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

We have recorded electrical activity from more than 200 neurons in the locus coeruleus (LC) in 2 behaving monkeys during the last year. We have made significant technical advances (e.g., use of 10 μm-diameter microwires for recordings, increased accuracy of electrode penetrations) which have increased the quality and quantity of data obtained. Results confirm our preliminary findings of the last period, i.e., LC neurons vary activity phasically and tonically during a vigilance task indicating a role for the LC system in regulating attentional lability and adaptive responsiveness to urgent stimuli. Moreover, extensive analysis of reversal performance reveals that LC neurons may have a close relationship with cognitive processes underlying stimulus analysis and decision-making. Finally, this analysis also reveals that LC neurons alter their responsiveness to stimuli after reversal of cue meaning in advance of corresponding alterations in behavioral responsiveness, indicating that LC neurons may play an important role in early learning processes, helping to "entrain" other brain systems to respond adaptively to new significant stimuli.

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training, (v) analysis of effects of local pharmacological activation of LC neurons on vigilance performance and attentiveness, (vi) initiate collaboration with Dr. J. Cohen and David Servan-Schreiber of Carnegie Mellon University and U. Pittsburgh to perform neural network analyses of LC function, and (vii) improvement in techniques to retrogradely label afferents to monkey LC.

1. Further improvement of techniques to record and localize LC neurons in behaving monkeys. We have developed methods for using very small diameter (10 μm) microwires for unit recordings. This greatly improves the signal-to-noise and general quality of unit recordings from the LC or other brain regions compared to larger wires we had been using (25 μm diameter). This smaller size wire also allows multiple penetrations through the same small brain region with minimal damage - in our current subject we have made >120 penetrations through a 2 X 2 mm area (LC nucleus) with no loss of recording capability. In addition, we have improved the cannula and microadvancer design so that we are considerably more accurate at placing electrodes in desired targets.

2. Quantitative analyses of LC responsiveness to target cues during performance of a vigilance task. Our continuing studies of LC neurons during the vigilance task support our previous observations that these cells are selectively activated by target cues in the task. Recent quantitative analysis on a population of single neurons revealed that LC neurons were phasically activated by target cues at a surprisingly short latency (mean \pm SEM onset latency of 90.7 \pm 6.0 msec, and a duration of 67.6 \pm 7.0 msec). These latencies were significantly shorter than the latencies of behavioral responses to target cues, which were 290.2 \pm 18.2 msec on average. Moreover, these latencies are among the shortest observed for brain neurons in response to discriminative stimuli, indicating that the LC response is in the early stages of brain circuits that process attention-related signals. In contrast, non-target stimuli elicited no significant activation of these same LC neurons in 100 trials. Similarly, no other LC neuron exhibited any apparent excitation following non-target stimuli when averaged over 100 trials. Weak excitatory responses to non-target stimuli were revealed in some neurons only when averaged over a very large number of trials (> 1000).

We calculated the ratio of response magnitudes for target cues/response magnitudes for non-target cues (as described in Methods) for the 9 individual LC neurons that yielded significant responses with 100 target trials described above. This ratio was 3.6, indicating that LC neurons were 3.6 times more active during the response period following target cues than during the same interval following non-target cues.

Inspection of LC responses over time during the task revealed that response amplitudes to target cues varied periodically, in accordance with the animal's level of behavioral performance. During periods of poor behavioral performance LC responses to target cues were smaller in amplitude than during epochs of excellent behavioral performance; most cells failed to respond at all during periods of poor performance. Neurons which were recorded during substantial epochs of both excellent and poor performance (> 30 min each) were subjected to quantitative analysis which revealed that this difference between LC response magnitudes during poor vs. excellent behavioral performance was significant ($p < 0.004$; $n = 6$ cells). It is noteworthy that LC responses to target cues were reduced during periods of poor performance even though these cues always yielded correct behavioral responses (hits).

The relationship between LC responses and behavioral responses were also analyzed in a trial-by-trial manner. Specifically, the latency of the first spike in an LC neuron following each target cue was compared to the latency of the corresponding behavioral response (lever release). This comparison was restricted to periods of excellent behavioral performance as LC responses to target cues only occurred during such times (as described above). This analysis revealed a highly significant positive correlation between LC response and behavioral response ($r = 0.30$; $p < 0.0001$; $n = 197$ trials for 5 cells), indicating that shorter latency LC responses were associated with shorter behavioral response latencies.

We also tested whether an LC response to a target cue altered the behavioral response to the following sensory cue. For this, we analyzed the rare occasions when the semi-randomly presented target cues occurred in pairs, and compared the latency of the lever releases for the first

and second cues in each pair. All of these target cue pairs were preceded by a non-target cue in the stimulus series. Examination of the corresponding PSTHs confirmed that LC neurons were activated by each of the cues in these pairs; moreover, the magnitude of response for the first target cue was significantly greater than that for the second target cue of the pair ($p < 0.05$). For the 7 sessions with 33 target-cue pairs examined, the lever response latency for the second target cue ($260 + 7$ msec) was significantly shorter than for the first cue ($283 + 8$ msec; $p < 0.01$, paired two-tailed t-test). This indicates that behavioral responses to target cues that are preceded by a cue-evoked LC response were faster than behavioral responses to the same cues preceded by non-target stimuli which did not evoke LC responses. We also examined bar release latencies for target cues that were preceded by a non-target cue which either generated no response (correct skip) or an incorrect bar release (false alarm). This analysis revealed that there was no consistent difference between bar release latencies for target stimuli depending upon whether the preceding trial elicited a bar release (8 sessions analyzed with 63 false alarm-target pairs and 1089 skip-target pairs). Thus, the shorter bar release latency for the second cue in the target cue pairs was not simply due to the preceding behavioral response.

LC neuronal responses to non-target stimuli that elicited lever releases (i.e., false alarms) were also analyzed. During periods of poor performance with frequent false alarms, LC neurons were not activated by non-target stimuli that evoked false alarm behavioral responses. Thus, none of the 17 cells analyzed exhibited a response to non-target stimuli that elicited either a behavioral response (false alarm) or no behavioral response (rejection; as described above). As noted above, the response of LC neurons to target stimuli that elicited lever releases (hits) was also markedly attenuated during periods of poor performance. Thus, LC neurons were relatively unresponsive overall during periods of poor behavioral performance.

In addition to these brief fluctuations in behavior, behavioral performance degraded with prolonged task activity, yielding a vigilance decrement typical of such tasks (Davies and Parasuraman, 1982; Parasuraman, 1984; Warm and Jerison, 1984). Comparison of performance in 30 min epochs at least 60 min apart during continuous task behavior revealed several changes in task performance in the later epochs compared to the early epochs: (i) the frequency of foveating the fix spot decreased substantially, (ii) the rate of false alarm responding increased significantly, and (iii) the latency of bar release for hits increased significantly, and became more variable. Responses of LC neurons also changed significantly between these same time epochs. LC responses to target cues in the later epochs of task performance were significantly smaller than for the same stimuli during the early epochs of task performance ($p < .01$). Thus, LC responses to target cues decreased significantly in parallel with behavioral performance during a time-dependent vigilance decrement.

Continuing experiments recording LC neurons during the vigilance task indicate that the activation of LC neurons by target cues is specifically related to the behavioral significance of the cue: (1) During a period of continuously excellent performance associated with high attentiveness LC responses to CS+ cues were large, whereas such responses virtually disappeared during poor performance, even for correct 'hit' trials. (2) LC responses also varied with target cue frequency, being smaller when target stimuli were presented at a probability of 0.5 compared to a probability of 0.1. (3) When targets were presented in pairs, the first (unexpected) target produced a significantly larger response than a second (expected) target. (4) In another experiment in which the target was cued by a preceding small visual stimulus, elevated LC activity preceded target presentation but no excitatory response followed for the target cue. (5) Infrequent (unexpected) non-target cues produced no response, similar to frequent non-target stimuli.

Our observations indicate that the response to target stimuli is not due to the frequency of stimulus presentation, to prediction of reward, or to motor performance, but rather depends on the urgency of the stimulus, i.e., on the perceived behavioral significance of the stimulus. This is consistent with the hypothesis that LC responses facilitate behavioral responses to CS+ and subsequent stimuli.

3. Quantitative analyses of changes in tonic LC activity with changes in attentiveness during vigilance performance. During drowsiness LC activity is very low (< 0.5 spikes/sec) and there is typically no task performance. We observed that during continuous alertness and task performance the frequencies of both LC discharge and successful foveation fluctuated over short (10-30 sec) and long time intervals (10-30 min). The long-term changes in LC discharge were consistently inversely correlated with task behavior, such that slightly elevated LC activity (by 0.5 to 1 spike/sec) was accompanied by decreased foveation frequency and poorer task performance. Correlation analyses revealed that this relationship was highly significant (of the 6 cells quantitatively analyzed to date, typically $r = -0.5$, $p < 0.001$). In addition, even short-term increases in LC tonic activity often corresponded to marked, similarly short-lasting reductions in foveation frequency. These results suggest that focused attentiveness varies with tonic LC discharge in an inverted U relationship. Very low LC activity is associated with drowsiness and inattentiveness, while high tonic LC discharge corresponds with labile attention and restlessness; optimal focusing of attention occurs with intermediate levels of tonic LC activity. Additional studies are underway to test whether fluctuations in tonic LC activity cause or reflect changes in attentiveness.

4. LC activity and behavioral performance during acquisition (learning) a new cue-contingency during reversal training. Impulse activity of LC neurons was recorded during the vigilance task and, to evaluate detailed aspects of lever responses, we recorded the signal from a strain gauge attached to the lever. The signal from another strain gauge attached to the head-mounted fixation post served to measure the animal's approach to the juice reward. As described above, LC neurons exhibited short-latency responses (about 100 ms onset) to target stimuli, while latencies of behavioral response were on the order of 300 ms. We found that both target and non-target stimuli elicited a slight lever release (below response threshold) until about 100 ms before the reaction time when the animal sharply released the lever for target trials or depressed it for non-target trials. This "decision point" was preceded by phasic LC activation for target stimuli by about 100 ms; no LC response occurred for non-target cues. In addition, during early trials after reversal of cue meaning animals frequently committed false alarms (lever releases to non-target cues). Lever release responses for both hits (correct responses to targets) and false alarms were followed by very similar approach signals from the fixation post strain gauge, suggesting that all lever releases were intentional and accompanied by anticipation of reward. However, after the first few trials LC cells were selectively activated only during hit trials; non-target cues did not elicit LC activation even though they frequently evoked false alarm behaviors. Also, LC activity did not vary with bar release outside of the task or with non-contingent delivery of juice reward. These findings indicate that (1) the LC may facilitate, but is not necessary for, behavioral responses. (2) LC responses do not reflect motor or pre-motor activity per se. (3) LC neurons rapidly alter their response in accordance with altered cue meaning, in advance of altered behavioral responses.

5. Effects of local pharmacological activation of LC neurons on vigilance performance and attentiveness. Our studies reveal a close correlation between tonic LC activity and attentiveness, whereby tonically elevated LC activity corresponds to markedly decreased focused attention (measured by frequency of foveating a fix spot required to initiate each task trial; described above). To test whether this correlation reflects a causal relationship whereby elevated LC activity is responsible for decreased attentional focusing, we examined the effects of activating an LC nucleus by local pharmacological stimulation in a monkey performing the vigilance task. The cholinergic agonist pilocarpine (approx. 100-200 nl) was infused into the LC unilaterally during task performance. In the 2 experiments to date of this nature, pilocarpine injections led to a rapid and profound decrease in foveation frequency, as would be expected if elevated LC activity was responsible for decreased attentional focusing. We have now improved our microinfusion techniques to allow repeated tests with minimal damage, and will carry out similar experiments soon in the 2 monkeys we are currently studying.

6. Collaboration with Dr. J. Cohen of Carnegie Mellon to perform neural network analyses of LC function. We have initiated a collaboration with Drs. Jonathan Cohen and David Servan-Schreiber of Carnegie Mellon University and U. Pittsburgh to develop neural network models of LC function. We have incorporated a well trained postdoctoral fellow in the activity, Dr. Marius Usher, who worked previously with Dr. Christoph Koch at Cal Tech. This collaboration is in its early stages. To date we have successfully transferred our electrophysiology data to Pittsburgh where Dr. Usher has analyzed on his Sun workstation and generated a set of initial ideas for modeling, which he is now in the process of implementing. Initial models will focus on alterations of tonic LC activity and changes in behavioral performance (error rates, reaction times) using back propagation methods.

7. Improvement in techniques to retrogradely label afferents to monkey LC. We have made injections of various retrograde tracers into the LC of several monkeys at the end of our recording experiments in these animals. We were surprised to find that many of the tracers used did not yield transport characteristic of that obtained in rat. Thus, attempts with wheat germ agglutinin-conjugated to horseradish peroxidase (WGA-HRP), Fluoro-Gold, or WGA-apoHRP-colloidal Gold did not yield transport of sufficient magnitude to allow study following large injections into the LC. However, our latest attempts employing the highly sensitive tracer cholera toxin b subunit (CTb) yielded robust retrograde labeling in each case following injections into the LC area of primates. We will use this tracer in the next animals following the physiology and behavioral experiments, and trace afferents to the primate LC.

Publications, Dec. 31, 1992-Dec. 30, 1993.

The following is a list of all publications during the reporting period, plus selected relevant publications after that time. These more current publications are also listed as there is a substantial lag in publishing finished work, and the experiments represented in these papers were performed largely or entirely during the reporting period.

1. Van Bockstaele, E., Akaoka, H. and Aston-Jones, G., Brainstem afferents to the rostral (juxtafacial) nucleus paragigantocellularis: Integration of exteroceptive and interoceptive sensory inputs in the ventral tegmentum. Brain Res. 603: 1-8 (1993).
2. Aston-Jones, G., Shiekhhattar, R., Rajkowski, J., Kubiak, P. and Akaoka, H., Opiates influence noradrenergic locus coeruleus neurons by potent indirect as well as direct effects. In: The Neurobiology of Opiates, R. Hammer, ed., CRC Press, New York, pp. 175 - 202 (1993).
3. Buda, M., Akaoka, H., Aston-Jones, G., Charley, P., Chergugi, K., Chouvet, G. and Luppi, P.-H., Modulation of locus coeruleus activity by serotonergic afferents. In: Serotonin, the Cerebellum and Ataxia. P. Trouillas and K. Fuxe, eds., Raven Press, New York, 1993, pp. 237-253.
4. Chiang, C. and Aston-Jones, G., Response of locus coeruleus neurons to footshock stimulation is mediated by neurons in the ventrolateral medulla. Neuroscience 53: 705-715 (1993).
5. Akaoka, H. and Aston-Jones, G., Indirect serotonergic agonists attenuate neuronal opiate withdrawal. Neuroscience 54: 561-565 (1993).
6. Chiang, C. and Aston-Jones, G. A serotonin-2-receptor agonist augments GABAergic and excitatory amino acid inputs to noradrenergic locus coeruleus neurons. Neuroscience 54: 409-420 (1993).

7. Grenhoff, J., Nisell, M., Ferre, S., Aston-Jones, G. and Svensson, T.H., Noradrenergic modulation of midbrain dopamine cell firing elicited by stimulation of the locus coeruleus in the rat J. Neural Trans. 93: 11-25 (1993).
8. Shiekhatar, R. and Aston-Jones, G., Sensory responsiveness of brain noradrenergic neurons is modulated by endogenous brain serotonin. Brain Res. 623: 72-76 (1993).
9. Harris, G. and Aston-Jones, G., Beta-adrenergic antagonists attenuate somatic and aversive signs of opiate withdrawal. Neuropsychopharmacology 9: 303-311 (1993).
10. Charley, P.J., Chergui, K., Akaoka, H., Saunier, C.F., Buda, M., Aston-Jones, G. and Chouvet, G., Serotonin differentially modulates responses mediated by specific excitatory amino acid receptors in the rat locus coeruleus in vivo. Europ. J. Neurosci. 5: 1024-1028 (1993).
11. Harris, G. and Aston-Jones, G., Beta-adrenergic antagonists attenuate withdrawal anxiety in cocaine and morphine dependent rats. Psychopharmacology 113: 131-136 (1993).
12. Shiekhatar, R. and Aston-Jones, G., Modulation of opiate responses in brain noradrenergic neurons by the cAMP cascade: changes with chronic morphine Neuroscience 57: 879-886 (1993).
13. Aston-Jones, G., Valentino, R.J., Van Bockstaele, E. and Meyerson, A., Nucleus locus coeruleus and post-traumatic stress disorder: neurobiological and clinical parallels. In: Catecholamine Function in Post-Traumatic Stress Disorder, M. Murburg (ed.), American Psychiatric Press, Wash., D.C., pp. 17-64 (1994).
14. Aston-Jones, G., Valentino, R.J., Van Bockstaele, E., Page, M. and Meyerson, A., Brain noradrenergic neurons, nociception and stress: Basic mechanisms and clinical implications. In: Nociception and the Neuroimmune Connection, F. Willard and M. Patterson, eds., University Classics, Athens, Ohio, pp. 107-154 (1994).
15. Aston-Jones, G., Rajkowski, J., Kubiak, P. and Alexinsky, T., Locus coeruleus neurons in the monkey are selectively activated by attended stimuli in a vigilance task. J. Neurosci. 14: 4467-4480 (1994).
16. Aston-Jones, G. and Siggins, G.R., Electrophysiology. In: Psychopharmacology: The Fourth Generation of Progress, D. Kupfer and F. E. Bloom, eds., Raven Press (in press).
17. Valentino, R. and Aston-Jones, G. Physiological and anatomical determinants of locus coeruleus discharge: Behavioral and clinical implications. In: Psychopharmacology: The Fourth Generation of Progress, D. Kupfer and F. E. Bloom, eds., Raven Press (in press).
18. Foote, S.L. and Aston-Jones, G., Pharmacology and physiology of central noradrenergic systems. In: Psychopharmacology: The Fourth Generation of Progress, D. Kupfer and F. E. Bloom, eds., Raven Press (in press).
19. Rajkowski, J., Kubiak, P. and Aston Jones, G., Activity of locus coeruleus neurons in monkey: Phasic and tonic changes correspond to altered vigilance. Brain Res. Bull. (in press).
20. Aston-Jones, G., Rajkowski, J., Kubiak, P. and Ivanov, S., The locus coeruleus and emotional activation: recent studies in behaving monkeys. (submitted journal article).

Abstracts:

21. Chiang, C., Page, M.E., Valentino, R.J., and Aston-Jones, G. Role of the nucleus paragigantocellularis (PGi) in the activation of locus coeruleus (LC) neurons by bladder distention. Soc. Neurosci. Abstr. 19: 486 (1993).
22. Chen, S. and Aston-Jones, G. Possible induction of nitric oxide synthase in Purkinje neurons following injury. Soc. Neurosci. Abstr. 19: 1876 (1993).
23. Aston-Jones, G., Hirata, H., and Zhu, Y. Collateralized projections from the ventrolateral medulla to the locus coeruleus and spinal cord: Linking alertness and sympathetic activation. Soc. Neurosci. Abstr. 19: 487 (1993).
24. Zhu, Y., Pieribone, V., Ennis, M., Shipley, M., and Aston-Jones, G. Prominent GABAergic projections to the locus coeruleus from the dorsomedial and ventrolateral medulla. Soc. Neurosci. Abstr. 19: 486 (1993).
25. Hirata, H. and Aston-Jones, G. A novel long-latency response of locus coeruleus neurons mediated by peripheral C fibers: Possible source of noradrenergic descending pain modulation. Soc. Neurosci. Abstr. 19: 1406 (1993).
26. Kubiak, P., Rajkowski, J. and Aston-Jones, G. Responses of monkey locus coeruleus (LC) neurons to CS+ stimuli reflect cognitive processing: Delayed activity during acquisition in a vigilance task. Soc. Neurosci. Abstr. 19: 974 (1993).
27. Rajkowski, J., Kubiak, P. and Aston-Jones, G. Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention. Soc. Neurosci. Abstr. 19: 974 (1993).
28. Harris, G.C. and Aston-Jones, G. A role for accumbal D2 receptor activity in the initiation and prevention of the opiate withdrawal syndrome. Soc. Neurosci. Abstr. 19: 1247 (1993).
29. Kubiak, P., Rajkowski, J., Ivanov, S. and Aston-Jones, G. Rapid acquisition of stimulus significance reflected in responses of monkey locus coeruleus (LC) neurons. Soc. Neurosci. Abstr. 20 (in press).
30. Rajkowski, J., Kubiak, P., Ivanov, S. and Aston-Jones, G. Responses of monkey locus coeruleus (LC) neurons are related to the behavioral significance of stimuli. Soc. Neurosci. Abstr. 20 (in press).
31. Kubiak, P., Rajkowski, J. and Aston-Jones, G., Locus coeruleus activity in behaving monkeys varies with autonomic activity and attentiveness, Abstr. First World Congress on Stress (1994).

Professional personnel.

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Jonathan Cohen, Ph.D., Assistant Professor, Carnegie Mellon University (no support from AFOSR)

Interactions (meetings where we presented results of our studies supported by this project).

1. American College of Neuropsychopharmacology (ACNP) Panel, "Neural Mechanisms of Learning and Memory: Relevance to the Consequences of Severe Psychological Trauma", San Juan, Puerto Rico, December, 1992.
2. Chairman and speaker, "Catecholamines and Attention: New Basic, Clinical and Modeling Approaches", Workshop, Winter Conference on Brain Research, Whistler, British Columbia, January, 1993.
3. Second International Symposium on the Neurobiology of the Locus Coeruleus, San Juan Islands, Washington, May 1993.
4. Society for Neuroscience meeting, 1993, 1994 - relevant abstracts are:
 - Kubiak, P., Rajkowski, J. and Aston-Jones, G. Responses of monkey locus coeruleus (LC) neurons to CS+ stimuli reflect cognitive processing: Delayed activity during acquisition in a vigilance task. Soc. Neurosci. Abstr. 19: 974 (1993).
 - Rajkowski, J., Kubiak, P. and Aston-Jones, G. Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention. Soc. Neurosci. Abstr. 19: 974 (1993).
 - Kubiak, P., Rajkowski, J., Ivanov, S. and Aston-Jones, G. Rapid acquisition of stimulus significance reflected in responses of monkey locus coeruleus (LC) neurons. Soc. Neurosci. Abstr. 20 (in press).
 - Rajkowski, J., Kubiak, P., Ivanov, S. and Aston-Jones, G. Responses of monkey locus coeruleus (LC) neurons are related to the behavioral significance of stimuli. Soc. Neurosci. Abstr. 20 (in press).