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# Final Technical Report AFOSR-87-0138 (1988-1991)

# "The role of central monoaminergic systems in arousal and selective attention"

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#### STATEMENT OF GOALS

Considerable evidence from a variety of behavioral, electrophysiological and neuroanatomical studies suggests that noradrenergic output from the nucleus locus coeruleus (LC) plays a role in regulating the transfer of information through sensory circuits during periods of arousal and selective attention. While many investigations from our laboratory as well as others have shown that local administration of norepinephrine (NE) can enhance the responsiveness of individual sensory neurons to synaptic stimuli, there are still many unanswered questions concerning the precise way in which output from the LC could invoke such changes in cell responsiveness and thus influence sensory signal processing. In particular, there have been few detailed studies which have assessed the potential impact of the LC-NE system on specific stimulus coding functions of sensory pathways.

Clarification of the role of the noradrenergic system in sensory circuit function requires advances in at least three specific directions. First, it is important to obtain a more sophisticated understanding of the anatomical relationship between LC and its efferent targets which transmit sensory information. Secondly, further extracellular single unit recording studies are necessary to more thoroughly characterize the dimensions of sensory stimulus coding that can be regulated by LC output. Finally, intracellular investigations are also needed to identify the membrane properties and cell types within a sensory neuronal network that are subject to regulation by synaptically released NE. The goal of ongoing studies has been to address these issues using cat and rat somatosensory and visual systems as model circuities which are targeted by LC efferent projections.

The underlying theme of this work has been that any consideration of the functional consequences of NE release in sensory regions of the brain must not only take into account effects on single cells but also must recognize the potential for the noradrenergic system to alter the signal processing capabilities of ensembles of interconnected neurons. To date our studies have provided significant new information concerning the potential for synaptically released NE to influence the central processing of sensory signals at the level of single cortical neurons and intact circuits. Despite this claim, it would be a gross oversimplification of the problem to expect that the results of studies described here are, by themselves, adequate to explain the physiological basis of selective attention; nor do we believe that the noradrenergic system is solely responsible for this cognitive function and the state of arousal. Nevertheless, the hope is that the results of these investigations begin

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to provide a link between the cellular actions of NE and changes in neural function which occur during arousal and selective attention.

Elucidation of the mechanisms responsible for maintaining vigilance of the sensory surround and orchestrating behavioral responses to task-related, novel or potentially threatening stimuli is of considerable importance for understanding the full range of human capabilities under normal and adverse conditions. Moreover, it is important to point out that many of the drugs commonly abused under stressful conditions such as caffeine, cocaine and amphetamine have a direct impact on central noradrenergic function. Thus, further clarification of the role of NE in the normal operation of primary sensory circuits will likely provide significant insights into how self-administered psychostimulant compounds may affect the performance of tasks requiring high levels of selective attention to sensory cues.

## SUMMARY OF RECENT PROGRESS

During the past 4 years of AFOSR support a number of experimental approaches including neuroanatomical labeling with retrograde tracers, intra- and extracellular recording of cells from cortical tissue slices and unit recording in awake behaving and anesthetized animals have been employed to further investigate the anatomical organization and physiological actions of the cortically projecting monoaminergic systems.

The aim of recent extracellular studies in intact animals has been to further refine the concept that not only NE but also serotonin (5-HT) might operate primarily as modulators of synaptic transmission in monoaminergic target circuits of mammalian brain rather than as neurotransmitters conveying specific details of moment to moment information. Additional electrophysiological investigations relying on extra- and intracellular recording procedures in tissue slice preparations have begun to identify the receptor- linked second messenger systems and membrane biophysical processes associated with NE's modulatory actions. Furthermore, we have started to identify classes of cortical cells which are capable of selectively expressing various noradrenergic modulatory actions.

Overall, the electrophysiological studies conducted during this phase of the project have further identified the parameters of neuronal function regulated by NE and 5-HT as well as begun to elucidate the mechanisms through which synaptically released NE may

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enhance the signal processing capabilities of individual cells in noradrenergic target circuits.

Complementing these efforts have been studies where the effects of cocaine on neuronal responsiveness have been characterized. The rationale underlying this work was that because of its ability to elevate central synaptic levels of NE and 5-HT, cocaine should exert monoamine-like modulatory influences on cell responsiveness to synaptic stimuli. The demonstration of such effects in sensory cortical circuits would provide a basis for linking the synaptic modulatory actions of NE and 5-HT with the behavioral arousal and heightened sensory perception that accompany cocaine administration.

Newer investigations conducted during the previous period of support have established topographical relationships between dorsal raphe and locus coeruleus projection neurons and cortical and sub-cortical regions of the rat forebrain that relay primary visual and somatosensory information. These studies are revealing unique organizational features of the monoaminergic projection systems which suggest that specific functional anatomical relationships exist between the dorsal raphe, locus coeruleus and their efferent targets. A brief synopsis of recent individual studies is given below.

#### Organization of Monoaminergic Projections to Sensory Pathways

Distribution of Dorsal Raphe and Locus Coeruleus Neurons Projecting to Visual Areas of Rat CNS: Retrograde transport studies using HRP have been conducted to examine the intranuclear distributions of dorsal raphe (DR) and locus coeruleus (LC) neurons that project to rat visual cortex, lateral geniculate, superior colliculus and paraflocculus. This study extends work reported in two previous publications concerning the topographic ordering of DR and LC neurons that project to rostrocaudally aligned regions of the neocortex (Waterhouse et al., 1983; 1986). The issue being explored in these studies is that monoamine-containing nuclei in the brainstem may be organized with respect to the sensory functions mediated by monoaminergic target areas in the forebrain.

The results collected to date indicate that cells projecting to the superior colliculus and lateral geniculate are concentrated in a dorsolateral zone of the DR whereas visual cortical and paraflocculus projection neurons are distributed within the ventromedial portion of the nucleus. Neurons projecting from the LC to the lateral geniculate, superior colliculus and paraflocculus are found bilaterally and are uniformly distributed within the nucleus,

whereas cortical projection neurons are restricted to the caudal half of the ipsilateral LC. In summary, discrete regions of the monoamine-nuclei appear to be organized in such a way that they might influence specific portions of the visual system according to behaviorally relevant contingencies. Such a topographic ordering of the LC and DR with respect to terminal field projections provides new insights into the possible operating mode of the noradrenergic and serotonergic systems.

**Distribution of LC Neurons that Project to Somatosensory Targets:** A preliminary investigation (Altman et al., 90) using fluorescent retrograde tracers has shown that LC efferents to target structures along the ascending somatosensory pathway in rat exhibit an orderly projection with respect to the crossed trajectory of this sensory system. Quantitative analysis of the distribution of labeled cells with respect to somatosensory projection targets revealed a bias such that output from one LC nucleus was heaviest to the contralateral principal nucleus of V, ipsilateral VPM thalamus and ipsilateral barrelfield cortex. Thus, based on the density of retrograde labeling, output from one LC nucleus appears capable of exerting its major influence on structures conveying tactile information from the contralateral side of the body.

Another preliminary finding of this study is that LC projection neurons to somatosensory structures are organized into overlapping subsets within the nucleus, thus raising the possibility that a significant proportion of these cells project to multiple, common somatosensory targets via axon collaterals. In pilot experiments (n=2), paired injections of different retrograde tracers in barrelfield cortex and ipsilateral VPM thalamus have shown that 35-40% of LC neurons which project to VPM also send collaterals to the somatosensory cortex. In contrast, an experiment following the same strategy but pairing retrograde tracer injections in dorsal lateral geniculate and barrelfield cortex yielded double labeling in only 2% of labeled LC cells. Further studies with additional controls are needed to expand on these findings and confirm or deny the existence of a functional topography for LC efferents to sensory pathways. The demonstration of such a functional organization of LC efferents would challenge the notion that all LC cells receive a common set of inputs and respond homogeneously to polymodal sensory stimuli. Instead under certain conditions individual LC neurons may be activated by a unique convergence of inputs and exhibit modality- or state-specific responses. Such findings would significantly alter our view of the selectivity with which the LC-NE system influences sensory signal processing.

## Noradrenergic Modulation of Sensory Neuron Function

NE Actions in Rat Visual Cortex: A recently published study (Waterhouse et al., 1990) demonstrated that locally applied NE could enhance responses of neurons in rat visual cortex (area 17) to moving visual stimuli. In addition to changes in magnitude of response, iontophoretic NE produced alterations in movement evoked discharges such that receptive field borders were more sharply defined. These results suggest that the noradrenergic system may be capable of fine tuning the feature extraction properties of neurons in visual and other sensory cortices.

Another finding reported in the same study was that in some cases NE revealed responses to visual stimuli which were not observed during the control condition. The implication of this result is that potentially threshold synaptic inputs may normally arrive at visual cortical neurons but not evoke spike discharges unless facilitated by NE. As such, NE may function to increase the sensitivity of sensory cortical neurons to near-threshold afferent inputs. At first glance, such an interpretation seems inconsistent with a role for NE in sharpening receptive field borders, however, since this effect was not observed routinely, it is possible that only specific cell types within the cortical circuitry are capable of expressing this mode of noradrenergic modulatory action. Furthermore, in addition to being cell specific such effects could also be input specific (Marrocco et al., 1987) such that under selected stimulus conditions NE facilitates activation of additional cells within the visual cortex and as a result generates a more robust response of the circuit to patterned inputs. T'so et al., (1986) have described horizontal connections within the visual cortex which may serve to "bind" the activation of individual cortical columns in response to complex continuous contours in the visual surround. Such connections could be the focus of NE's "gating" action on otherwise subliminal inputs.

Overall, the results of studies in the rat visual cortex have indicated that the LC-NE system may be capable of not only increasing the magnitude of neuronal responses to synaptic inputs, but also may alter the feature extraction properties of individual cells and/or local circuits.

NE Influences on Receptive Field Properties of Cat Visual Cortical Neurons: A recently completed study (McLean et al., 1990; McLean and Waterhouse, 1992) examined the effects of iontophoretically applied NE on specific receptive field properties (direction selectivity, orientation and velocity tuning) of simple and complex neurons in cat striate

cortex. The goal of these experiments was to contrast the effects of NE on simple and complex cell responses to optimal vs non-optimal visual stimuli. The results of this work indicate that NE can cause selective shifts in velocity tuning as well as increase the direction selectivity of individual neurons. These results go well beyond the simple demonstration that NE can amplify neuronal responses to synaptic inputs and begin to show that this monoamine can influence specific signal processing functions of individual sensory cortical neurons. The implication of these findings is that during periods of increased synaptic release of NE, visual cortical cells may be able to more precisely encode information from the visual scene.

## **Cellular Actions of NE**

Gating Effects of NE in Mammalian CNS: This report (Waterhouse et al., 1988) surveys the evidence from our own studies and the work of others which suggests that a "gating" effect of NE on subliminal synaptic inputs may be a prominent noradrenergic modulatory action in at least some cell cells of central neuronal circuits. Specifically, iontophoretically applied NE can reveal (i.e. "gate") neuronal responses to otherwise subthreshold synaptic stimuli in the cerebellum and visual cortex (see above) of intact, anesthetized rats; as well as in neurons recorded from lateral hypothalamic and cortical (see below) tissue slices. These observations provide the basis for predicting "gating" effects at times in the behaving animal when LC output is high.

Pharmacological Characterization of NE Modulatory Interactions with Glutamate: A recently completed extracellular study (Mouradian et al., 1990) has established that NE-induced potentiation of glutamate-evoked excitatory discharges in somatosensory neurons recorded from cortical tissue slices is mediated by activation of alpha type adrenoceptors. In some cells, NE and alpha agonists are also capable of revealing robust excitatory discharges in response to otherwise subthreshold doses of glutamate. Overall, the results of this extracellular study contradict previous findings of intracellular experiments in cortical layer V pyramidal neurons (Foerhing et al., 1989) which showed that beta agonists could mimic NE-induced changes in neuronal excitability. Nevertheless, these results are in complete agreement with our own previous studies in intact anesthetized animals.

NE-induced Changes in Membrane Responsiveness to Subthreshold Synaptic Inputs: A preliminary experiment (Mouradian et al., 1991) has already shown that in the absence of a direct hyperpolarizing action and under current clamp conditions NE can increase the probability of cortical neuronal spiking in response to otherwise subthreshold postsynaptic potentials. Initially this effect does not appear to be due to de-inactivation of a low voltage calcium conductance (Llinas, 1988), yet provides further evidence of NE's ability to shift the threshold of detection for cortical neuronal responses to subliminal inputs.

Noradrenergic Influence on GABA-induced Membrane Conductance Changes: Recently initiated studies (Liu et al., 1989; Sessler et al., 1990; Waterhouse et al., 1990) using intracellular recording procedures in somatosensory cortical tissue slices have demonstrated for the first time that NE can enhance GABA-induced membrane conductance changes. As was shown previously in an extracellular study (Sessler et al., 1989), such GABA potentiating actions are mimicked and blocked by beta agonists and antagonists, respectively; and also mimicked by agents which elevate intracellular levels of cyclic AMP (eg. forskolin and 8- bromo-cyclic AMP). As such these noradrenergic influences on transmitter-induced conductance changes are consistent with previously observed effects of iontophoretically applied NE on extracellularly recorded responses of neocortical neurons to GABA. Overall, these data provide the basis for predicting that NE will increase the magnitude and/or duration of synaptically evoked GABAergic IPSP's in somatosensory cortical neurons.

Many of the cells in which such NE-induced membrane effects have been observed have been positively identified as layer III or layer V pyramidal neurons by intracellular staining with biocytin or Lucifer yellow. Although such experiments are tedious in that they require stable intracellular recordings for long periods of time, this approach has provided detailed physiological and pharmacological information on identified populations of sensory cortical cells. Such data is needed in order to begin predicting the influence of the noradrenergic system on ensembles of morphologically heterogeneous but functionally related cells in sensory cortical circuits.

## **Network Models of NE Function**

Computer Modeling of the Impact of NE on Thalamocortical Circuit Function: An ongoing project (Utz et al., 1991) being conducted in collaboration with John Chapin (Hahnemann University) is the development of a simplistic model of the thalamocortical circuitry which incorporates realistic membrane properties for individual neurons as derived from electrophysiological experiments. Effects of NE are modeled by increasing synaptic efficacies in a manner consistent with results of previous in vivo and in vitro electrophysiological experiments. Under simulated physiological conditions. noradrenergically- induced increases in synaptic efficacies enhance the ability of the thalamocortical network to discriminate stimulus inputs. This model demonstrates that when applied to functional assemblies of single units, the cellular modulatory actions of NE can improve the stimulus discriminating properties of a sensory neuronal network. Such modeling approaches have enormous potential for 1) testing hypotheses concerning NE actions on neuronal networks, 2) revealing emergent properties based on complex circuit interactions and 3) guiding future "wet" experiments whose aim is to elucidate the circuit level actions of the LC-NE system. However, the validity of these models and the physiological relevance of their predictions depends upon principles derived from studies of NE action on identified cell types in actual brain circuits.

#### **Electrophysiological Actions of Cocaine**

Cocaine Effects on Synaptic Transmission in Somatosensory Cortex: The goal of this study was to characterize the effects of systemically administered cocaine on somatosensory cortical neuronal responses to stimulation of thalamocortical afferent pathways. Cocaine over a range of parenteral doses, 0.5 to 2.0 mg/kg (i.p.), was found to enhance evoked excitatory discharges and stimulus bound inhibitions relative to suppression of spontaneous discharge in a majority of cells tested. In some cases, a long latency excitatory response that was not apparent during the pre-drug condition was revealed following cocaine injection. These results indicate that systemically administered cocaine can alter sensory cortical neuronal responsiveness to synaptic inputs in a manner similar to that observed previously for NE.

Cocaine Interactions with Purkinje Cell Responses to Iontophoretic GABA: This investigation surveyed the effects of parenterally (0.25-35.0 mg/kg i.p.) and microiontophoretically (5-60nA) applied cocaine on spontaneous discharge and GABA-induced suppression of Purkinie cell firing rate. At high doses (10-35 mg/kg, i.p.) cocaine had an overall depressant effect on Purkinje cell discharge, whereas lower doses (0.25-10 mg/kg, i.p.) were more likely to produce an augmentation of GABA-induced inhibitory responses relative to little or no suppression of spontaneous firing. Other experiments demonstrated that local iontophoretic (or micropressure) ejection of the drug could mimic the GABA potentiating actions of systemically administered cocaine. Cocaine was ineffective in augmenting GABA responses in cerebellar neurons recorded from animals pre-treated with the noradrenergic toxin DPS4, thus suggesting that the drug's effects in cerebellum are dependent upon intact noradrenergic terminals. This study provides evidence that systemically or locally administered cocaine can alter central neuronal responsiveness to GABA in a manner similar to that shown previously for NE. Such an effect of an exogenous compound on GABAergic synaptic transmission in sensory circuits could markedly influence central processing of sensory information.

Actions of Cocaine on Neurons Recorded from Awake, Behaving Animals: Previous work by Chapin et al., (Hahnemann University) in awake rats established that cortical and thalamic neuronal responses to electrical stimulation of the forepaw can be suppressed by repetitive locomotor activity. Results of a recently completed investigation suggest that cocaine at 1.0 mg/kg, i.p., can selectively facilitate neuronal responses to forepaw stimulation during both resting and movement (forced treadmill locomotion) conditions, thus counteracting movement-induced suppression of sensory responsiveness. These initial findings confirm, the expectation based on results of acute, anesthetized studies, that cocaine can facilitate sensory neuronal responsiveness in central circuits of intact, unanesthetized animals.

Overall, the results of studies investigating cocaine's actions suggest a link between the psychostimulant effects of this compound and the postulated role of the noradrenergic system in arousal and selective attention.

#### Publications Supported by AFOSR-87-0138 (1988-1991)

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- 5. Mouradian, R.D., Sessler, F.M. and Waterhouse, B.D. 1990. Noradrenergic potentiation of excitatory transmitter action in cerebrocortical slices: evidence for mediation by alpha receptor linked activation of protein kinase C. Brain Res. 546:83-95.
- 6. Jimenez-Rivera, C. and Waterhouse, B.D. 1991. Effects of systemically and locally-applied cocaine on cerebrocortical neuron responsiveness to thalamocortical inputs and glutamate. Brain Res. 546:287-296.
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- 9. Waterhouse, B.D., Border, B., Wahl, L. and Mihailoff, G.A. Organization of efferent projections from the rat locus coeruleus: innervation of visual system structures. J. Comp. Neurol. (submitted).
- 10. Waterhouse, B.D., Border, B., Wahl, L. and Mihailoff, G.A. 1992. Organization of efferent projections from the rat dorsal raphe: innervation of visual system structures. J. Comp. Neurol. (submitted).
- 11. Altman, D., Lin, C.-S., Wang, Li and Waterhouse, B.D. Lateralization and functional organization of the locus coeruleus projection to the somatosensory pathway in rats. J. Neurosci. (submitted).

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- A2. Liu, W., Sessler, F.M., Lin, C.-S. and Waterhouse, B.D. 1989. Intracellular study of the effect of norepinephrine on somatosensory cortical neuronal response to GABA. Soc. Neurosci. Abst. 15:1011.
- A3. McLean, J., Lin, C.-S. and Waterhouse, B.D. 1990. Effects of norepinephrine on velocity tuning and direction selectivity of cat visual cortical neurons. Soc. Neurosci. Abst. 16:1219.
- A4. Altman, D.W., Lin, C.-S. and Waterhouse, B.D. 1990. Distribution of locus coeruleus neurons that project to rat VB thalamus and barrelfield cortex. Soc. Neurosci. Abst. 16:1126.
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