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The following findings were reported: 1) Oxotremorine-M binding in rabbit thalamus & cingulate cortex increased during discriminative avoidance conditioning (DAC). 2) Excitatory & discriminative neuronal activity was documented throughout DAC and there were relationships between training-induced neuronal activity and changes in binding. 3) Turnover of noradrenaline was signaficantly elevated during DAC suggesting a role for this transmitter in long-term memory. 4) Anterior cingulate cortex lesions uncover discriminative neuronal activity in the striatum and amplify activity in thalamus. 5) The structure connections and spontaneous activity of the lateral magnocellular nucleus in thalamus were described. 6) A review was written of the structure and function of cortical layer I and its role in learning and memory analyzed.

These are the first studies to document physiological regulation of receptors and transmitters that occur during avoidance learning and provide the basis for a comprehensive analysis of the molecular bases for learning and memory.

14. SUBJECT TERMS
muscarinic acetylcholine receptors; discriminative avoidance learning; training-induced neuronal activity; noradrenaline; cortical layer I; molecular bases of learning and memory

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FINAL TECHNICAL REPORT

Receptor Subtype Alterations: Bases of Neuronal Plasticity and Learning

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SUMMARY

The following projects were completed: 1) It was shown that oxotremorine-M binding in rabbit anterior thalamus and cingulate cortex increased during the course of discriminative avoidance conditioning (DAC). Since there was no change in pirenzepine binding, it was suggested that this change was associated with muscarinic (m2) receptors. 2) Excitatory and discriminative neuronal activity was documented in five thalamic nuclei and different layers of posterior cingulate cortex throughout DAC. There were striking relationships in the anterior thalamus between training-induced neuronal plasticities and changes in oxotremorine-M binding. 3) The concentrations of noradrenaline, serotonin and dopamine and their principal metabolites were measured in five rostrocaudal levels of cingulate cortex with HPLC and coulometric detection in animals that were trained to different levels of behavioral performance. Noradrenaline turnover was significantly elevated during DAC. 4) Anterior cingulate cortex lesions were shown to uncover discriminative neuronal activity in the striatum and amplify neuronal activity in the mediodorsal thalamus. 5) The structure, connections and spontaneous activity of neurons in the lateral magnocellular nucleus in rabbit thalamus were described. 6) A review was written of the structure and function of cortical layer I and its role in learning and memory. 7) Apparatus with computer control was built for DAC. 8) The Boston laboratory was dismantled and moved to Bowman Gray School of Medicine. Most of the third year of funding was devoted to this move, submission of a competitive renewal and termination of operations during the last three months when funding was withdrawn.

RESEARCH OBJECTIVES

There were four goals of the original application which sought to 1) specify behavioral stage-related alterations in muscarinic acetylcholine and GABA receptor subtype binding in cingulate cortex and limbic thalamus that occur during the acquisition and performance of an active avoidance task, 2) determine which neurons have increased muscarinic receptor binding, 3) investigate which cingulate cortical afferents to thalamus trigger such alterations in binding and 4) analyze the role of cingulate afferents to thalamus in stage-related alterations in thalamic receptor subtype binding. Receptor subtype binding to cortical layers and thalamic nuclei was to be evaluated in cryostat sections with coverslip autoradiography and single grain counting techniques. Ligand binding protocols included the following: m1, m3 and m4, ^{3}H-pirenzepine; m2, ^{3}H-oxotremorine-M in the presence of unlabeled pirenzepine; $GABA_a$, ^{3}H-muscimol; m1 and m2 muscarinic binding in dissociated neurons, ^{3}H-propylbenzilylcholine mustard.

Three experiments were proposed to accomplish the above stated goals. **First,** alterations in binding to muscarinic and GABA receptors at different stages of active avoidance learning were to be analyzed in cingulate cortex and limbic thalamus. The stages included naive, pretraining, first exposure to paired conditional and unconditional stimuli, first significant behavioral response, criterial performance, overtraining and animals that were yoked to criterial performance. **Second,** neurons involved in up regulation of muscarinic receptors and afferents triggering these events were to be analyzed with dissociated neuron and deafferentation lesions. The latter lesions were to be placed in the diagonal band of Broca, limbic thalamus or subiculum. **Third,** lesions of the lateral dorsal tegmental nucleus were to be made followed by behavioral training and muscarinic receptor binding assay.

STATUS OF THE RESEARCH

I. Prologue

This research was as a collaboration between the P.I. and Dr. Michael Gabriel at the University of Illinois. The projects were particularly unique because they united two established programs in receptor pharmacology and behavioral neurophysiology. We are pleased to report that this collaboration has provided important new findings about alterations in receptor binding which occur during discriminative avoidance learning. The original proposal of the P.I. was funded at Boston University School of Medicine and completed at Bowman Gray School of Medicine.

The original proposal was based on a pilot study of training-induced changes in receptor binding in 14 rabbits. During the first year of funding we explored our tentative conclusions with further testing. These findings led us to alter our goals in a number of important ways. **First**, the increase in pirenzepine binding in the pilot study could not be confirmed and so we have not pursued the neuron dissociation experiment. This latter experiment was intended to explore changes in binding on cortical neuron dendrites and was not necessary if we could not consistently demonstrate changes in binding to postsynaptic receptors. **Second**, there were consistent changes in binding of oxotremorine-M to what is most likely a presynaptic, m2 receptor. These studies required many more cases than we had originally planned to prepare; 82 in all. In addition, we developed ligand binding protocols for many other receptors and analyzed binding in these cases to determine if other transmitter systems might also be involved. Processing many more cases and ligands meant that we were not able to fully explore the consequences of deafferentation lesions during this grant period. **Third**, during the third year we analyzed the above data and published these and electrophysiological findings. The influences of lateral dorsal tegmental and mammillary body lesions on alterations in muscarinic and GABA receptor binding in the thalamus could not be performed during the third year due to the time needed for reapplication and the fact that further support could not be provided to complete these studies in future years. **Finally**, samples from many of these brains were analyzed with a 16 coulometric electrode system in conjunction with high pressure liquid chromatography. This study was not originally proposed, but it has shown an important involvement of noradrenaline in the acquisition of this task.

II. Progress Toward Research Objectives

A. Alterations in Muscarinic Receptor Binding

Vogt, Gabriel, Vogt, Poremba, Jensen, Kubota and Kang (1991) reported for the first time that ^{3}H-oxotremorine-M binding in the presence of unlabeled pirenzepine (OXO-M/PZ) was increased in the anterior thalamus and cingulate cortex of rabbits throughout the course of discriminative avoidance training. Upon reaching a particular stage of training the brains were removed and autoradiographically assayed for oxotremorine-M, pirenzepine, muscimol, enkephalin, serotonin, neurotensin, and paraaminoclonidine binding in 9 limbic thalamic nuclei and throughout cingulate cortex. Binding was assessed in the following thalamic nuclei: parvocellular and magnocellular divisions of the anterodorsal nucleus (ADp and ADm, respectively); parvocellular and magnocellular divisions of the anteroventral nucleus (AVp and

AVm, respectively); anteromedial nucleus (AM); lateral magnocellular and laterodorsal nuclei (LM and LD, respectively); parvocellular and magnocellular divisions of the mediodorsal nucleus (MDp and MDm, respectively). Specific OXO-M/PZ binding increased progressively in AVp throughout training, reached peak levels at the criterial stage of performance and returned to control values during extinction training. The increase during criterion performance was significantly different than that for animals who were yoked to criterial performance. Thus, these changes in binding are likely due to discriminative learning processes because the training-induced progression in binding changes and the differences from yoked control cases. In ADp there was an increase in OXO-M/PZ binding early in training when the animals were first exposed to pairing of the conditional and unconditional stimuli, while that in the AVm nucleus occurred late in training during criterial performance. Neither of these latter changes were significantly elevated over the animals that were yoked to criterial performance, and binding was unaltered in any other thalamic nuclei.

A thorough analysis of OXO-M/PZ binding was made throughout the rostrocaudal extent of cingulate cortex. Specific OXO-M/PZ binding increased in most layers of rostral area 29c when subjects first performed a significant behavioral discrimination. Binding in more rostral and caudal levels of cingulate cortex was unchanged. The differences in rostral area 29c were significantly elevated over naive control cases. Although they were not significantly elevated over animals yoked to criterial performance, we are in need of cases which were yoked to first significant performance in order to have a valid comparison, i.e. it is not appropriate to compare animals yoked to criterial performance to those that were trained to the stage of first significant performance. OXO-M/PZ binding was also altered in area 29d, the dorsal division of cingulate cortex, but only in layer V. Specific binding of pirenzepine was unaltered in any thalamic or cortical area analyzed.

It is known from previous receptor localization studies (Vogt and Burns, 1988, J. Neurosci. 8: 643-652) that anterior thalamic lesions reduce OXO-M/PZ binding in cingulate cortex in a laminar pattern which is similar to that of the distribution of thalamic axon terminals in cingulate cortex. Therefore, it was hypothesized that training-induced increases in OXO-M/PZ binding in AVp might actually be responsible for changes in OXO-M/PZ binding in layer Ia of area 29c. There was a very high correlation between OXO-M/PZ binding in AVp and layer Ia of cingulate cortex. This suggests that binding changes in cortex may be "driven" by anterior thalamic neurons.

Increases in OXO-M/PZ binding but not pirenzepine binding suggests that binding to m2 receptors is altered throughout discriminative avoidance training. It is possible that part of the change in cingulate cortex is associated with thalamic neurons because AV projects to layer I of area 29 and has neurons which synthesize m2 receptors. Finally, since training-induced neuronal plasticities parallel changes in OXO-M/PZ binding, elevated m2 binding may be a prerequisite for this activity in parts of the limbic system.

B. Neuronal Plasticities in Thalamus and Cortex

Gabriel, Vogt, Kubota, Poremba and Kang (1991) reported the findings of multi-unit recording studies which were conducted in five limbic thalamic nuclei and in layers of posterior cingulate areas 29c/d and 29b during the acquisition and performance of the discriminative avoidance task. Excitatory training-induced unit activity (TIA), i.e. increased

tone-elicited activity during training relative to a pretraining session with unpaired tone-shock presentations, and/or discriminative TIA, i.e. greater discharges to the warning than to the safe tone, developed during training in 11 of the 13 areas analyzed. Discriminative TIA in the thalamic nuclei increased monotonically as learning progressed. AD and AVp excitatory TIA peaked early during the first session of training, LD excitatory TIA peaked in an intermediate stage when the first behavioral discrimination occurred and AVm and AM excitatory TIA peaked in a late stage of training when the first significant behavioral discrimination had occurred. The excitatory TIA in these nuclei declined as training continued beyond the stage in which peak activity occurred.

In cingulate cortex there were laminar differences as to when TIA occurred during the acquisition and performance of this task. Peaks of excitatory TIA developed in area 29c/d in the early (layer VI), intermediate (layers I-III and V) and late (layer IV) training stages as defined above. Only layer IV in area 29b of posterior cingulate cortex exhibited a peak of excitatory TIA which occurred in the early and intermediate training stages. As in limbic thalamus, discriminative TIA increased monotonically over training stages in layers V and VI of area 29c/d and in layer VI of area 29b. However, layers I-III and IV in area 29c/d exhibited peak discriminative TIA in the intermediate and late training stages, respectively.

One interpretation of these findings is that the training-stage specificity of the thalamic and cortical excitatory peaks of TIA may reflect consolidation processes and provide a temporal label for the learned discrimination. Furthermore, it is important to notice that there are some relationships between alterations in OXO-M/PZ binding and TIA in the anterior thalamic nuclei. The increase in binding in ADp occurred during the first stage of training as did excitatory TIA in this nucleus. However, the binding remained high throughout training, while TIA was reduced with subsequent training. Specific binding of OXO-M/PZ in AVp peaked at the same stage as did discriminative neuronal activity during the session of first significant behavioral discrimination. Finally, binding in AVm peaked late in training during criterial stages of performance as was true for discriminative TIA in this nucleus.

C. Alterations in Thalamic $GABA_A$ & Opioid Receptor Binding

Specific muscimol binding to $GABA_A$ receptors was reduced in most limbic thalamic nuclei during first exposure to pairing of the positive conditional and unconditional stimuli (FE). This reduction was due to the conditioning contingency because there was no change in muscimol binding during pretraining when conditional stimuli and explicitly unpaired footshocks were presented. In addition, there were no differences between yoked and naive control groups and, with further training to criterial levels of performance, muscimol binding returned to control values. This pattern in binding was most pronounced in ADp where OXO-M/PZ binding was elevated during FE. The inverse regulation of binding to $GABA_A$ and m2 receptors is an intriguing phenomenon both in terms of its behavioral significance and in terms of the mechanisms of receptor regulation.

Specific binding of (D-Ala^2-$MePhe^4$-Gly-ol^5)-enkephalin (DAGO) to mu opioid receptors or of a cyclic penicillamine containing enkephalin analogue (DPDPE) to delta opioid receptors was analyzed in 45 animals trained to different stages of performance and in 12 naive and 10 yoked control cases. Changes in DAGO binding were most pronounced in ADp, while those for DPDPE were most pronounced in the two divisions of AV. Specific DAGO binding in ADp

fell from naive and yoked control values during pretraining and FE. Cases which received further training to first significant or criterial performance had control levels of DAGO binding. In contrast, binding of DPDPE was stable in ADp but was modulated during training in AVp and AVm. Thus, highest binding of DPDPE in these nuclei occurred during pretraining when the noxious footshocks were explicitly unpaired with one of the two conditional tones. Following FE and subsequent conditioning, levels of DPDPE binding returned to control values. Thus, this is another form of inverse changes in binding in the anterior thalamic nuclei.

D. Noradrenaline Turnover During Training

Monoamines have been implicated in a number of neuronal plasticities including active avoidance conditioning. Lesions in cingulate cortex impair the acquisition and performance of discriminative avoidance learning and depletion of noradrenaline in posterior cingulate cortex impairs performance (Sparenborg and Gabriel, unpublished observations). The study by Vogt, Volicer, Schnepper and Gabriel (1991) employed high pressure liquid chromatography and a 16 electrode coulometric detection system to analyze the concentrations of noradrenaline, serotonin and dopamine and their principal metabolites in rabbit cingulate cortex in subjects that had reached different levels of performance. Since cingulate cortex is not homogeneous in terms of the distribution of monoamines in its anterior and posterior cytoarchitectural divisions, measurements were made in tissue dissected from 5 rostrocaudal levels of cingulate cortex.

Concentrations of dopamine and its metabolites were unchanged throughout training. The noradrenaline metabolite 3-methoxy, 4-hydroxyphenylglycol reached its highest concentration in posterior cingulate cortex during FE. In anterior cingulate cortex the level of this noradrenaline metabolite was elevated during all stages of training including in yoked control cases in animals that were overtrained, i.e. given three days of training beyond criterial performance. The turnover of noradrenaline reached a peak in anterior cingulate cortex later in training when subjects first performed a significant behavioral discrimination. Turnover of serotonin was inversely related to that of noradrenaline in that the ratio of its metabolite 5-hydroxyindoleacetic acid to serotonin was highest in naive and overtrained animals when noradrenaline turnover was lowest. These data demonstrate that noradrenaline turnover progressively increases throughout the course of discriminative avoidance training and that these changes are not due to general arousal or stress. Training beyond criterial performance reduces noradrenaline turnover to basal levels.

E. Effects of Cingulate Lesions on Behavior and Neuronal Activity

A study by Gabriel, Kubota, Straube and Vogt (1991) analyzes the role of anterior and posterior cingulate cortex in discriminative avoidance learning in rabbits as well as the influence of anterior cingulate lesions on training-induced neuronal activity in posterior cingulate cortex, mediodorsal thalamus and striatum. Rabbits with anterior and posterior cingulate cortex lesions took more than twice as many days to acquire this task than it did for control cases. Although there was only a mild retardation in acquisition of this task with ibotenic acid lesions in area 24, there was no evidence of "escape learning." This latter process refers to a progressive decrease in the latency of unconditioned responses which occurs during training in control animals. Ibotenic acid lesions in anterior cingulate cortex significantly increased positive

conditional stimulus evoked neuronal activity during training but not pretraining sessions. These same lesions uncovered training-induced unit activity in the caudate nucleus during the stage of first significant behavioral discrimination and during criterial performance which was not present in the control cases. Finally, the anterior lesions removed early-developing, training-induced activity in posterior cingulate cortex, but they did not affect later-developing activity.

These data suggest that anterior cingulate cortex is crucial for processes that occur early in training. It has been postulated that anterior cingulate cortex, the laterobasal nucleus of the amygdala and mediodorsal thalamic nucleus are involved together in the "recency" or "working" memory system. The dependency of posterior cingulate cortex on anterior cingulate cortex function is clarified with the lesion and recording data and it can now be argued that the caudate nucleus is actually involved in discriminative neuronal processes.

F. Lateral Magnocellular Nucleus in Rabbit Thalamus

The lateral magnocellular nucleus (LM) contains the largest neurons in the rabbit thalamus, yet its cortical connections have not been detailed and nothing is known of its activity during the progression of discriminative avoidance training. The study by Vogt and Sikes (1990) evaluated the architecture, cingulate cortical connections and spontaneous rate of neuronal discharges in LM.

At its maximal mediolateral extent in coronal sections, LM underlies the laterodorsal and lateroposterior nuclei. It has a short medial and long lateral limb, both of which have high levels of cytochrome oxidase activity. On the basis of horseradish peroxidase and fluorescent dye injections, LM projects primarily to area 29 and posterior area 24. Projections to area 29d are topographically organized. The medial limb of LM projects to rostral area 29d, mid levels of LM where the limbs join project to midlevels of area 29d and lateral parts of the lateral limb project to posterior area 29d. It is mainly the midportion of the lateral and medial limbs that projects to areas 29b and 29c. The anterior parts of these areas receive input from dorsal parts of LM, whereas posterior levels of these areas receive input from ventral LM. The midregion of LM also projects to caudal area 24. Injections of ^{3}H-amino acids into area 29d anterogradely labeled neuronal processes in LM. Finally, single unit electrophysiological recordings from LM in halothane-anesthetized rabbits showed a unique pattern of spontaneous discharges. Over 70% of the LM neurons cycled through a number of different phases from very high levels of 82 Hz to relatively low levels of 21 Hz.

Their size, high levels of cytochrome oxidase activity and spontaneous discharge rates suggest that LM neurons have a high level of metabolic activity and may share similarities to the centrolateral nucleus in other species. Furthermore, the extensive projections of LM to posterior cingulate cortex suggest that neurons in LM likely play a critical role in the functions of area 29.

G. Layer I Structure and Function and Role in Memory

The review of layer I structure, connections and receptor binding is the first synthesis of its kind (Vogt, 1991) and provides hypotheses regarding the role of particular cortical afferents in parallel processing of sensory afferents, learning and memory and the

consequences of its disruption in "primary subcortical gliosis." This analysis of layer I provides an important context in which to interpret changes in receptor binding throughout the course of discriminative avoidance training. The following premises were made: 1) Layer I function must be defined in terms of its primary components; apical dendritic tufts and afferent axons. 2) Apical dendritic tufts are a displaced integrative region in pyramidal neurons with a distinct morphology and GABAergic input. Inhibitory projections to layer I likely gate excitatory input from apical dendrites in layer I to those in deeper layers. 3) Disruption of layer I interferes with perceptual processes and learning and memory. 4) Layer II neuron physiology likely reflects activity in layer I because the preponderance of its input is from layer I. Thus, afferent transmission through the midline and intralaminar thalamic nuclei to layer I in all sensory systems evoke activity which has a slow conduction velocity from the periphery and whose receptive field information is degraded along the course of central transmission. 5) Interactions between the distal and proximal integrative regions are assured by the following neuronal characteristics. a) Pyramidal neurons are electrotonically compact and so current is likely transmitted from apical tufts to somata in deeper layers. b) Calcium currents enhance transmission along apical dendrites. c) Cholinergic projections to both distal and proximal dendritic compartments further reduce the electrotonic length of dendrites and generally enhance neuronal excitability. This point is emphasized with our earlier work in the *in vitro* callosal slice preparation. Application of acetylcholine to the slice in 2 and 4 amplified electrically-stimulated callosal-responses in cingulate cortical neurons both in terms of duration of excitatory postsynaptic potentials and the number of evoked action potentials when compared to evoked activity without acetylcholine in the bathing medium as shown in 1 and 2. 6) Layer I connections are ultimately involved in converting transient events into permanent memory via joint cholinergic and noradrenergic projections. Thus, when connections of this layer are disengaged, pyramidal neurons are capable of responding to transient sensory events, but are unable to parallel process information among a number of sensory areas and are unable to establish a permanent.

III. Publications Completed During October 1988-November 1991

Vogt, B.A., Gabriel, M., Vogt, L.J., Poremba, A., Jensen, E.L., Kubota, Y. and Kang, K. (1991) Muscarinic receptor binding increases in anterior thalamus and cingulate cortex during discriminative avoidance learning. J. Neuroscience.

Gabriel, M., **Vogt, B.A.**, Kubota, Y., Poremba, A. and Kang, E. (1991) Training-stage related neuronal plasticity in limbic thalamus and cingulate cortex during learning in rabbits. Behav. Brain Res., in press.

Vogt, B.A., Volicer, L., Schnepper, P.W. and Gabriel, M. (1991) Elevated turnover of noradrenaline in cingulate cortex during discriminative avoidance learning. Experimental Brain Research, submitted.

Vogt, B.A. and Sikes, R.W. (1990) Lateral magnocellular thalamic nucleus in rabbits: Architecture and projections to cingulate cortex. J. Comparative Neurology 299: 64-74.

Vogt, B.A. (1991) The role of layer I in cortical function. In: Cerebral Cortex 9: 49-80, A. Peters and E.G. Jones (eds.), New York, Plenum Publishing.

Gabriel, M., Kubota, Y Sparenborg, S., Straube, K., and **Vogt, B.A.** (1991) Effects of cingulate cortical lesions on avoidance learning and training-induced unit activity in rabbits, Experimental Brain Research, submitted.

IV. Participating Professionals

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V. Other Progress and Accomplishments

The laboratory and three investigators (B.A. Vogt, L.J. Vogt and E.L. Jensen) moved from Boston University School of Medicine to Bowman Gray School of Medicine at the end of year 2. This move meant a complete dismantling and reconstruction of our research facilities and resubmission of this AFOSR grant for year 3. It took four months for us to complete this process. One of the principal reasons for making this move is that the new research environment in the Department of Physiology and Pharmacology is very conducive to continuation of behavioral research funded by the AFOSR. Dr. Samuel Deadwyler is an important player in the field of learning and memory and his interests in information processing and long-term potentiation in the hippocampal formation including subicular projections to cingulate cortex will dovetail well with the intent and future directions of the research embodied in our behavioral work. Dr. Linda Porrino is one of the world's leading experts in the use of metabolic markers to study brain function and Dr. Steven Childers is a receptor pharmacologist with whom we are collaborating to unravel the mechanisms by which binding to muscarinic and other receptors is regulated throughout the course of discriminative avoidance learning. There are many other investigators in our department who are involved in studying the mechanisms of reward (Dr. James E. Smith, Chairman) and the molecular biology of peptide synthesis and release (Drs. William Sonntag and Mariana Morris). This is an outstanding environment in which to continue the proposed studies.

Computerized behavioral training apparatus has now been installed at Bowman Gray School of Medicine. We have purchased new equipment with AFOSR and departmental funds

so that mechanistic receptor studies can be completed. The equipment includes a) Hacker-Bright cryostat, b) Sorval RC5B superspeed centrifuge, c) Beckman ultracentrifuge, d) Revco ultralow freezer for brain storage, e) Brandell 48 chamber cell harvester for in vitro receptor binding assays and f) scintillation counter. Thus, in addition to the fine roster of colleagues at this institution, we have three times the space we had at Boston University and a full complement of equipment with which to perform the next generation of behavioral studies.