4

NOREPINEPHRINE

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This chapter reviews findings from basic research concerning brain norepinephrine (NE) systems. The focus is on work that is relevant to the mechanisms of psychiatric disorders, or the actions of drugs used to treat such disorders. The locus ceruleus (LC) system receives most of the attention here, but recent findings concerning the role of the A2/A1 medullary cell groups in drug abuse are also reviewed. Emphasis is placed on studies published since the last version of this volume. Space limitations prevent a thorough review of the involvement of any brain NE system in mental function and dysfunction, so that only a fraction of the relevant research can be covered. Apologies are offered to those whose work could not be included.

MOLECULAR–GENETIC STUDIES

Previous studies have revealed molecular properties of NE neurons and their effector systems that have extended our understanding of the function and pharmacology of this system. For example, Duman et al. (1) have shown that acute opiate administration decreases cyclic adenosine monophosphate (cAMP) and adenylate cyclase activity in LC neurons, whereas long-term use of opiates or opiate withdrawal results in elevated activity in this second messenger mechanism. Continuing studies in this vein have resulted in a more complete picture of molecular events and properties within LC neurons that help regulate their discharge activity. Thus, the adenylate cyclase/cAMP system is up-regulated with chronic stress but down-regulated with long-term antidepressant treatment (2). Additional studies indicate that impulse activity of LC neurons may be regulated in part by a nonspecific cation current that is activated by this second messenger system (2). These findings suggest a molecular mechanism whereby the overall excitability of LC neurons may be modulated in accordance with long-term environmental or pharmacologic conditions and may be involved in the mechanisms of action of antidepressant and other psychopharmacologic agents.

Recent genetic studies have also revealed important aspects of NE systems relevant to their role in psychopharmacology. Xu et al. (3) studied the brains of mice with a knockout of the NE transporter (3). These mice exhibited characteristics of animals treated with antidepressants (i.e., prolonged clearance of NE and elevated extracellular levels of this catecholamine). In a test for antidepressant drugs, the NE transporter knockouts behaved like antidepressant-treated wild-type mice, being hyperresponsive to locomotor stimulation by cocaine or amphetamine. Importantly, these animals also exhibited dopamine D2/D3-receptor supersensitivity. Thus, NE transporter function can alter midbrain dopaminergic systems, an effect that may be an important mechanism of action of antidepressants and psychostimulants.

NEUROANATOMY

Chemoanatomy of the LC

The neuroanatomy of the major brain NE systems has been recently reviewed in detail (4), and only the most salient features are described here. In the rat and primate (but not cat, guinea pig, and most other species), virtually all neurons located within the compact LC nucleus are noradrenergic. It is notable that LC neurons also often contain other possible neurotransmitters (e.g., neuropeptides), and subsets of rat NE neurons can be distinguished by neurotransmitter molecules that they co-localize (see ref. 4 for review). Additional work is needed to determine the functional significance of co-localization of other transmitter molecules within LC neurons.

Peri-LC Dendritic Shell

A prominent feature of LC neurons in all species is that their dendrites typically extend hundreds of micra from the parent cell body. Our recent studies have revealed that these dendrites in rat are organized into two prominent collections that project outside the nuclear core in the caudodorsal

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and rostroventromedial directions (5). This work has also demonstrated that these dendrites receive numerous synaptic contacts, indicating that the extranuclear peri-LC processes serve as a substantial receptive surface for LC neurons.

Afferents to the LC

Prior studies indicated that prominent afferents to the LC include the nucleus paragigantocellularis (PGi) and the ventromedial aspect of the prepositus hypoglossi (PrH) in the rostroventrolateral and dorsomedial medulla, respectively (6,7). These nuclei provide strong excitatory and inhibitory influences on LC neurons, respectively, and are also sources of several neurotransmitter inputs to the LC nucleus (see below) (4,8). However, as previously stated, LC dendrites that extend outside the LC nucleus proper provide a prominent receptive surface for inputs to LC neurons (5). Studies of inputs to these peri-LC dendritic zones indicate several additional possible strong inputs to LC neurons, including the periaqueductal gray, medial preoptic nucleus, prefrontal cortex, and hypothalamus (4,8). Recent work has confirmed some of the proposed inputs, showing direct contacts onto peri-LC dendrites from amygdala (9) and nucleus tractus solitarius (NTS) (10). Additional work is needed to test some of the other possible inputs to LC distal dendrites. These dendritic inputs are important in revealing additional functional circuitry linked to the LC system (e.g., limbic, autonomic, and cognitive functions).

A host of immunohistochemically defined fibers have been found in LC afferents (see ref. 4 for review). The sources of some of these inputs have been determined. Strong glutamate (11) and epinephrine inputs (12) originate in the PGi, γ-aminobutyric acid (GABA) inputs arise from the PrH (13), and strong enkephalin projections to the LC originate in both the PGi and the PrH (14). Histamine fibers innervate the LC, presumably originating in the tuberomammillary nucleus (15). A particularly dense innervation by serotonin fibers also exists; the origin of this projection has not been determined. Ultrastructural analyses have shown that several of these inputs directly innervate LC neurons (16–20).

Most recently, the novel neuropeptide hypocretin (synonymous with orexin) has been shown to innervate the LC densely in rats and monkeys (21–24) (Fig. 4.1). This projection presumably originates in the hypothalamus (the sole location of hypocretin-producing cells) and is mirrored by dense projections to other nuclei associated with sleep and arousal functions (e.g., the raphe serotonin neurons, tuberomammillary histamine cells, and cholinergic neurons of the brainstem). Initial studies of this peptide suggested a role in feeding (24,25). However, more recent work has stimulated considerable interest in this neurotransmitter by closely linking its function to sleep regulation. Specifically, mutations of the gene that makes a hypocretin receptor (26), or

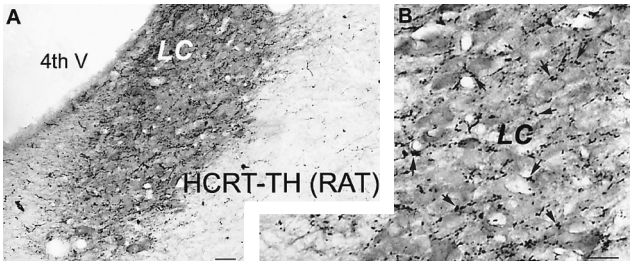

FIGURE 4.1. Photomicrograph showing dense innervation of the locus ceruleus (LC) by hypocretin/orexin Fibers. Low-power **(A)** and high-power **(B)** photographs of frontal sections through the rat LC after staining with antibodies for hypocretin and tyrosine hydroxylase (TH). Note the proximity of numerous black, punctate hypocretin fibers and brown TH-positive NE somata and dendrites. (From Horvath TL, Peyron C, Sabrina D, et al. Strong hypocretin (orexin) innervation of the locus coeruleus activates noradrenergic cells. *J Comp Neurol* 1999;415:145–159, with permission.) See color version of figure.

of another gene that makes hypocretin itself (27), produced narcolepsy symptoms in animals. This finding supports the long-standing belief that the LC system is important in sleep–waking processes (28) and indicates that sleep disorders may involve anomalies in this hypocretin projection to the LC. These findings also offer a novel target for pharmacologic manipulation of the LC and other systems involved in sleep function.

The functions of the different inputs to LC neurons or their dendrites are being revealed in behavioral and neurophysiologic studies. Stimulation of the PGi strongly excites LC neurons (11). The PGi has strong autonomic functions, an observation consistent with the marked parallel found between LC and sympathetic activities (29). These findings, together with the strong cortical projections of LC neurons, suggest that the LC acts as a cognitive component of a global sympathetic system (8). In contrast, strong inhibition is produced by PrH stimulation (13); the functional significance of this input is unclear. That inhibitory adrenergic input also arises from the PGi is revealed when the strong glutamate input is antagonized pharmacologically (30). Inputs to distal LC dendrites from the amygdala (9) or NTS (10) may convey limbic/emotional or autonomic information to the LC, respectively, although an influence of activity in these afferents on LC activity has not yet been found (8, 31). Our unpublished studies in monkey indicate that the anterior cingulate cortex strongly innervates the LC (32). Some of our other recent results suggest that this input may modulate the mode of LC activity and thereby its influence on cognitive performance (described below) (33). Finally, our recent studies using transsynaptic retrograde tracing reveal that the suprachiasmatic nucleus is a prominent indirect afferent to the LC (34–36). This is the first demonstration of a circuit that links the circadian suprachiasmatic nucleus mechanism with the arousal/alerting LC system. Inasmuch as other studies have linked circadian disturbances with

depression (37), and the LC system is also associated with depression and other mood disorders (38), this pathway may also be important for affective function.

Topography of LC Efferents

It is well-known that LC axons are highly branched and have extensive efferents that ramify throughout the central nervous system, providing NE innervation at all levels of the neuraxis (see ref. 4 for review). Previous studies have found topography among these efferent projections (39), but the degree of specificity for projections of different LC neurons appears to be quite limited. Recent studies by Simpson et al. (40) have revealed topography of a novel type. They report that LC neurons selectively collateralize to different nuclei of the somatosensory system, so that individual neurons are more likely to send branches to thalamic and cortical areas within the somatosensory system than to, e.g., a somatosensory thalamic nucleus and a visual cortical area. This "functional topography" for projections of individual LC neurons provides a new dimension for the anatomic organization of this ubiquitous brain system and may indicate a means for coordination or synchronization of NE release along relays in serial functional pathways.

A2 NE Neurons of the Caudal Medulla

Norepinephrine neurons in the A2 group (caudal NTS) have recently been implicated in behavioral functions of psychiatric importance. Previously relegated solely to autonomic and visceral control (e.g., see ref. 41), the strong ascending projections of these NE cells to forebrain areas such as the hypothalamus (42), bed nucleus of the stria terminalis (BNST) (43), nucleus accumbens (44), and amygdala (45,46) have now been shown also to be important in affective and cognitive processes (43,47). As described below, these findings identify new circuits for understanding affective and mnemonic functions.

NEUROPHYSIOLOGY

Several recent findings regarding the neurophysiology of LC neurons have extended our understanding of this system. Notably, integration of studies at the cellular and behavioral levels indicates a potentially important role of coupling among LC neurons.

Electrotonic Coupling

Experiments by Christie and Williams and colleagues (48–50) showed that LC neurons may be regulated by electrotonic coupling, not only during development but also in adults. Additional studies by these workers indicate that such coupling may be modulated by inputs to LC neurons that alter cAMP (51). This is significant because electrotonic coupling allows rapid, powerful cell-to-cell communication (electrically and biochemically) via large transmembrane channels between neurons (called *gap junctions*). Once relegated to the domain of the esoteric but unimportant, electrotonic coupling is now being demonstrated in an increasing number of central neurons. Of great interest is the fact that such coupling is readily modulated by other inputs to coupled cells—for example, in the retina, coupling is strongly attenuated by dopamine inputs in a cAMP/protein kinase A manner. This line of work is very promising in neuropsychopharmacology because it suggests a novel set of targets (receptors that regulate electrotonic coupling) that could be used to develop new drugs to modulate the function of systems important in mental function and dysfunction (such as the LC). Our recent work (described below) shows how modulation of such coupling can have profound influences on behavior and cognitive performance (33). It is noteworthy that electrotonic coupling has been reported among striatal neurons in a dopamine-modulated manner (see Chapter 9, *this volume*), as well as among interneurons in the cerebral cortex (52,53).

LC Activity, Electrotonic Coupling, and Cognitive Performance in Behaving Monkeys

A possible role for electrotonic coupling among LC neurons in cognitive performance was revealed by combining our recordings of LC neurons in monkeys performing a signal detection task with neural network modeling (33). In these recordings, LC neurons exhibited two modes of activity during task performance: a phasic mode, in which LC cells responded phasically to target stimuli, and a tonic mode, in which the tonic baseline activity of LC neurons was high but responses to target cues were absent. Moreover, the phasic mode corresponded closely to focused attention and good task performance, whereas the tonic mode was associated with scanning attentiveness and poor performance in this task, which requires focused attention. Task performance could be improved by systemic or local (intra-LC) injection of clonidine during poor performance, which indicates a causal influence of these patterns of LC activity on performance. A neural network model was constructed to investigate mechanisms involved in generating these modes of LC activity and the corresponding task performance. Space limitations prohibit a full discussion of the findings, which are reported and reviewed in recent publications (33, 54). In brief, the model showed that modulated electrotonic coupling among LC neurons could produce the patterns of LC firing observed in the monkeys, and that known modulatory effects of NE could then translate these modes of LC activity into corresponding levels of task performance, also observed in the monkeys (Figs. 4.2 and 4.3). These findings have a number of implications for neuropsycho-

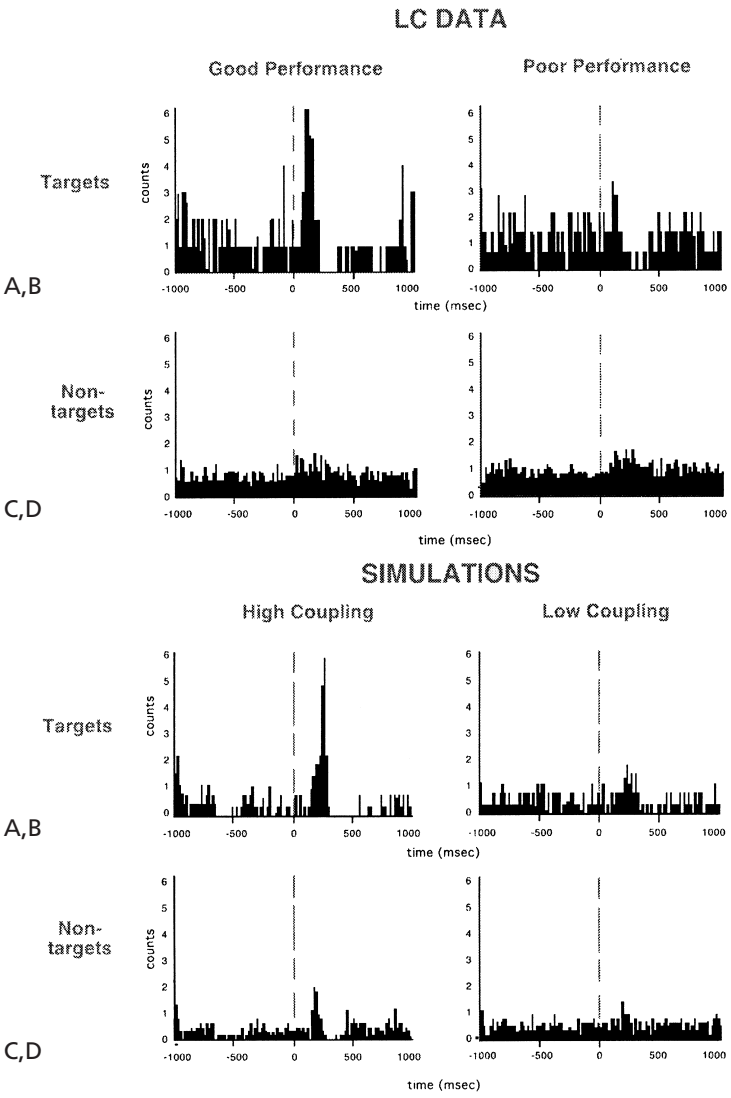

FIGURE 4.2. Simulation of locus ceruleus (LC) activity by modulated electrotonic coupling. **Upper:** Post-stimulus time histograms (PSTHs) for LC activity during the visual discrimination task. **A,B:** Response for targets. **C,D:** Response for distractors. **A,C:** Periods of good performance (phasic LC mode). **B,D:** Poor behavioral performance (false alarm rate typically > 7%; tonic LC mode). Stimuli occur at time zero. All histograms are normalized to a standard of 100 trials. Note that the phasic LC mode is found during periods of good performance, and that the tonic mode corresponds to poor performance on this task. Bin width, 10 ms. **Lower:** Simulation of LC responses. **A,B:** Response to targets. **C,D:** Response to distractors. **A,C:** Coupling among LC neurons. **B,D:** No coupling among LC neurons. These simulation PSTHs are normalized for 100 trials, as for the empiric data. Note that coupling reduces tonic (baseline) LC activity but increases phasic (transient) response to target stimuli, capturing the phasic mode of LC neurons in our recordings. See Fig. 4.3 for corresponding behavioral simulation results. (From Usher M, Cohen JD, Rajkowski J, et al. The role of locus coeruleus in the regulation of cognitive performance. *Science* 1999;283:549–554, with permission.)

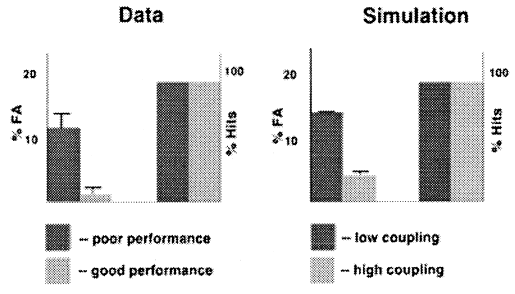

FIGURE 4.3. Simulation of behavioral performance by modulated coupling among locus ceruleus (LC) neurons. **Left:** Graphs showing higher rate of false alarm errors (% FA) during epochs of poor versus good performance by monkeys in the visual discrimination task (33). No differences were noted in the percentage of hit responses during the various levels of performance, as misses were rare. **Right:** Graphs showing higher % FA in the simulated data from our model (33) during epochs of low versus high coupling among LC neurons. Note similarity to empiric data at left. See Fig. 4.2 and ref. 33 for further details.

pharmacology. First, they support the view that the LC has an important role in attentional processes, and that pathology in LC function could contribute to mental disorders with attentional components [e.g., attention-deficit/hyperactivity disorder (ADHD), stress disorders, schizophrenia]. These results also indicate that alterations in coupling among widely projecting neurons can have profound mental and behavioral consequences, offering a new dimension for analyzing the function of highly divergent modulatory brain systems. Finally, these results, in view of other findings that electrotonic coupling can be rapidly modulated by neurotransmitter inputs (55), indicate that coupling may be a valuable new target for pharmaceutical development in neuropsychopharmacology.

Opiate Withdrawal

A long series of studies has implicated the LC system in opiate withdrawal (see ref. 56 for review). Recent work has

shed light on molecular and cellular changes that occur in LC neurons during long-term opiate exposure that may underlie their strong activation during withdrawal (reviewed above). It is generally acknowledged that the bulk of this hyperactive LC response is mediated by glutamate inputs from the PGi (11,57,58). However, a possible intrinsic source of withdrawal-induced hyperactivity in LC neurons has been somewhat controversial. Although some studies find no evidence for withdrawal-induced activation of LC neurons in slices taken from morphine-dependent rats (59, 60), others have presented evidence for such intrinsically mediated withdrawal responses in LC (61–64). Our study of local intra-LC microinfusion of opiate antagonists in morphine-dependent rats has confirmed the likelihood that intrinsic changes with dependence contribute to the hyperactivity of these neurons during withdrawal (65). Different studies have suggested different mechanisms for this locally mediated withdrawal effect. Lane-Ladd et al. (62) and Nestler and Aghajanian (66) have presented evidence from slice experiments consistent with the possibility that long-term morphine exposure causes a sustained increase in a tetrodotoxin-insensitive Na^+ current, linked to the increase in cAMP, adenylate cyclase activity, and cAMP response element-binding protein (CREB) that occurs in the LC during withdrawal. In their view, this inward current causes LC hyperactivity when the inhibitory influence of morphine is removed during withdrawal. Our recent *in vitro* studies suggest a different mechanism. These results indicate that long-term opiate administration produces a decrease in K^+ conductance in LC cells that leads to a state of increased excitability when the inhibitory influence of morphine is removed during withdrawal (63,64). The decreased K^+ conductance during long-term morphine administration may be a direct compensatory response to the increased K^+ conductance evoked by acute opiates (49). In either case, it seems clear that the local component of withdrawal-induced activation of LC neurons is small compared with the strong excitation evoked by the increased glutamate input from the PGi (see above).

Hypocretin/Orexin

As discussed above, the hypothalamic neuropeptide hypocretin, which is strongly implicated in sleep regulation, densely innervates the LC in rat and monkey (21). Recent studies have revealed that this peptide activates LC neurons both *in vitro* (21,67) and *in vivo* (68). The activation is associated with a mild depolarization but is independent of tetrodotoxin and Ca^{2+} (67). The results have led to the tentative conclusion that hypocretin activates LC neurons by decreasing a resting potassium conductance (67). Overall, the results are important because they indicate a possible pathway and transmitter mechanism by which the LC becomes activated during arousal from sleep, which may in turn help to drive a sleep-to-waking transition. This pathway could be involved also in the psychiatric disorders associated with sleep dysfunction (e.g., depression, stress disorders, ADHD).

Cortical Influences on LC Activity

Tract-tracing studies have revealed that the prefrontal cortex may directly innervate LC neurons. Our retrograde and anterograde studies in rat find a projection from the medial prefrontal cortex to the extranuclear peri-LC dendritic zone (69). Another of our studies confirms a projection from the cingulate cortex to the LC in the monkey (32). In line with these findings, additional experiments have revealed prominent effects of cortical stimulation on LC activity. As shown in Fig. 4.4, we found that electric stimulation of the medial prefrontal cortex in rats activates LC neurons; similar results were obtained with chemical stimulation (70). We also found this activation to be mediated by glutamate release within the LC, as would be expected for a direct cortical (presumably glutamatergic) input (71). In contrast, Sara and Herve-Minvielle (72) reported that medial prefrontal stimulation in rats results in inhibition of LC activity. Procedural differences may underlie the different results. In particular, the study by Sara and Herve-Minvielle used ketamine anesthesia, a potent glutamate antagonist. Thus, the results may indicate an underlying inhibitory effect of prefrontal activation on LC activity when the more potent glutamate-mediated excitation is antagonized. In any case, the results reveal that the prefrontal cortex can strongly influence activity of LC neurons.

Postsynaptic Actions of NE

The proposed role of the NE–LC system in arousal was confirmed by Berridge and Foote (73), who showed that local activation of LC neurons by microinjection of bethanechol produces EEG activation in the halothane-anesthetized rat. Similar studies demonstrated that LC inactivation by local microinfusion of clonidine decreases EEG arousal (74). Additional experiments revealed that the arousing effects of LC stimulation are mimicked by stimulation of β adrenoceptors within the medial septum and are blocked by β-receptor antagonists infused into this area (75). Continuing studies along these lines confirmed that local LC stimulation in waking animals increases EEG and behavioral indices of arousal (76). Additional studies found, however, that septal infusion of β antagonists in unanesthetized animals does not decrease arousal (77). Thus, in the waking rat, actions at other NE or non-NE receptors may also be necessary for arousal. Together, these studies indicate that LC activity is an important regulator of EEG arousal, and that these effects are mediated, at least in part, by β receptors in the medial septum area. Additional studies are needed to determine the precise location of these actions and what other systems and receptors may be important for maintaining the alert state.

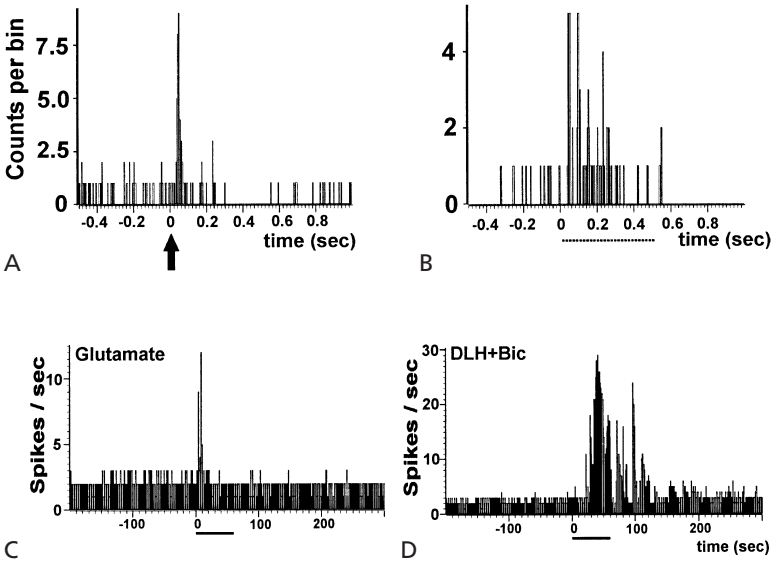

FIGURE 4.4. Activation of locus ceruleus (LC) neuron by stimulation of medial prefrontal cortex (PFC) in rat. **A:** Cumulative post-stimulus time histogram (PSTH) for single-pulse electric stimulation of the PFC. Stimulation presented at *arrow.* **B:** PSTH for train stimulation (20 Hz for 0.5 s) given during the epoch designated by *small dots.* Bin width in each PSTH, 5 ms. **C:** Response of an LC cell to stimulation of PFC with 100-mM glutamate (at *bar* below). **D:** Response of an LC neuron to stimulation of PFC with 10-mM D,L-homocysteic acid plus 50-μM bicuculline (DLH + bic; 60-nL injection). (From Jodo E, Chiang C, Aston-Jones G. Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons. *Neuroscience* 1998;83:63–80, with permission.)

Studies in intact animals have shown that β-receptor activation from the LC can induce plasticity in hippocampal responses. Chaulk and Harley (78) found that *in vivo* or *in vitro* administration of β- or α-receptor agonists significantly potentiates the population spike amplitude recorded in the dentate gyrus in response to perforant path stimulation. Because the LC is the sole source of NE in the hippocampus, these findings confirm previous results that LC stimulation also potentiates such dentate gyrus responses (79,80). These results indicate a role for NE from the LC in plasticity in hippocampal activity, and may provide evidence for a role of this system in memory consolidation (described below).

BEHAVIOR

Opiate Withdrawal and the LC

Several recent studies in which behavioral pharmacologic techniques were used have reexamined the role of the LC system in opiate withdrawal and abuse. The results of lesion studies by Chieng and Christie (81), Caille et al. (82), and Delfs et al. (43), in which different methods and approaches were used, all agree that the LC system is not necessary for physical signs of morphine withdrawal (Fig. 4.4). This finding contrasts with previous ideas and represents a significantly changed view of the role of the LC system in withdrawal. Although some studies involving microinjection of agents that alter LC activity (83) or molecular events within LC neurons (62,84) implicate the LC in withdrawal responses, their results must be viewed with caution because diffusion of injected substances from the small LC nucleus to adjacent areas that have been implicated in withdrawal, such as the periacqueductal gray (85), difficult to rule out. Further studies are needed to determine the behavioral consequences of LC hyperactivity during opiate withdrawal.

Critical Role of A2 NE Neurons Innervating the BNST in Aversion Induced by Opiate Withdrawal

Our recent work has demonstrated that NE innervation of the BNST from A2 noradrenergic neurons is critical for affective responses to opiate withdrawal (43,86). We demonstrated that antagonists of β receptors injected into the BNST, or lesions of the ventral NE bundle that carries fibers from the A2 group to the BNST, eliminate aversive responses to withdrawal (Fig. 4.5). Interestingly, these same manipulations had almost no effect on the physical withdrawal response. These findings, and other results showing that aversive responses to withdrawal can occur in the absence of somatic responses (87,88), indicate that withdrawal aversion is not simply a consequence of physical symptoms, and that separate pathways are involved in physical and affective withdrawal responses (Figs. 4.5 and 4.6). This is important for neuropsychopharmacology because the affective response during withdrawal is the most potent motivator of further drug seeking (89). Thus, studies to develop pharmacotherapies for opiate abuse should focus on aversive withdrawal responses specifically, rather than examining only physical signs. Lesions of the LC system had no effect on aversive or physical signs of withdrawal, findings that corresponded to other recent results (discussed above).

Memory and the LC

Recent studies by Clayton and Williams (90) have indicated new evidence for involvement of the NE–LC system in memory. Inactivation of the PGi (a major input to the LC, described above) with either lidocaine or the GABA agonist muscimol immediately after acquisition in a one-trial inhibitory avoidance task produced marked deficits on a retention test given 48 hours later. Conversely, chemical stimulation

of the PGi with glutamate following training in either an inhibitory avoidance or spatial delayed matching to sample radial maze task enhanced retention performance when assessed 48 or 18 hours later, respectively (91). Given the excitatory connections between PGi and LC, these findings suggest that pharmacologic manipulation of PGi neuronal activity may affect memory formation via influences on LC and subsequent NE release in brain systems involved in the encoding of new information.

Recent studies by Przybyslawski et al. (92) have also indicated a role for the LC–NE system in memory. These experiments indicate that memories are normally reconsolidated each time they are reactivated by relevant cues. They found that blockade of β adrenoceptors after memory reactivation, during the consolidation process, produced impairment on future tests of the same memory. These results indicate that reactivation of memory produces a β receptor-dependent intracellular cascade that reenacts the consolidation process

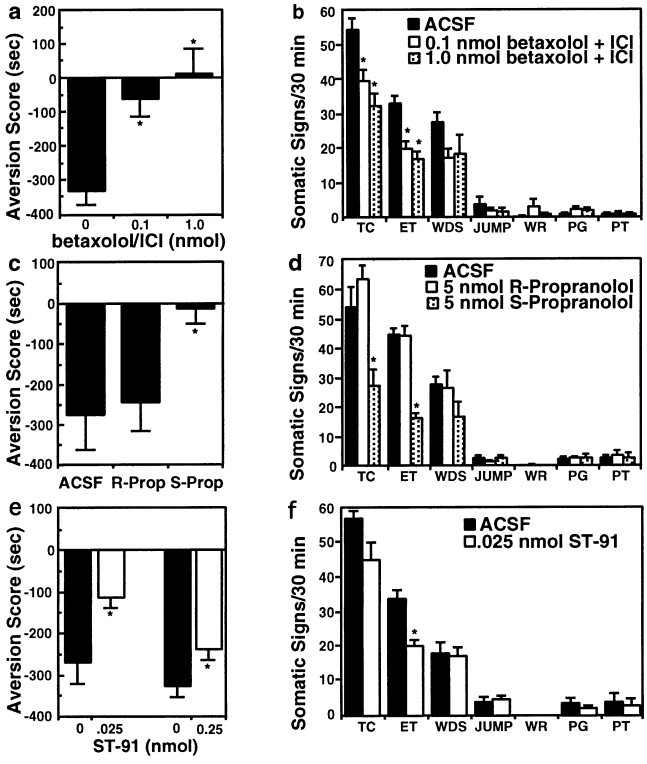

FIGURE 4.5. Effects of intra-BNST (bed nucleus of the stria terminalis) injection of noradrenergic drugs on conditioned place aversion and somatic signs of opiate withdrawal. **A–D:** Effects of the β-antagonist cocktail betaxolol/ICI 118,551 (A,B) or propranolol isomers (C,D) on place aversion and somatic signs. **E,F:** Effects of ST-91 on place aversion and somatic signs. TC, teeth chatter; ET, eye twitch; WDS, wet dog shakes; JUMP, jumping; WR, writhing; PG, penile grooming; PT, paw tremor. All data are expressed as mean ± standard error of the mean (n = 6 to 8 animals per dose). For A–D, $p < .05$, analysis of variance followed by Fisher's PLSD test for multiple comparisons. For E,F, $p < .05$, Student's t-test. (From Delfs J, Zhu Y, Druhan J, et al. Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. *Nature* 2000;403:430–434, with permission.)

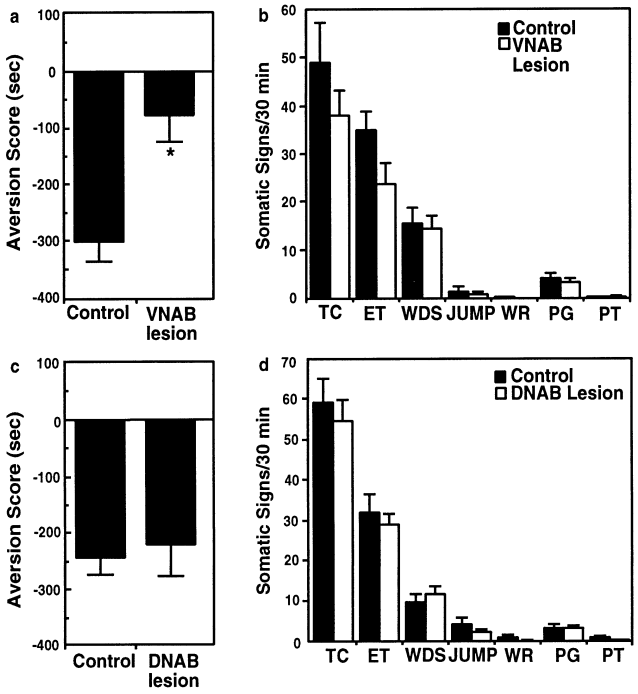

FIGURE 4.6. Effects of dorsal (DNAB) and ventral (VNAB) noradrenergic bundle lesions on aversive and somatic signs of opiate withdrawal. **A,C:** Aversion scores. Aversion score equals time in the naltrexone-paired side on the test day minus the preconditioning day. **B,D:** Number of somatic counts in 30 minutes. See Fig. 4.5 legend for details and abbreviations. Nondependent lesioned animals exhibited neither aversion nor somatic signs following naltrexone (data not shown). All data are mean ± standard error of the mean (n = 6 to 8 control, 10 to 11 lesioned animals per group). $p < .05$, analysis of variance followed by Fisher's PLSD test for multiple comparisons. (From Delfs J, Zhu Y, Druhan J, et al. Noradrenaline in the ventral forebrain is critical for opiate withdrawal-induced aversion. *Nature* 2000;403:430–434, with permission.)

responsible for the initial memory acquisition. This NE-dependent lability of active memory traces indicates a novel mechanism to target in pharmacologic manipulation of memory-related disorders, such as posttraumatic stress disorder and Alzheimer's disease.

Studies by Mao et al. (93) have found a role for α_1 and α_2 NE receptors in the dorsolateral prefrontal cortex in memory. Infusion of α_1 agonists into the monkey prefrontal cortex produced deficits in working memory (93), whereas similar treatments with α_2 agonists improved memory performance (94).

Memory and the A2 NE System

Studies by McGaugh (95) during the last several years have established a role for NE stimulation of β receptors in the amygdala in the strong memories that are established for emotionally salient events. Recently, this line of work has shown that the NTS is involved in this process, as lidocaine anesthesia of the NTS prevents the memory-enhancing effects of peripheral epinephrine (47). Because the A2 neurons

of the NTS strongly innervate the amygdala, this finding indicates that the A2 neurons may be importantly involved in memory modulation. These studies suggest that a ''central nervous system–periphery–central nervous system long-loop'' circuit may be involved, in which descending activity in response to emotional events produces a peripheral response (e.g., epinephrine release); this response in turn stimulates receptors on vagal afferents that then stimulate the NTS to release NE in its hypothalamic and forebrain targets. This possible route for enhancement of emotional memories and other cognitive processes has received little attention previously. Such a loop may also be involved in the activation of A2 neurons during opiate withdrawal that leads to the corresponding aversive response (described above) (43). This is potentially important clinically and psychopharmacologically because peripheral receptors on visceral afferent fibers that may be involved in mental disorders represent a novel mechanism and target for new pharmacotherapies.

PSYCHOPATHOLOGY

Depression

Recent work by Miller et al. (96) has increased our understanding of the role of NE systems in depression. In their studies, reduction of NE metabolites (presumably reflecting decreased NE turnover) after treatment with α-methyl-*p*-tyrosine (AMPT) caused no change in scores on the Hamilton Depression Rating Scale in normal human subjects. In contrast, AMPT administration and reductions in NE turnover in patients in remission from depression after treatment with desipramine or mazindol significantly increased the Hamilton Depression Rating Scale measures of depressive symptoms (97). This change was not seen in patients under treatment with serotonin antidepressants (fluoxetine or sertraline). The results indicate that monoamine deficiency alone may not produce depressive symptoms, but that different types of depression exist that respond to manipulations of different monoamine systems.

Advances in understanding the actions of antidepressant drugs have highlighted the possible role of NE systems in depression. New drugs such as venlafaxine, which inhibits reuptake of both serotonin and NE, have been found to be effective, particularly in refractory depression (98). In addition, the highly effective antidepressant paroxetine, which was previously thought to act selectively to block serotonin reuptake, has recently been found also to inhibit NE reuptake (99,100). These findings confirm long-held beliefs that NE is importantly involved in depression, and indicate that blockers of NE uptake, including drugs that selectively act at the NE transporter, such as reboxetine (101,102), may be effective in treating at least certain types of affective illness (103).

Anxiety

Brain NE has long been implicated in anxiety disorders (104). Our studies with cocaine- and morphine-dependent animals have provided new evidence for a role of central NE systems in anxiety. By means of a place-conditioning paradigm, we found that withdrawal from long-term administration of morphine or cocaine is associated with strong anxiety, measured by the conditioned burying paradigm (105). Importantly, the anxiogenic response to drug withdrawal is strongly attenuated by administration of the β-receptor antagonist propranolol, and by similar doses of the lipophobic β_1 antagonist atenolol, which is believed to act primarily peripherally. These findings indicate that at least some types of anxiety involve stimulation of peripheral β adrenoceptors.

ADHD

The firing patterns of LC neurons in behaving monkeys indicate that this system plays an important role in attention and performance (reviewed above) (33,54,106). In particular, one mode of LC activity, characterized by elevated tonic discharge, corresponds to poor performance on a continuous performance task that requires focused attention, with a high rate of false alarm errors. These and other results have led us to propose that this tonic mode of LC activity promotes high behavioral flexibility and disables focused or selective attention (33,54). This view also implies that attentional disorders may be associated with LC dysregulation in which the proper mode of activity is not engaged adaptively for the context at hand. Specifically, several parallels have been noted between behaviors in monkeys during the tonic mode of LC activity and symptoms of ADHD, including hypervigilance, irritability, poor focused attentiveness, and a high false alarm rate in continuous performance tasks. These findings indicate that the LC may play an important role in ADHD, and that drugs that modulate LC mode, or switching between modes, may be helpful in treating this disorder. In fact, many of the stimulants that are effective in treating ADHD decrease tonic LC activity.

A role for the LC–NE system in attentional disorders is also indicated by behavioral pharmacology experiments by Arnsten and colleagues (107). These investigators have found that overstimulation of α_1 receptors in the prefrontal cortex produces deficits in behaviors that depend on prefrontal function (107). Because ADHD includes symptoms of prefrontal dysfunction, these findings raise the possibility that an overactive LC system may contribute to ADHD by overstimulation of α_1 receptors in prefrontal areas (108).

CONCLUSIONS

An impressive amount of research on NE systems has been performed since the previous edition of this volume was

published. This work is revealing an increasingly important role for brain NE in mental function and dysfunction. Mechanisms by which NE systems are involved in cognitive, addictive, stress-related, and other behavioral functions are being elucidated. This progress not only reinforces the importance of this system for neuropsychopharmacology, but also indicates that NE systems represent a promising area for discovering new and fruitful approaches to developing treatments for psychiatric disorders.

ACKNOWLEDGMENTS

This work was supported by PHS grants NS24698, DA06214, DA10088, MH55309, and MH59978. Comments on the manuscript by Drs. Glenda Harris and Jon Druhan are greatly appreciated.

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