

The Locus Coeruleus

Behavioral functions of locus coeruleus derived from cellular attributes

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The electrophysiological activity of noradrenergic neurons in the locus coeruleus (LC) was examined in unanesthetized rats during spontaneously occurring behavior and sensory stimulation. The pattern of spontaneous and evoked discharge during sleep, grooming, drinking, and orienting behaviors, considered in light of other cellular anatomic and physiologic attributes, implicates the LC system in the control of vigilance and initiation of adaptive behavioral responses.

Many hypotheses have been generated concerning the role of the noradrenergic locus coeruleus (LC) system, ranging from emotions and affective disorders to control of cerebral blood flow (for a review, see Aston-Jones, Foote & Bloom, 1984). However, there is as yet no single theory to unify the vast array of observations relevant to this nucleus. To more fully elucidate the overall role of the LC in brain and behavioral processes, my collaborators and I have sought a more complete understanding of the cellular anatomic and physiologic properties of this system (Foote, Bloom, & Aston-Jones, 1983). There are at least four essential questions to be answered in achieving such a cellular understanding: (1) Where do LC neurons project, (2) what effect does norepinephrine (NE) released from LC terminals have on target neurons, (3) when are LC neurons active (and presumably releasing NE) during behavior, and (4) what afferents are responsible for controlling LC discharge.

Although a great deal is known about the efferent anatomy and postsynaptic physiology of the LC system (briefly reviewed below), data pertinent to the third question above, that is, the sensory/behavioral conditions that determine impulse activity in LC neurons, have not been available until recently. The present article addresses this question by presenting data from our studies of LC neuronal discharge in behaving animals (performed in collaboration with Stephen Foote and Floyd Bloom). Similarly, very little is known about the fourth question above, concerning afferents responsible for controlling LC discharge. Our results for LC activity in behaving animals

lead us to propose some general properties of inputs that control LC discharge. Following the data presentations, functional implications of these findings in the context of overall cellular physiologic and anatomic properties of the LC system are considered, and a new working hypothesis of LC function is presented. Finally, implications of this hypothesis for behavioral studies of the LC system are discussed.

Locus Coeruleus Efferent Anatomy and Postsynaptic Physiology

For the first of the above questions, studies during the last 20 years have revealed uniquely divergent and ubiquitous efferent trajectories of the LC system (for a review, see Foote et al., 1983). In sum, the LC projection system is extremely global, innervating all major regions of the neuraxis. This tiny nucleus (consisting of about 1,600 neurons per hemisphere in rat) provides the sole NE innervation of the cerebral, hippocampal, and cerebellar cortices. Although some investigators have argued that NE may be released from LC fibers in a nonsynaptic manner, providing a hormone-like influence on all neurons within a diffusion-limited area (Beaudet & Descarries, 1978), more recent studies have shown that LC terminals in several brain structures make conventional synapse-like appositions with postsynaptic specializations on target neurons (Koda, Shulman, & Bloom, 1978; Olschowka, Molliver, Grzanna, Rice, & Molliver, 1981). There is, in fact, a great deal of both regional and laminar specificity in the innervation of target structures by LC axons (e.g., Morrison, Foote, O'Connor, & Bloom, 1982). Thus, in spite of the enormous divergence in the LC efferent projections, this system exhibits the anatomic landmarks that convey the spatial and temporal specificity characteristic of other synaptically organized neurotransmitter systems.

Regarding the question of postsynaptic effects, the actions of NE on LC target neuronal activity are described for one sample target system in this volume by Segal

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(1985). These and other studies have found, for several target areas, that although NE most often inhibits spontaneous discharge, it may also enhance the selectivity of target cell discharge, so that in the presence of this neurotransmitter neurons respond with increased preference to their most strongly determined inputs. Thus, for example, NE inhibits spontaneous discharge of monkey auditory cortex neurons to a greater extent than it does the discharge driven by preferred auditory stimuli (Foote, Friedman, & Oliver, 1975). This effect has been termed an enhancement of "signal-to-noise" ratios in target cell activity, and has been replicated for several brain regions (for a review, see Foote et al., 1983). Although other effects of NE have been described for various target areas, such biasing of target cell responsiveness to other of their inputs is most significant for the present analysis.

LC Electrophysiology: Methodological Considerations

Before considering data concerning when LC neurons are active in a behaving animal, it is pertinent to point out some important technical issues. Our recordings of LC discharge have utilized species (rat and monkey) whose LC is composed of entirely noradrenergic neurons, thereby allowing confident assessment of NE-containing LC neural activity. This is an important consideration, since the long-standing wide interest in LC stems from its noradrenergic cell population. This property also allows identification of a select cell type in recording experiments, an important factor in the interpretation of any such physiologic study. Similar experiments in other species (e.g., cat, rabbit, guinea pig) lacking a homogeneously noradrenergic LC cannot positively ascribe discharge to NE-containing neurons (unless intracellular staining and double-labeling is carried out).

In studies of LC discharge, it is also important to use unanesthetized behaving animals whenever possible. Several physiologic parameters (some reviewed below) are markedly different in anesthetized versus unanesthetized behaving animals, or even vary with the type of anesthesia employed (see Foote et al., 1983). Therefore, many physiologic results on LC obtained in anesthetized animals must be considered tentative until confirmed in animals in a more behaviorally physiologic context.

Spontaneous LC Discharge and the Sleep-Waking Cycle

Addressing the third question above, we investigated discharge of NE-containing LC neurons in behaving animals. One predominant hypothesis of LC function is that these neurons control various stages of the sleep-waking cycle (Jouvet, 1969; McCarley & Hobson, 1975). Therefore, we examined the discharge of individual NE-containing LC neurons in unanesthetized rats during spontaneously occurring sleep and waking. We found that spontaneous LC discharge covaries consistently with stages of the sleep-waking cycle (Figure 1), firing fastest during waking, more slowly during slow-wave sleep, and

becoming virtually silent during paradoxical sleep (PS) (Aston-Jones & Bloom, 1981a; Hobson, McCarley, & Wyzinski, 1975). The marked quiescence of LC neurons during PS deserves special note, since nearly every other brain structure examined to date exhibits activity during this stage that closely resembles that seen in waking—hence the term "paradoxical" sleep (Steriade & Hobson, 1976). In rat, the nearly total lack of activity in this nucleus during PS is evident not only from the consistent quiescence of single neurons, but especially when several neurons in the densely packed noradrenergic cell group are recorded simultaneously, as illustrated in Figure 1. In such cases, the entire population typically becomes silent, with a prominent decrease in "background noise" as well. These observations, the first of their kind for known NE-containing neurons, support previous proposals that a similar subpopulation of cat LC neurons may be noradrenergic (Hobson et al., 1975; Jacobs, Rasmussen, & Morilak, 1984). However, other activity profiles of purported noradrenergic neurons have been reported in cat LC (Chu & Bloom, 1973, 1974).

Further analysis revealed that, in addition to distinct average discharge rates for different sleep-waking cycle stages, LC impulse activity changes *within* stages of the sleep-waking cycle, in anticipation of the subsequent stage. Thus, during waking, LC neurons progressively decrease in activity as slow-wave sleep approaches, and likewise during slow-wave sleep before the onset of PS (Aston-Jones and Bloom, 1981a; Hobson et al., 1975). However, if waking rather than PS follows slow-wave sleep, LC neurons abruptly emit phasically robust activity 100-500 msec prior to waking (see Figure 1). The one exception to such stage-anticipation in LC discharge occurs for the PS-to-waking transition. Rat LC neurons return to activity characteristic of waking either coincident with or slightly after the cessation of PS (and the onset of waking) as measured by the electroencephalogram (EEG). This conflicts with a previous report (Hobson et al., 1975) that the subpopulation of cat LC neurons that become silent during PS (putatively noradrenergic) begin rapid discharge during PS just before the onset of waking. However, in that study, the PS-to-waking transition was scored at the return of tonic activity in the electromyogram (EMG). Indeed, we also found that rat LC discharge precedes the EMG index of PS-to-waking transitions, so that when analyzed by this criterion rat and cat LC data are in good agreement. However, the PS-to-waking transition in rat EEG precedes that seen in the EMG, so that although LC discharge anticipates the transition in peripheral EMG activity, it does not anticipate the central EEG index of this state transition (Aston-Jones & Bloom, 1981a). Thus, although anticipatory LC activity during most stage transitions is consistent with a role in generating the subsequent stage, it seems that this nucleus is not responsible for the termination of PS, but rather that its activity during this stage is controlled by other brain areas that are more primarily involved in generating the transition to waking (Aston-Jones et al., 1984).

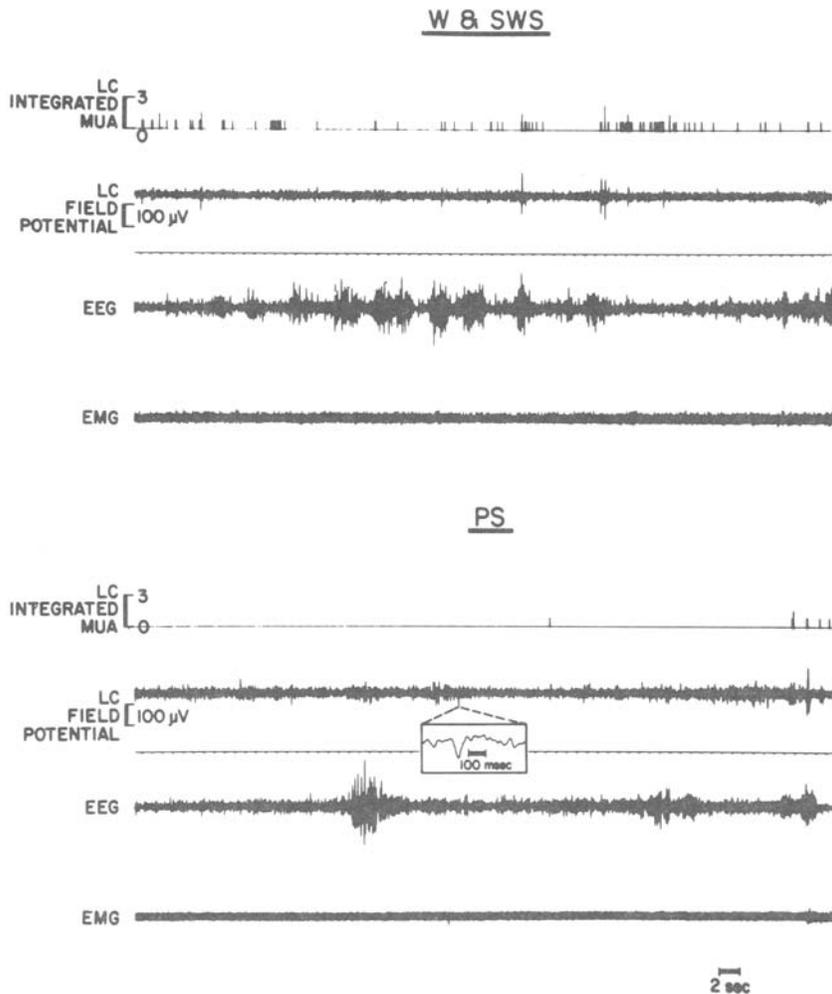


Figure 1. Polygraph records of multiunit activity (MUA) recorded from rat locus coeruleus (LC) during waking and slow-wave sleep (W & SWS; upper panel) and during paradoxical sleep (PS; lower panel). Each panel contains integrated MUA and field-potential signals recorded simultaneously from the same LC electrodes, as well as EEG and nuchal EMG activities. Note the state-related discharge, with more MUA during waking (low-amplitude EEG, upper panel) than during slow-wave sleep (high-amplitude EEG, upper panel), whereas activity in the entire MUA population is virtually nil during PS (lower panel; waking at far right). Note also the field potentials that are coincident with bursts of impulse activity during W & SWS, but that occur in the absence of such activity during PS. Insert in lower panel illustrates sample field potential at greater temporal resolution.

Field Potentials in LC

In addition to impulse activity, we simultaneously recorded spontaneously occurring field potentials in the LC of behaving rats (Figure 1; Aston-Jones & Bloom, 1981a). Such field potentials presumably reflect the concerted response of a group of neurons near the recording electrode to excitatory afferents (Steriade & Hobson, 1976). This view is supported by our consistent observation that field potentials in LC are synchronized with bursts of impulse activity recorded simultaneously from the same electrodes. Most interestingly, however, this close association between field potentials and heightened discharge apparent during waking and slow-wave sleep does not hold during PS. These two measures exhibit a marked dissociation during this stage of sleep, with field

potentials occurring at their highest spontaneous rate in PS while impulse activity is virtually nil (Figure 1). This result indicates that LC neurons may be actively inhibited during PS while receiving robust phasic barrages of excitatory input, generating substantial excitatory postsynaptic potentials, reflected in rapid field potential rates (Aston-Jones & Bloom, 1981a). In addition, recent observations of others (Aghajanian, Vandermaelen, & Andarde, 1983; Williams, Egan, & North, 1982; Williams, Henderson, & North, 1984) indicate that LC neurons *in vitro*, which apparently lack spontaneous synaptic excitation, exhibit regular spontaneous discharge due to intrinsic pacemaker activity. This supports our proposal (Aston-Jones & Bloom, 1981a) that periods of quiescence (such as PS) reflect active inhibition of these cells. This, in turn, im-

plies that the LC plays a critical but permissive role in the maintenance of PS, as previously proposed by McCarley and Hobson (1975). That is, undisturbed PS may require that LC be prevented from discharging in response to concurrent, intense excitatory inputs. In this way, LC neurons resemble motoneurons, whose discharge is actively inhibited during PS (despite receiving strong barrages of excitatory influence), presumably to prevent disruption of this state (Chase, 1980). Thus, robust LC discharge may disrupt behavioral states such as sleep.

Spontaneous LC Discharge and Waking Behavior

We further observed that LC discharge is altered during certain spontaneous waking behaviors. During both grooming (but not similarly intense motor activity such as struggling during restraint) and consumption of a preferred water solution, spontaneous LC discharge is decreased compared with adjacent epochs of similar EEG arousal (Aston-Jones & Bloom, 1981a). These results indicate that LC discharge is reduced not only for periods of low arousal (such as during sleep), but also during certain specific behaviors (such as grooming and drinking) when animals are highly aroused.

LC discharge also varies strongly with orienting behavior. In fact, the highest discharge rates observed for LC neurons in our studies were consistently associated with spontaneous or evoked orienting responses. LC discharge associated with orienting behavior is most intense when automatic, tonic behaviors (such as sleep, grooming, or consumption) are suddenly disrupted and the animal orients toward the external environment. Such phasic transitions in behavioral state are closely accompanied by a short, but robust, period of LC discharge (e.g., a burst of 5-7 spikes within 200 msec). Thus, as found for reduced spontaneous LC discharge during uninterrupted sleep, grooming, or consumption, there is close correspondence between spontaneous bursts of discharge and interruption of such automatic, preprogrammed behaviors.

LD Discharge and Vigilance

These observations indicate that arousal may not be the most appropriate framework for interpreting changes in spontaneous LC discharge. One property more common to sleep, grooming, and consumption than simply arousal level is the minimal surveillance of the external environment characteristic of these behaviors; that is, during such behaviors animals are relatively unresponsive to the great majority of external stimuli. The degree of attention or surveillance over the environment can be conveniently described in terms of *vigilance*, a general framework that incorporates behaviors as well as arousal levels. In this viewpoint, periods of high vigilance are defined by acute global attention and behavioral responsiveness to external environmental stimuli, whereas low-vigilance epochs are times when all but very select external stimuli have little influence on behavior, as occurs during bouts of

preprogrammed or automatic behaviors (e.g., sleep, grooming, or consumption). Times of low LC discharge (e.g., sleep, grooming, and consumption) are consistently behaviors or states of low vigilance. On the other hand, a marked orienting response, associated with intense LC discharge, represents an abrupt transition to heightened vigilance, so that behavior suddenly changes from automatic, tonic activity not requiring phasic attention to the global environment (e.g., sleep, grooming, or consumption) to a state of high vigilance or attention to a wide range of impinging external stimuli. This transition can occur spontaneously, or it can be evoked by sufficiently intense external stimuli that are incompatible with the ongoing behavioral activity. Such a transition in vigilance levels may also be accompanied by a change in arousal level (e.g., sleep-to-waking transition), or it can occur during a state of continuously high arousal (e.g., interrupting consumption). In either case, it is accompanied by a transition in LC neurons from little or no activity to phasically robust discharge. Such an analysis of our data indicates that spontaneous LC discharge is better understood as varying with the degree of vigilance typifying different behavioral states, rather than with the overall level of arousal only (Aston-Jones & Bloom, 1981a).

LC Sensory Responsiveness and Behavioral State

In addition to the above fluctuations in LC spontaneous discharge, we found that these neurons in unanesthetized behaving rats and monkeys were responsive to low-level, nonnoxious environmental stimuli (Figure 2; Aston-Jones & Bloom, 1981b; Foote, Aston-Jones, & Bloom, 1980). In awake rats, LC activity is markedly phasic, yielding short-latency (15-50 msec) responses to simple stimuli in every modality tested (auditory, visual, and somatosensory). These responses are similar for the various sensory modalities, and consist of a brief excitation followed by diminished activity lasting a few hundred milliseconds. This is in marked contrast to the generally tonic and unvarying discharge found for these cells in anesthetized animals, in which responses are elicited only to strongly noxious stimuli (see Foote et al., 1983, for review). It may be that the spontaneously phasic nature of LC discharge in waking animals reflects responses of these neurons to low-level background stimuli in the environment.

As found for spontaneous bursts of discharge in LC, sensory-evoked activity is accompanied by field potentials, temporally synchronized with evoked impulse activity (Figure 3; Aston-Jones & Bloom, 1981b). Thus, both spontaneously occurring and sensory-evoked barrages of excitatory input to LC may be recorded as similar field potential events. As also found for spontaneous activity, sensory-evoked impulse and field potential responses are time-locked during waking and slow-wave sleep, but become dissociated during PS, when responses in discharge cease to occur but field potentials continue

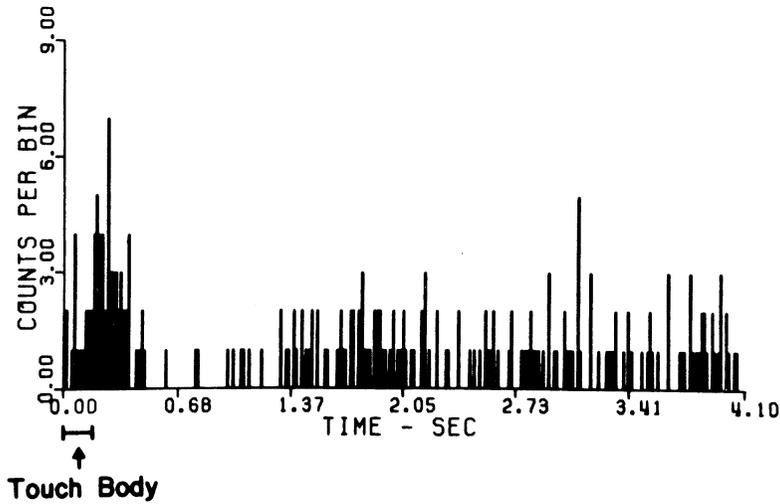


Figure 2. Peristimulus time histogram accumulated for discharge of a typical LC neuron during 50 consecutive trials of mild tactile stimuli presented (approximately at arrow) to an awake, behaving rat. Note characteristic biphasic response, consisting of excitation followed by inhibition.

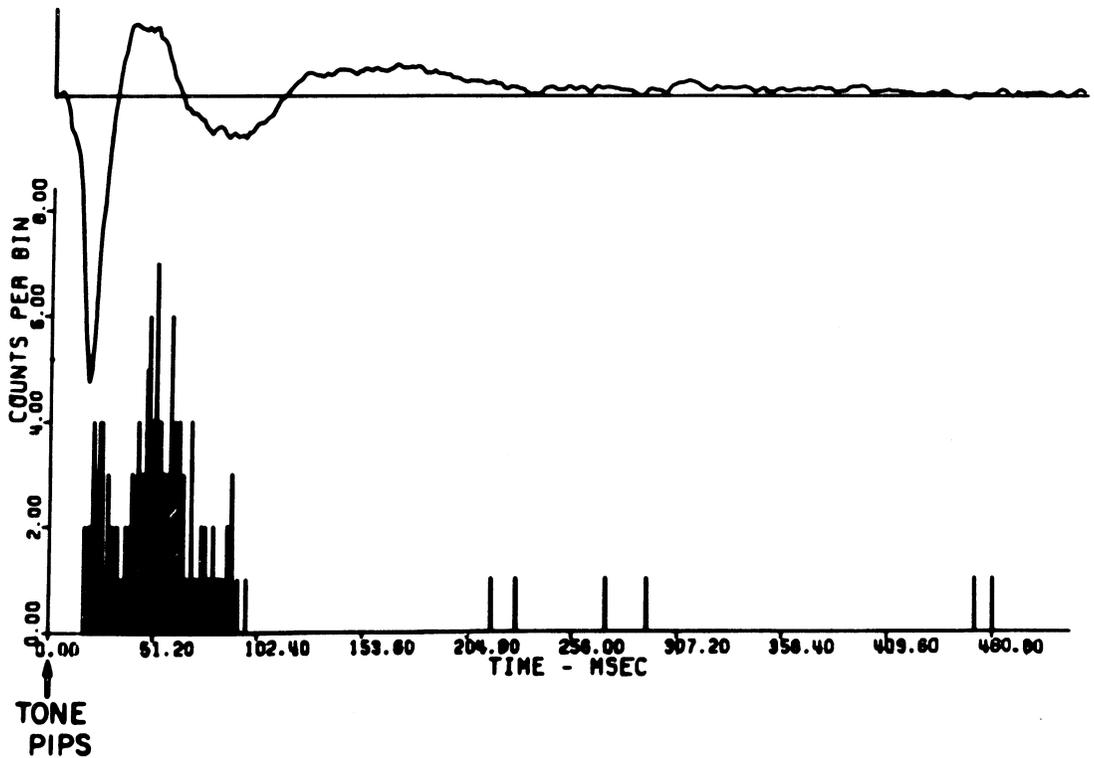


Figure 3. Peristimulus time histogram of LC discharge accumulated for 50 tone pip stimuli, collected simultaneously with the averaged evoked potential (waveform above histogram), recorded from the same electrodes but filtered to selectively pass slow-frequency signals. Note the close temporal synchrony between evoked impulse and field potential responses.

to be elicited. This result is consistent with our general conclusion that LC neurons are actively inhibited during PS.

During the course of monitoring LC responses to trains of sensory stimuli, fluctuations in the response magnitudes were apparent (Aston-Jones & Bloom, 1981b). On first analysis, these fluctuations resembled habituation and dishabituation, with initial responses being large, followed

by reduced response magnitudes for a few stimulus trials, which, in turn, were followed by markedly larger responses, and so on. However, further examination revealed that response magnitudes varied closely with spontaneous fluctuations in the animals' behavioral state. The largest responses were elicited by stimuli that cause an abrupt transition from sleep to waking. Responses elicited during continuous waking were larger than those

evoked during uninterrupted slow-wave sleep, whereas no response occurred during uninterrupted PS. Thus, sensory response magnitudes of LC neurons vary markedly with arousal. In addition to these results for sleep, we found that response magnitudes during uninterrupted grooming or consumption of sweet water were reduced (compared with other epochs of waking), whereas stimuli that disrupted such activity and generated orienting behavior elicited strong responses. Thus, as found for spontaneous discharge, sensory-response magnitudes of LC neurons vary with levels of vigilance (rather than simply with arousal levels), which in turn are associated with different behavioral states. Habituation independent of behavioral state was not found to occur, and response magnitudes for stimuli following even 100 or more presentations were similar to those for initial stimuli when presented during apparently similar behavioral states.

Thus, it appears that both spontaneous and sensory-evoked LC discharge fluctuate with behavioral state, and that the most significant behavioral state variable associated with altered LC excitability is vigilance, or the degree of attention to the external environment. Times of high vigilance, as occurs for sudden waking after sleep, interruption of ongoing behavior such as grooming or consumption, or presentation of an unexpected stimulus that evokes an orienting behavioral response by the animal, are associated with the most intense spontaneous or sensory-evoked discharge in LC, and represent times of highest excitability for LC neurons. Conversely, periods of low vigilance, such as during sleep, grooming, or consumptive behaviors, are associated with diminished LC excitability. The time of least excitability for LC is during PS, when the neurons appear to be under a strong tonic inhibitory influence and animals are least vigilant.

A View of LC Function Based on Cellular Attributes: The Vigilance/Response Initiation Hypothesis

The results described here for LC impulse activity in behaving animals have a number of functional implications when considered in light of other findings relevant to a cellular anatomic and physiologic understanding of the LC system. As outlined at the beginning of this article, such an understanding requires knowledge of (1) the efferent projections of LC neurons, (2) the effects of NE released from LC terminals on target neuron activity, (3) the conditions under which LC neurons are active and releasing their transmitter, and (4) the factors controlling LC discharge.

First, the broad efferent trajectory of the LC system implies that its function is a very global one, with widely distant and disparate brain areas receiving innervation from individual LC neurons. This notion is underscored by our physiologic studies, revealing that LC neurons are markedly homogeneous in their discharge characteristics; for example, LC neurons throughout the nucleus exhibit very similar rates and patterns of spontaneous or sensory-evoked impulse activity (Aston-Jones & Bloom, 1981a,

1981b). Thus, our data, in combination with the efferent anatomic results reviewed above, indicate that robust LC discharge results in globally synchronized release of NE onto target neurons located throughout the neuraxis.

Postsynaptically, NE influences target cells so as to relatively promote responses to other, strong afferent input while reducing spontaneous or low-level activity. Such an enhancement of postsynaptic "signal-to-noise" ratios can lead to increased selectivity of target cell discharge to favor specific aspects of their response profiles, as discussed in this volume for the work of Segal (1985) and his collaborators.

In the context of these previous findings, the specific conditions of LC activation in unanesthetized behaving animals lead us to a global hypothesis for the function of the LC system in brain and behavioral activities, suggesting a role of this system in the control of vigilance and initiation of adaptive behavioral responses (Aston-Jones & Bloom, 1981a, 1981b; Aston-Jones et al., 1984). As illustrated in Figure 4, we propose that the LC is strongly influenced by two general classes of extrinsic afferents (each possibly derived from two or more separate groups of neurons): excitatory inputs mediating sensory-evoked (or state transition-related) activity in LC neurons, and a more tonically active set of inhibitory afferents serving to modulate overall LC excitability in accordance with the vigilance state associated with the concurrent behavior. The level of LC activity at any time may be a consequence of the relative influence of each of these two classes of inputs. Strong tonic inhibition (such as found during PS) could serve to prevent LC neurons from responding to environmental stimuli. This may be necessary, since NE released from LC terminals in response to a sensory event could globally enhance strongly determined activity in target neurons (e.g., activity associated with salient sensory stimuli) and thereby promote transmission of corresponding relevant information through the nervous system for expression in behavior, interrupting this sleep state. That is, increased LC activity may interrupt automatic, internally driven or vegetative behaviors (such as sleep, grooming, or consumption) that are incompatible with phasic behavioral responding to the wide range of current environmental events and, instead, engage a mode of brain and behavioral activities characterized by a high degree of vigilance or interaction with diverse environmental stimuli. This theoretic framework is consistent with our observation that LC activity is most intense just before interruption of low-vigilance behaviors such as sleep, grooming or consumption, giving rise to alert orienting behaviors. Intense LC activation may occur when either tonic inhibition of LC neurons (engaged for automatic or vegetative behaviors) has suddenly decreased, or when excitation impinges on these cells (in response to a strong, unexpected sensory event) that is sufficiently intense to overcome concurrent tonic inhibitory inputs. Conversely, low vigilance programs may predominate in behavior when either LC discharge is effectively inhibited from responding to unexpected external stimuli, or when strong

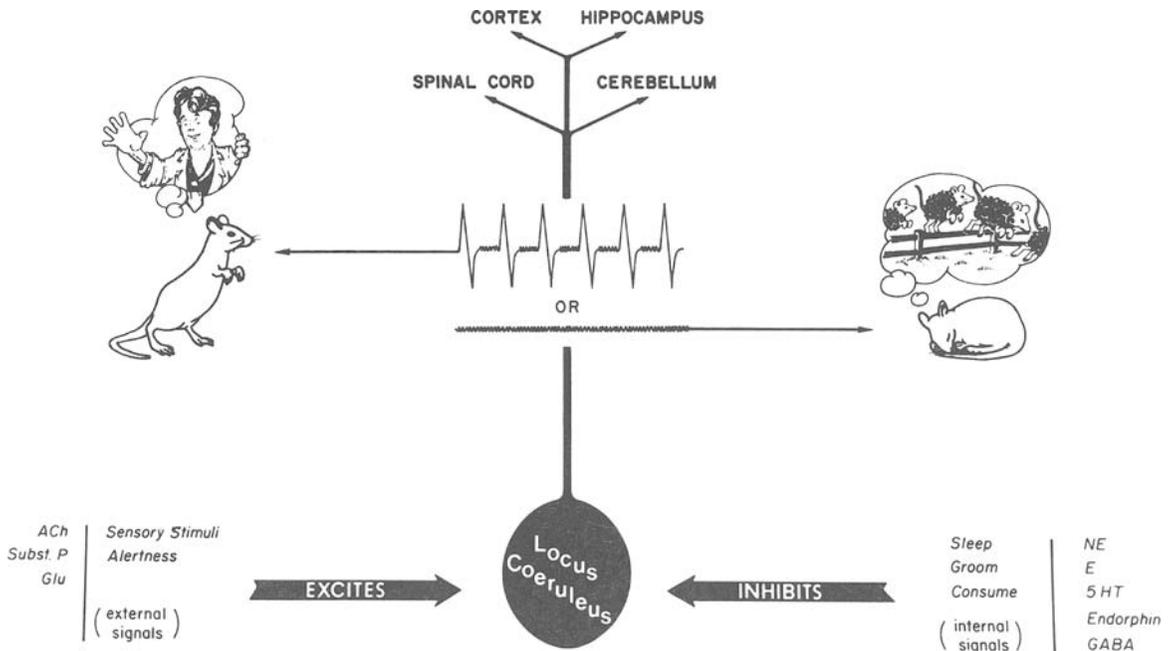


Figure 4. A schematic drawing to illustrate the proposed function of LC. At lower left is indicated the proposed excitatory afferents that mediate sensory responses of LC neurons, as well as possible transmitters involved. Conversely, this hypothesis proposes that behavioral states associated with reduced vigilance may lead to active inhibition of LC neurons, as illustrated at lower right for some possible transmitter candidates. The present hypothesis states that robust LC activity releases NE in a global and synchronous fashion throughout most of the neuraxis, serving to bias the brain and behavioral activities to preferentially respond to physically imperative external stimuli. This also serves to engage a random search through possible behaviors (see text), a step leading to adaptive behavioral response to environmental events. Conversely, decreased LC activity favors automatic preprogrammed behavior by allowing external events to be relatively ignored (figure taken from Aston-Jones et al., 1984).

unexpected stimuli are not present in the environment. In this way, the LC may serve as a gate to determine the relative influences of two mutually exclusive sets of behavioral programs. In general terms, the LC may function to influence the overall orientation of behavior or mode of sensorimotor activities, to favor either automatic or vegetative behavioral programs, or phasic adaptive responding to salient environmental stimuli.

Note that an alternative, but equivalent, expression of this proposed role for the LC in the regulation of vigilance is a role in the initiation of adaptive behavioral responses. Pronounced LC activity is associated with abrupt attention to external stimuli, which itself is a necessary component of, and immediately precedes, initiation of adaptive motoric response to salient external stimuli. This analysis suggests that the LC could logically be placed in either the sensory or the motor domain, in addition to its probable role in state regulation. To separate the sensory versus motoric versus behavioral state nature of LC discharge may be futile in this view, since the LC may function at the intersection of the sensory-motor-state realms.

This overall hypothesis of LC function can be stated in more abstract terms of nervous system operation. One view of heightened vigilance (e.g., startle, awakening, or stimulus-evoked disruption of ongoing behavior) is that this state represents a time of conflicting patterns of neu-

ral activity, brought about, for example, by a disrupting stimulus that does not fit into (i.e., conflicts with) the set of stimuli that is predicted or expected to accompany the ongoing behavioral paradigm. The ensuing state of heightened vigilance consists, in this view (Fuller & Putnam, 1966), of a set of behaviors aimed at reducing or resolving this conflict, so that impinging stimuli are once again predicted by behavior. The mode of achieving this resolution involves investigating or exploring different behaviors in the animal's repertoire (that may have had a weak relationship to a similar stimulus in the past). This "internal exploration" activity can be likened to a random search process, exploring the field of possible behaviors to emit in response to the unexpected stimulus event. In our hypothesis, robust LC discharge accompanying such a stimulus would serve to engage a random search process of this type, by terminating ongoing low-vigilance activity and rearranging precedence for transmission of neural activity through the nervous system to favor responses to, and activity in elements associated with, the most salient current stimuli. This proposed role of the LC as a random search generator is consistent with the proposed roles in vigilance regulation and adaptive response initiation; the latter are different syntactical statements of the same overall function.

Note that, in the present theoretic framework, very little integration or information processing takes place within

LC itself. Rather, this nucleus serves more as a channel or gate through which the results of information pertaining to the appropriate global level of vigilance is transmitted to the central nervous system as a whole. The information as to what external event will receive the most attention and serve to guide behavior (i.e., the information guiding "selective attention") is not proposed to be present within LC itself. Rather, activation of LC by a strong external stimulus releases NE in a global fashion, and this NE "sets the stage" in LC terminal areas so that the most salient or intense stimuli will preferentially influence overall brain activity, and thereby control attention and behavior as well. In this way, the LC system may serve as a simple, but important, gating mechanism for determining the global level of vigilance or attention to environmental stimuli, while the interaction of NE in LC terminal areas with particular sensory afferent information further shapes or specifies the selectivity of such attention, helping to initiate adaptive behavioral responding.

Implications for Behavioral Studies of LC Function

Although correlative measures of cell discharge and behavior are useful for suggesting behavioral functions of the neurons under study, they cannot lead to confirmation of causal postulates. Any hypothesis of the function of LC in behavior must include (at least implicitly) predictions for behavior following holistic manipulations of the LC, that is, following lesion or stimulation of the system. The hypothesis described above predicts several such behavioral results. One prediction is that animals lacking LC should be less attentive to, and therefore less distractible by, environmental stimuli presented during low-vigilance behaviors (such as sleep, grooming, or consumption). Equivalently, this hypothesis predicts that such low-vigilance behaviors would be less disruptable by environmental events without the influence of the LC system. Note that it would be crucial to test distractibility *during* times of low vigilance, since the LC may not be crucially involved in distraction by stimuli when vigilance is already high.

This theory also indicates that the LC may be important for learning the significance of certain sensory events. On a global level, the above argument that LC-lesioned animals should be less attentive to external stimuli implies a role in learning as well as in distractibility. In addition, the effect of NE to enhance the selectivity of target cell responsiveness to strong or preferred inputs implies that without LC, sensory selectivity in brain (and behavioral) activities should be reduced. Note, however, that such a lesion effect may be apparent only when subtle discrimination is required, since the enhancement of selectivity by NE may not be necessary for discrimination between widely differing sensory cues. Recent results of Robbins, Everitt, and their colleagues for learning deficits following LC lesions (Everitt, Robbins, Gaskin & Fray, 1983; Robbins, 1984) are consistent with this notion. Such enhancement of response selectivity in LC

target cells may also be necessary for acquisition of a subtle sensory cue after training has been established using a strong cue. Note again that it may be important that the new cue be a low-level or subtle one, since NE's augmentation of postsynaptic neuronal response selectivity may not be necessary for attaining the significance of a strong stimulus.

There are various possible reasons why some effects of LC lesions have been difficult to discern in behavioral studies. One is that central systems (including the LC) are plastic, often exhibiting substantial recovery following a lesion. Even non-LC systems may change to replace the functions of LC (perhaps only partially), and thereby obscure LC lesion effects (see Sara, 1985). Therefore, behavioral tests of functional hypotheses for the LC system may be best carried out with pharmacologically specific, but acute, inactivation of LC, as for example by local injection of clonidine. Secondly, the proper questions or behavioral tests may not have been posed—for example, distractibility by stimuli presented during low-vigilance behaviors has not been tested. However, recent studies (Britton, Ksir, Thatcher-Britton, Young, & Koob, 1984) report inappropriate responding to novel stimuli following lesions to the LC system, a finding easily incorporated by the present theoretic viewpoint.

Results described herein for the cellular anatomic and physiologic attributes of LC deserve careful consideration in behavioral studies employing LC lesions or stimulation. Knowledge of the behavioral conditions during which LC neurons are normally most active should give useful direction to the design of behavioral tasks for elucidating effects of such LC manipulations. Future studies along these lines should prove to be very valuable in testing behavioral hypotheses of LC function.

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