AD-A186 354 BIOREACTIVITY: REGULATION OF NEURONAL RESPONSIVENESS--ROLE OF LOCUS(U) PRINCETON UNIV NJ B L JACOBS 12 JUL 87 AFOSR-TR-87-1154 $AFOSR-85-0034

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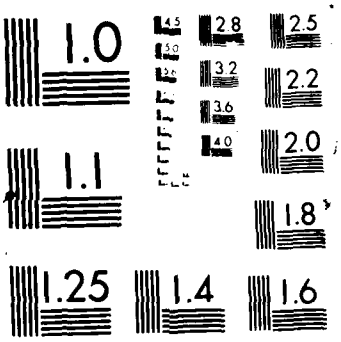
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19. ABSTRACT (Continue on reverse if necessary and identify by block number) In mammals, a group of neurons localized in an area of the brainstem called the locus coeruleus (LC) utilize norepinephrine (NE) as their neurotransmitter and are believed to be important in attention, vigilance, anxiety, and arousal. Studies supported by this grant over the past 2½ years explored these issues by means of chronic single unit recordings in unrestrained and unanesthetized cats. The work has been highly productive and has resulted in a number of major findings, most of which have been published or will be published within the next six months. We have completed a detailed analysis of the response of LC-NE neurons to repetitive presentation of simple sensory stimuli and how this response is altered by systemic administration of anxiolytic and anxiogenic drugs. We have also finished a study which examined the activity of these neurons during appetitive and aversive conditioning. In our most comprehensive investigations in this series we recently completed studies of LC-NE neurons in response to a series of environmental and physiological challenges (stressors). Overall, our experiments indicate an important role for this system in vigilance and bioreactivity, especially in situations that can be regarded as challenging or stressful to the organism.

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## 1. SUMMARY

In mammals, a group of neurons localized in an area of the brainstem called the locus coeruleus utilize norepinephrine as their neurotransmitter and are believed to be important in attention, vigilance, anxiety, and arousal. Studies supported by this grant over the past 2½ years explored these issues by means of chronic single unit recordings in unrestrained and unanesthetized cats. The work has been highly productive and has resulted in a number of major findings, most of which have been published or will be published within the next six months. We have completed a detailed analysis of the response of LC-NE neurons to repetitive presentation of simple sensory stimuli and how this response is altered by systemic administration of anxiolytic and anxiogenic drugs. We have also finished a study which examined the activity of these neurons during appetitive and aversive conditioning. In our most comprehensive investigations in this series we recently completed studies of LC-NE neurons in response to a series of environmental and physiological challenges (stressors). Overall, our experiments indicate an important role for this system in vigilance and bioreactivity, especially in situations that can be regarded as challenging or stressful to the organism.

## 2. RESEARCH OBJECTIVES

The neural mechanisms mediating the bioreactivity of mammalian organisms, including humans, are highly complex, involving a number of different brain areas and various interactive functional systems. In spite of this complexity, however, it is possible to specify a few systems that appear to play a primary or critical role in processes such as attention, arousal, vigilance, and anxiety (for the sake of economy, here subsumed under the rubric "bioreactivity"). Chief among these is the brain noradrenergic (NE) system, especially its subcomponent of NE neurons found in the dorsolateral pons in and around the locus coeruleus (LC). Because of its diffuse and widespread projection domain and because its cell bodies lie within the brain stem, LC neurons occupy a strategic position for influencing general organismic functions such as bioreactivity.

Most of the data which provide the evidence for a relationship between the LC and bioreactivity derive from studies employing brain lesions, systemic drug treatments, or electrical stimulation of the brain. Because these methodological approaches are somewhat gross or non-specific, the resulting data and hypotheses are, of necessity, also imprecise. Therefore, despite a good deal of general evidence implicating the LC and brain NE in bioreactivity, the details of precisely when and how this occurs are still obscure. One factor common to the various conceptualizations of the role of the LC in behavior is in influencing the processing of sensory inputs, especially under conditions that evoke affective responses.

If this view of the LC's role in behavior is valid, then single cell recordings provide an alternative method of experimental investigation for addressing these issues. The utility of this approach for understanding brain function has been amply demonstrated in the mammalian visual and motor systems. This approach has also been applied to the study of neurochemically identifiable neurons, such as those containing NE. Recently, a major advance in the study of the behavioral and physiological roles of brain NE neurons has occurred with our ability to examine the activity of these neurons in unanesthetized, freely moving animals. Therefore, the present research examined the response of LC-NE cells in freely moving animals under conditions of bioreactivity. We hypothesize, as have many others, that the activity

of the LC-NE system is engaged only under specific instances of what could generally be described as bioreactivity. In particular, we suggest that only those stimuli that represent a challenge, either real or potential, will engage this system. The ultimate goal of this research is to understand better the neural substrates of human bioreactivity. This would provide potential tools for influencing important human processes such as attention, vigilance, anxiety, and arousal.

## 3. STATUS OF THE RESEARCH

When our Air Force grant (AFOSR 85-0034) was initiated 2½ years ago, our objective was to shed light on mammalian bioreactivity. We proposed to do this by examining the single unit activity of NE neurons in the LC of behaving cats under physiological and/or ecologically relevant conditions. This work is now completed.

Our initial studies demonstrated that NE-LC neurons could be identified and recorded from for long periods of time in behaving cats. As had previously been reported in rats (Aston-Jones and Bloom, 1981), these neurons in cats: had relatively long duration action potentials; fired in a slow and somewhat regular manner; displayed activity that decreased across the arousal-waking-sleep continuum (to become virtually silent during REM sleep); were excited by repetitive presentation of phasic sensory stimuli; and had activity that was completely suppressed by systemic administration of the $\alpha_2$ agonist clonidine (Rasmussen et al., 1986a). One of our other important initial studies demonstrated the necessity of carrying out these studies in behaving animals. We found that an analgesic dose of systemically administered morphine significantly <u>increased</u> the activity of NE-LC neurons in behaving cats, whereas administration of the same dose to an animal anesthetized with chloral hydrate produced a significant <u>decrease</u> in NE-LC neuronal activity (Rasmussen and Jacobs, 1985).

In our first study directed explicitly at a bioreactivity issue we found that the response of cat NE-LC to phasic sensory stimuli is a dynamic one (Rasmussen et al., 1986b). Presentation of clicks or flashes reliably evokes an excitatory response in NE-LC neurons. With repetition, however, this response changes in two stages. Over the first 3-5 presentation (once/2 sec) there is a significant reduction in the probability of eliciting spikes (or in the number of spikes elicited), which is most likely attributable to decreased arousal or attention. Following this, over tens of repetitions, there is a more gradual decrease in neuronal responsiveness that does not appear to be attributable to overt changes in behavioral state. These data are consistent with an hypothesized important role of the LC in bioreactivity.

A series of studies explored the issue of what types of stimuli or conditions are capable of tonically activating LC neurons. These studies have led us to our present thinking about this system, that is, that these neurons are preferentially stress activatable. A number of conditions that are arousing to the animal (e.g. presence of another cat, walking on a treadmill, inaccessible food or inaccessible rats) produced no significant increase in LC unit activity above that seen during an active waking baseline condition (Rasmussen et al., 1986a). However, when a noxious component is part of the stimulus (e.g. threat, pain, or nausea), the activity of these neurons is significantly elevated above that seen during active waking. In a similar vein, we went on to show that conditioning which involved an appetitive stimulus (food) did not increase LC unit activity, but, conditioning with an aversive stimulus (air puff to the face) did activate this system (Rasmussen and Jacobs, 1986). This latter series of studies also examined NE-LC unit activity in relation

to anxiety. We found that the anxiogenic drug, yohimbine, significantly increased the activity of these neurons, while diazepam, a benzodiazepine type anxiolytic, decreased their excitability by afferent input (interestingly, this occurred in the complete absence of an effect of this drug upon tonic single unit activity). Most recently, we reported that buspirone, a novel non-benzodiazepine type anxiolytic, exerted virtually no effect on any aspect of LC unit activity (Wilkinson et al., 1987).

Results from the preceding experiments provided the primary thrust for our most recent research. We examined explicitly the hypothesis that NE-LC neurons are preferentially stress activatable (other work in our laboratory has shown that brain serotonin neurons and a group of brain dopamine neurons are not stress activatable). It is well known that stress research is plagued by a definitional problem. Therefore, we began by defining stress as an activation of the sympathoadrenal system, as reflected in increased levels of plasma NE or epinephrine, and tonic increases in heart rate. We found that stimuli that were arousing to the cats, such as the presence of inaccessible rats, were not stressful (no significant increase occurred in either heart rate or plasma NE) and produced no significant activation of LC unit activity. However, when the cats were exposed to stimuli that significantly increased heart rate and plasma levels of NE, such as restraint or 100 db white noise, LC unit activity was concomitantly increased (there was, in fact, a close temporal correlation between changes in these peripheral physiological variables and LC unit activity) (Abercrombie and Jacobs, in press a). In an important extension of these basic studies we found that when the same physical stimuli were either presented repeatedly (white noise) or maintained for a long duration (restraint) they lost their efficacy "to be stressful" as reflected in changes in the physiological indices, and they likewise lost their efficacy to activate NE-LC neuronal activity (Abercrombie and Jacobs, in press b).

In the final set of experiments completed under the sponsorship of AFOSR 85-0034, we examined the effects of various physiological stressors (challenges) upon NE-LC unit activity in behaving cats. The experiments involved manipulation and examination of many of the major physiological systems: cardiovascular, glucoregulatory, thermoregulatory, respiratory, and sodium regulatory. The results were quite complex, but can be summarized as follows: LC neurons in behaving animals do respond to physiological challenges, and they can do so independent of changes in behavioral arousal; they do not appear to play a specific role in any of the aforementioned systems, but, they may play a more global modulatory function, since they respond less sensitively and more universally than primary mechanisms, and their activity can be dissociated from the regulatory systems examined; and, finally, NE-LC neurons are generally coactivated with the sympathoadrenal system, though they are not correlated perfectly with either the neural or hormonal components of this system (Morilak et al., in press a, b & c).

In the aggregate, consideration of these data in conjunction with those from the existing literature lead to the conclusion that NE-LC neurons play an important role in mediating and integrating the response of the mammalian CNS to behavioral, environmental and physiological challenges (stressors). The phasic response of these neurons to brief sensory inputs is also consistent with this view if one considers them to be inputs which are novel and/or of potential importance to the animal, and thus require that some response or decision be made. As noted above, when such stimuli lose their novelty, they often simultaneously lose their ability to activate NE-LC neurons.

As with most experiments, these raise more questions than they answer. The research program begun under the sponsorship of AFOSR-85-0034 is continuing under the sponsorship of an additional three-year AFOSR grant.

## 4. PUBLICATIONS


Jacobs, B.L. Single unit activity of brain monoamine-containing neurons in freely moving animals. Annals, New York Academy of Science, 1986, 473, 70-77.

Jacobs, B.L. Brain monoaminergic unit activity in behaving animals. In: Progress in Psychobiology and Physiological Psychology. A.N. Epstein and A.R. Morrison (Eds.) Academic Press, New York, 1987, 171-206.

Jacobs, B.L. Central monoaminergic neurons: Single unit studies in behaving animals. In: Psychopharmacology, The Third Generation of Progress. H. Meltzer et al. (Eds.) Raven Press (in press).

Rasmussen, K. and Jacobs, B.L. Locus coeruleus unit activity in freely moving cats is increased by systemic morphine administration. Brain Research, 1985, 344, 240-248.

Rasmussen, K., Morilak, D.A. and Jacobs, B.L. Single unit activity of locus coeruleus neurons in the freely moving cat: I. During naturalistic behaviors and in response to simple and complex stimuli. Brain Research, 1986, 371, 324-334.

Rasmussen, K. and Jacobs, B.L. Single unit activity of locus coeruleus neurons in the freely moving cat: II. Conditioning and pharmacologic studies. Brain Research, 1986, 371, 335-344.

Rasmussen, K., Strecker, R.E. and Jacobs, B.L. Single unit response of noradrenergic, serotonergic and dopaminergic neurons in freely moving cats to simple sensory stimuli. Brain Research, 1986, 369, 336-340.

Jacobs, B.L. Single unit activity of locus coeruleus neurons in behaving animals. Progress in Neurobiology, 1986, 27, 183-194.

Morilak, D.A., Fornal, C. and Jacobs, B.L. Single unit activity of noradrenergic neurons in locus coeruleus and serotonergic neurons in the nucleus raphe dorsalis of freely moving cats in relation to the cardiac cycle. Brain Research, 1986, 399, 262-270.

Wilkinson, L.O., Abercrombie, E.D., Rasmussen, K. and Jacobs, B.L. Effect of buspirone administration on single unit activity in locus coeruleus and dorsal raphe nucleus in behaving cats. European Journal of Pharmacology, 1987,136, 123-127.

Abercrombie, E.D. and Jacobs, B.L. Microinjected clonidine inhibits noradrenergic neurons of the locus coeruleus in freely moving cats. Neuroscience Letters, 1987, 76, 203-208.

Abercrombie, E.D. and Jacobs, B.L. Single unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. I. Acutely presented stressful and non-stressful stimuli. Journal of Neuroscience (in press a).

Abercrombie, E.D. and Jacobs, B.L. Single unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. II. Adaptation to chronically presented stressful stimuli. Journal of Neuroscience (in press b).

Morilak, D.A., Fornal, C. and Jacobs, B.L. Effects of physiological manipulations on locus coeruleus neuronal activity in freely moving cats: I. Thermoregulatory challenge. Brain Research (in press a).

Morilak, D.A., Fornal, C. and Jacobs, B.L. Effects of physiological manipulations on locus coeruleus neuronal activity in freely moving cats: II. Cardiovascular challenge. Brain Research (in press b).

Morilak, D.A., Fornal, C. and Jacobs, B.L. Effects of physiological manipulations on locus coeruleus neuronal activity in freely moving cats: III. Glucoregulatory challenge. Brain Research (in press c).

5. PROFESSIONAL PERSONNEL

Professor Barry Jacobs - Principal Investigator

Dr. Casimir Fornal - Research Associate

Dr. Kurt Rasmussen - Graduate student who eared his Ph.D. in Neuroscience and Psychology in 1985 -- Thesis title: Single unit activity of noradrenergic neurons in the locus coeruleus of the freely moving cat.

Dr. Elizabeth Abercrombie - Graduate student who earned her Ph.D. in Neuroscience and Psychology in 1986 -- Thesis title: Stress-relatedness of noradrenergic neurons in the locus coeruleus: Single unit studies in the behaving cat.

Dr. David Morilak - Graduate student who earned his Ph.D. in Neuroscience and Psychology in 1986 -- Thesis title: The influence of physiological homeostatic manipulations on the single-unit activity of noradrenergic neurons in the locus coeruleus of freely moving cats.

Mr. Eric Levine - Graduate student

6. INTERACTIONS (spoken papers)

a. Seminars

Medical College of Pennsylvania, Department of Pharmacology
Amherst College - Program in Neuroscience
University of California at San Diego, Deptartment of Neuroscience
University of California at Irvine, Department of Psychology
University of California at Los Angeles, Psychology Department
Hopital Pitie - Salpetriere (Paris, France)
INSERM Unite 161 (Paris, France)
Universite Claude Bernard (Lyon, France)
Wyeth Laboratories
Johns Hopkins University School of Medicine, Department of Neuroscience
Stanford University Medical School, Department of Psychiatry
College de France
Synthelabo, Inc. (Bagneux, France)
Pharmacology Department, Mt. Sinai Medical School
National Institutes of Health
Neurology Department, Cornell University Medical School
Ciba Geigy Corporation
Rockefeller University
Downstate Medical Center
Department of Pharmacology, Loyola University Medical School
Department of Psychology, Brown University
Department of Psychiatry, New York University Medical School
Ayerst Corporation
Biology Department, Rutgers University
Pfizer Central Research
Robert Wood Johnson School of Medicine
New York University, Neuroscience Program

b. Meeting Presentations

Society for Neuroscience, Annual Meeting

Neuronal and Endogenous Chemical Control Mechanisms on Emotional Behavior - Fukuoka, JAPAN

Neurochemical Analysis of the Conscious Brain: Voltammetry and Push-Pull Perfusion - New York Academy of Sciences

American College of Neuropsychopharmacology Meeting, "Stress and Brain Catecholamines" Annual Meeting, Maui, Hawaii

California Sleep Society, Annual Meeting, Malibu, CA

American College of Neuropsychopharmacology Meeting "Neuroanatomy, Neurochemistry and Neurophysiology of the Aminergic Systems," Washington, D.C.

b. Meeting Presentations (continued)

International Brain Research Organization Meeting, "Cellular Bases of Neural Integration," Montevideo, URUGUAY

International Catecholamine Meeting, Jerusalem, ISRAEL

4th Symposium on "Catecholamines and Other Neurotransmitters in Stress, Smolenice Castle, CZECHOSLOVAKIA

ASPET (Mid-Atlantic Chapter)

All India Institute of Medical Sciences, New Delhi, INDIA, "Neuro-receptor plasticity and brain function"

New Jersey Neuropharmacology Society

7. NEW DISCOVERIES

None

8. OTHER STATEMENTS

None

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