellar Purkinje cells. Soc. Neurosci. Abst. 11:552.

A2. Michael, A.J., West, M.O., Chapin, J.K., Waterhouse, B.D. and Woodward, D.J. 1985. Actions of d-amphetamine on cerebellar Purkinje cells in freely moving rats. Soc. Neurosci. Abst. 11:552.

A3. Woodward, D.J., Stowe, Z.N., Smith, W.K., McEachron, D.L., Chapin, J.K. and Waterhouse, B.D. 1985. 2-DG uptake patterns in rat CNS following administration of abuse potential substances: a computer facilitated analysis. Soc. Neurosci. Abst. 11:552.

A4. Cheng, J.-T., Azizi, S.A., Chapin, J.K. and Waterhouse, B.D. 1985. An in vitro study of norepinephrine effects on lateral hypothalamic neuronal responses to GABA. Soc. Neurosci. Abst. 11:1078.

5. Professional Personnel directly involved in AFOSR-85-0155

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6. Coupling Activities

AFOSR 1985 Fall Task Review
Wright - Patterson Air Force Base, Ohio
November 12-13, 1985
"The role of Central Monoaminergic Systems in Arousal and Selective Attention."
Summary presentation of data to AFOSR Life Sciences Directorate and other research personnel from DoD and AFOSR supported laboratories

7. New discoveries, inventions, etc.

Not applicable

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