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Review

Peripheral, autonomic regulation of locus coeruleus noradrenergic neurons in brain: putative implications for psychiatry and psychopharmacology

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Abstract. In 1946 von Euler identified the major transmitter of sympathetic nerve fibers, norepinephrine (NE), and about a decade later Vogt (1954) provided the first evidence that NE may also serve as a neurotransmitter in the central nervous system (CNS). Since that time, a literal explosion in CNS neurotransmitter research has taken place involving histological, biochemical, physiological, pharmacological and clinical investigations, Yet, it is only now that we are beginning to understand the biological function of NE in brain, in particular because of recent advances regarding the physiology and regulation of NE neurons in locus coeruleus (LC), a bilateral pontine structure with a uniquely wide-spread terminal network reaching throughout the neuroaxis and in primates accounting for about 70% of all brain NE. Recently, the neurobiology of the LC noradrenergic network was extensively reviewed by Foote et al. (1983), and its implication in vigilance as well as global orientation of behavior towards imperative, environmental sensory stimuli was outlined. Yet, more recent information regarding the peripheral, autonomic regulation of LC neurons in brain provides fundamentally new biological aspects on behavior and mental function which seem to allow a more integrated view of the rôle of brain NE in the overall function of the individual than previously understood. The purpose of this review is to summarize these findings and, furthermore, to outline some putative implications for psychiatry and neuropsychopharmacology. In particular, the new data seem to allow a better understanding of how autonomic vulnerability or visceral dysfunction may precipitate or aggravate mental symptoms and disorder.

Key words: Locus coeruleus – Physiology – Psychiatry – Psychopharmacology

Early pharmacological experiments suggested that brain NE may generally be implicated in the control of alertness and exploratory responses to novel, environmental stimuli (cf. Svensson and Waldeck 1969; Fuxe et al. 1970). Yet, it was not until recently that direct recordings from brain NE neurons in the LC of awake animals produced more substantial, physiological information about their behavioral function. Such experiments, as initially reported by Foote and Bloom (1979) and later very elegantly extended (Foote et al. 1980; Aston-Jones and Bloom 1981; for review see Foote et al. 1983), revealed a number of interesting findings. Generally, the LC activity was found to correlate with vigilance and the neurons showed phasic activation responses to a number of environmental, sensory stimuli, particularly if associated with novelty or fear. In contrast, a low LC activity was observed in association with behaviors such as sleep, grooming or sweet water consumption. The hypothesis was advanced that such low LC activity might be a prerequisite for tonic vegetative functions and that vigourous LC discharge, as elicited by external, environmental stimuli, would disrupt such vegetative functions by means of enhancing signals in brain systems engaged by the external stimuli and, at the same time, suppressing CNS signals in other brain systems engaged by the tonic vegetative functions. In other words, a behaviorally significant, sensory biasing function for the LC was proposed, which for obvious reasons should be of importance for the discriminative capacity of the individual, particularly under stressful conditions (cf. also Bloom 1979). The abundant physiological information as regards the influence of LC NE neurons on CNS target sites also seems consonant with a behavioral function of the LC to enhance the reliability and efficiency of feature extraction from sensory inputs, i.e., to bias the global orientation of behavior towards imperative stimuli in the external environment (cf. Foote et al. 1975; Segal and Bloom 1976; Freedman et al. 1977; Moises et al. 1979; Waterhouse and Woodward 1980; Rogawski and Aghajanian 1980; for review see Foote et al. 1983). In accordance with this behavioral function of the LC neurons, activation of the LC has been found associated with fear and alarm reactions in monkeys (Redmond et al. 1976). Moreover, following bilateral lesions of the LC animals failed to show normal cardioaccelerator responses to threatening stimuli as well as associated behavioral fear responses (Snyder et al. 1977; see Redmond 1977). In general, the LC projects to many regions of the brain associated with responses to pain and fear, and also the cerebral cortex which might be involved in the interpretation of the "meaning" or relevance of a stimulus as well as its cognitive aspects. It also projects to limbic areas such as the amygdala, i.e., brain regions of importance for emotional and cardiovascular control.

Interestingly, very similar reactions of peripheral, sympathetic nerves have long been known to occur in response to external, sensory stimuli of salient nature, particularly in association with the so-called defense reaction (cf. Folkow 1984). This reaction, which perhaps is the best charac-

terized emotional and behavioral response pattern influencing blood pressure control, is elicited by external, sensory stimuli, particularly when of threatening character. In principle, any interesting or novel environmental stimulus will elicit minor reactions of this type (Folkow 1984). The defense reaction, originally described by Hess in Munich in the early 1940s, can be elicited from stimulation of hypothalamic sites as well as, for example, the amygdala and serves to mobilize the individual for fight or flight or, better, to cope with the environmental stimulus and involves, apart from the vigilance reaction, a neurogenic activation of sympathetic fibers to the heart, splanchnic region and kidneys, central suppression of the vagal restraint of the heart and an ensuing blood pressure elevation, mainly caused by the increased cardiac output. The sympathetic activation to the kidneys is associated with increased renin release and the renin-aldosterone axis as well as glucocorticoids are subsequently mobilized. In short, this is the most classical, initial sympathoadrenal stress reaction. From all we know, the LC responds by activation to the same triggering, environmental stimuli and, as mentioned above, the fear response as well as the cardiovascular core of the defense reaction, the tachycardia in association with a threatening stimulus, seems abolished by LC lesions. Thus, from a physiological standpoint it appears quite clear that the defense reaction, as elicited by salient environmental stimuli, involves initially not only activation of peripheral noradrenergic, sympathetic nerves but also concomitant activation of the major central noradrenergic LC system and, moreover, under physiological conditions the LC appears critical in this reaction.

Apart from sensory, environmental stimuli, we know a number of other stimuli for sympathetic activation. Thus already in 1929, Cannon mentioned pain, a sudden drop in blood pressure, hemorrhage and hypercapnia as well as hypoxia. Following von Euler's identification of the transmitter of sympathetic fibers, NE, an increased peripheral release of catecholamines was subsequently demonstrated in association with these stimuli as well as anxiety or apprehension reactions. Thus, physiological and biochemical evidence shows that somatosensory and internal, autonomic stimuli have a profound influence on the activity of sympathetic noradrenergic fibers. What is then the effect of such stimuli on the activity of brain NE neurons such as those in the LC? Recently we have in a series of experiments addressed this question with a quite remarkable result. This large central NE system, for decades thought to be involved in behavioral and mental function, was indeed found to be controlled by very similar, peripheral autonomic regulatory mechanisms as those controlling sympathetic nerve fibers.

These findings will here be reviewed against the above background, with some putative implications for psychiatry and psychopharmacology.

Somatosensory and peripheral cardiovascular regulation of the LC

About a decade ago Korf et al. (1974) observed that a painful, cutaneous noxious stimulus causes immediate activation of LC neurons in brain followed by a quiescent interval. In our recent studies we have observed that in this regard the LC and a major division of the peripheral, sympathetic nervous system, the splanchnic nerves, respond in a virtually identical fashion (Elam et al. 1986a). In fact, a literally parallel activation of LC neurons and splanchnic, sympathetic nerves is produced by noxious stimuli and, moreover, cutaneous sensory stimuli of both noxious and non-noxious, thermal character were found to activate both the central and the peripheral noradrenergic systems simultaneously (Elam et al. 1986a).

The LC activity was (like sympathetic, splanchnic activity) also found to be highly responsive to various peripheral, cardiovascular events (Svensson and Thorén 1979; Elam et al. 1984, 1985), such as alterations in blood volume or blood pressure (for example an acute reduction in blood pressure). Whereas the sympathetic responses were found to be elicited from both arterial baroreceptors and cardiac volume receptors, the LC responses to peripheral cardiovascular stimuli were found to be exclusively mediated via vagal afferent nerves from the cardiopulmonary region. Moreover chemoreceptor activation by means of experimentally-induced acute hypercapnia was found associated with concomitant and essentially parallel activation of sympathetic, splanchnic nerves and LC neurons in brain (Elam et al. 1981). In addition, hypoxia was, in principle, found to cause similar reactions, although this condition represents a physiologically very complicated situation. In short, the LC was found to be controlled by cardiovascular afferent, regulatory mechanisms. Since anesthesia, as used in our experiments, if anything would be expected to blunt such physiological reflexes, the reactions of LC neurons in awake animals to cardiovascular events might be even more pronounced as well as more dynamic in character. In fact, subsequent experiments in cats confirm the responsiveness of the LC to cardiovascular stimuli in unanesthetized animals also (see Jacobs 1986). The high sensitivity of the reciprocal LC responses to even very small changes in blood volume thus indicates that they are likely to occur under physiological conditions such as, moderate hemorrhage or changes in posture. The redistribution of blood associated with a reclining position may thus turn off the LC by means of its afferent, cardiac vagal input.

Although the LC system was found very responsive to both somatosensory stimuli and various cardiovascular events, our studies revealed a certain discriminatory capacity of the LC in its monitoring of these stimuli. Thus, internal events of obviously salient nature for survival, such as blood loss, an increase in pCO_2 or a marked reduction in blood pressure, caused marked and long-lasting increases in LC activity, whereas a noxious, somatosensory stimulus or a moderate increase in blood pressure showed only transient responses of LC neurons. Generally, it follows from our results, that the LC cannot be considered as a specific nociceptive nucleus in brain (Elam et al. 1986a) or, for that matter, a specific center for blood pressure control (Elam et al. 1985) regulating sympathetic nerve activity. Yet, the profound vagal afferent input to the LC, monitoring the peripheral cardiovascular state is indeed of interest in relation to behavior, given the previous information in this regard (cf. introduction). The obvious implication is that peripheral autonomic events or dysfunction may, via the LC system in brain, affect behavior and the mental state. This hypothesis seems somewhat born out by experimental evidence. Thus we have found that an entirely peripherally elicited, cardiovascular event, blood volume load, is associated not only with LC inhibition in brain but also with reduced NE metabolism in brain regions directly innervated by the LC as well as reduced exploratory behavior in a novel environment (Persson and Svensson 1981).

Visceral influence on the LC

In our most recent experiments other peripheral visceral stimuli for the control of the LC were also identified (Elam et al. 1986b). Thus, it was shown that distension of the urinary bladder, distal colon or rectum as well as a rapid distension of the stomach produce LC activation in the rat brain. The progressive and marked activation of the LC in association with, e.g., progressive filling of the urinary bladder within a physiological range, is in all probability mediated by activation of mechanoreceptors in the walls or mesentery of the organ, and the LC responses were clearly more pronounced than those of the peripheral, splanchnic nerves. In addition, the LC activation disappeared in direct association with emptying of the urinary bladder. Generally, our findings in conjunction with other data implicate the LC in the overall physiology of micturition (for detailed discussion see Elam et al. 1986b), and obviously the robust LC discharge may serve to alert the individual to a significant event in the internal environment. Our findings make it very likely that spontaneous and intense contractions of the distal colon are, indeed, associated with LC activation in brain and the LC responses to internal visceral events cannot be ascribed to noxious stimulation but must be assumed also to occur under physiological conditions (Elam et al. 1986b).

Thus, the LC monitors not only the peripheral cardiovascular state but also quite closely the internal visceral state, and particularly vegetative stimuli of salient nature such as, for example, distension of the urinary bladder. Generally, it was hypothesized that a high LC activity might be facilitatory to phasic vegetative functions such as micturition or defecation (Elam et al. 1986b) in the sense of enhancing signals in brain systems engaged by the phasic vegetative stimulus and, at the same time, suppressing signals in other brain areas engaged by, for example, tonic vegetative functions in analogy with previous hypotheses as regards external, environmental salient stimuli and LC function (cf. introduction). At any rate, it seems very clear that the visceral state just like the cardiac state inter alia by means of the LC network in brain will influence behavioral functions, such as responses to a novel, external environment, since this large central NE system responds to important stimuli both from the external and the internal environment of the animals. Thus, a biologically integrative function of the LC system in brain and in the animal must be assumed.

Physiological, integrative aspects on brain NE-LC neurons

The physiological findings mentioned put the largest brain NE system, for decades thought to be involved in behavioral and mental functions, in a new and very interesting biological perspective, 30 years after Marthe Vogt's original discovery of NE of brain. The previous behavioral evidence thus indicates that this central neurotransmitter system responds to external, sensory stimuli to provide an accurate accommodation of the individual with the external environment. The new data suggest a very similar function as to accommodation with the internal, vegetative environment. Thus, this large central NE network may determine whether the individual turns the attention to external, sensory stimuli or to internal vegetative events, particularly as regards stimuli of a salient nature, whether external or internal. Such a biological, integrative system thus ultimately subserves the function of alerting the individual to stimuli of importance for survival. It is within this context of considerable interest both from a physiological and psychiatric standpoint that some of our findings (Persson and Svensson 1981) indicate that cardiovascular stimuli from the internal environment seem to predominate over external, environmental stimuli as regards the global orientation of behavior.

It can be argued that major questions as regards the putative functional subdivision of the LC remain to be elucidated. Yet, in most of the studies referred to here the LC appeared to respond as a rather homogenous ensemble of neurons and robust discharge was generally seen. The associated beochemical changes in NE turnover in major brain areas innervated by the LC in conjunction with cardiovascular afferent inhibition of the LC by means of blood volume load (Persson and Svensson 1981) further support this contention.

The dual sets of environmental stimuli, external and internal vegetative, feeding into the same noradrenergic LC network in brain thus present some very intriguing aspects on behavior as well as the mental state. Several putative implications for psychiatry, as well as cardiovascular disorders and stress-related, psychosomatic disease in general, appear quite reasonable to discuss in view of this new information, since external, environmental stimuli will be processed by means of the LC noradrenergic network in brain against a background of vegetative monitoring by the same central neurotransmitter system. Moreover, some internal stimuli, such as internal bleeding, may cause LC activation and ensuing vigilance or alarm reactions without reaching a cognitive level of understanding, either for the individual or for his environment. Yet, such vegetative stimuli may still interfere with the purported behavioral function of the LC of adequate feature extraction from the external environment (Foote et al. 1983). It remains to be established whether the vegetative LC-regulatory mechanisms found in rodents and subsequently in behaving cats (see Jacobs 1986) are also operating in primates and man. However, given the phylogenetically ancient systems and mechanisms involved and the similarities between rats and monkeys as regards the LC (see Foote et al. 1983), this appears very likely. Consequently, a number of putative clinical implications of this new biological perspective on brain NE neurons will be principally discussed in a systematic way.

Stress and its vicious circle

Without our parasympathetic system we would die. Without our sympathetic nervous system we would not die but would tolerate considerably less stress (Cannon 1932), thus showing an important, well-known biological rôle of peripheral noradrenergic nerves. In 20 years, an abundant literature has also implicated brain NE systems in stress responses of various kinds and, as mentioned, the largest brain NE network originating in the LC seems profoundly involved in vigilance reactions in response to various environmental stimuli of a salient nature, just like peripheral sympathetic nerves. Clearly, a multitude of such external stimuli represents a mentally stressful situation for the individual, often perceived as triggering various kinds of psychosomatic disorders such as, for example, essential hypertension (cf. Folkow 1984), and/or mental fatigue, probably depending on the premorbid disposition of the individual.

Generally, the present demonstration of a profound peripheral, vegetative input to the LC from the "internal environment" thus indicates that mental stress responses, as reflected in profound activation of NE-containing neuronal networks in brain as well as sympathetic nerves, may also be generated from the internal, vegetative environment, as elicited by autonomic or visceral dysfunction or disorder. Firstly, a great number of stimuli when signalled into the LC network from the two sets of environments may, in general, present an overwhelming load on the LC system in brain, thus straining the overall capacity of the individual to cope, particularly if continued over time. Secondly, we might here begin to understand the so-called vicious circle of stress at a primary, physiological level. Thus, a psychosomatically-induced peripheral vegetative disorder or dysfunction may secondarily, via peripheral signalling into the LC system in brain, add to the mental stress of the individual and in this sense make the accommodation with external, environmental stimuli and demands even more difficult. Thus, such stimuli will most probably interfere with the postulated behavioral function of the LC: to bias the global orientation of behavior and to enhance the reliability and efficiency of feature extraction from external, sensory stimuli (Foote et al. 1983). In fact, such a vicious circle of stress may well start with a peripheral vegetative dysfunction or disorder, which by activating the LC network in brain makes coping with the external environment more difficult; i.e., a feed-forward circuit in generating stress responses can be conceived in which an external, stressful environment and a dysfunctioning vegetative state enhance each other as regards the biological consequences for the individual in terms of the overall capacity to cope. In other words, a well-known experience of most physicians seems understandable at a primary physiological level. In addition, several putative, direct implications for psychiatry, psychopharmacology and medicine seem well worth considering.

Psychiatric, putative implications of LC regulation by internal autonomic stimuli

A. Anxiety disorders

The most obvious implication is that here we seem to understand how, in general physiological terms, autonomic vulnerability may serve as the immediate precursor of the anxiety, alarm or fear reactions in panic attack disorder (Klein and Gorman 1984).

A connection between the emotional state and cardiovascular function has been recognized for many decades. This is, in principle, of little surprise since brain sites for the control of emotions are in part overlapping with those concerned with the regulation of blood pressure (cf. introduction). In general, it appears as if the defense reaction is triggered abnormally easily in anxious patients (Kelly 1980) and, as mentioned, LC activation seems to be an integrated response in this reaction under physiological conditions, if not a critical triggering component.

Consequently, the demonstration of a profound cardiovascular and visceral input to the LC clearly suggests that vegetative dysfunction may, via the LC, serve to elicit anxiety reactions in panic attack disorder.

Peripheral cardiovascular stimuli which thus could elicit reactions of apprehension, alarm or anxiety both in physiologically normal individuals and probably more so in anxiety-prone patients include hypercapnia, blood loss, or even a sudden fall in blood pressure as elicited by changing posture in a hypotensive or orthostatic patient. Even the statistical association between panic attack disorder and mitral valve prolapse (Klein and Gorman 1984) should perhaps be reconsidered in a physiological sense in view of the profound influence of cardiac receptors on LC function in brain. The beneficial effect of carotid sinus massage in some patients with attacks of paroxysmal, supraventricular tachycardia also includes prompt reduction of associated anxiety reactions. Although often assumed to be psychological, this action may physiologically involve vagal inhibition of the LC system in brain. Consequently, the value of such simple physical treatment procedures in panic attack disorder might be explored.

The visceral input to the LC might explain, or help to explain, the mental symptoms of tension or anxiety associated with the irritable bowel syndrome, with its often spastic colon contractions, which in primates also may cause profound LC activation in brain. Even the mental distress often subjectively reported by patients with constipation, consequently may have a physiological correlate in LC activation in brain.

In addition, whether the irritable bowel syndrome is a primary bowel disorder or a primary anxiety disorder, the vicious circle of stress, as discussed above, would contribute to explaining how in the long run the original cause, whether central or peripheral, may have similar behavioral consequences for the individual.

Generally, the hypothesis was advanced that a high LC activity in brain might be facilitatory to phasic vegetative functions such as micturition or defecation (Elam et al. 1986b). Since a robust LC activation is seen in conjunction with profoundly alarming events in the external environment, our findings and hypothesis may provide a physiological clue to the fact that spontaneous urination and/or defecation quite frequently occur in association with such alarming environmental stimulation. Speculatively, one may suggest that a very low level of environmental stimulation would, if anything, promote the development of constipation in part because of an associated low level of LC activation in brain.

Other peripheral, visceral stimuli associated with a sense of urgency or distress involve a filled urinary bladder or a distended stomach, perhaps elicited by excessive ingestion of air, as often seen in elderly or anxious patients. Since such peripheral vegetative stimuli were found to cause LC activation in brain, they might also in this way contribute to elevated vigilance, distress or anxiety reactions, perhaps with a lower threshold in anxiety-prone patients. A bladder disorder may accordingly contribute to the generation of anxiety, tension or fatigue in the patient, i.e., provide an internally generated mental stress response, superimposed upon a primary anxiety disorder in a feed-forward circuit. In particular, as will be further discussed below, the input to the same CNS neurotransmitter system from two simultaneous sets of stimuli of salient nature may add, in a physiological sense, to mental symptoms such as ambivalence, as often encountered in anxiety neurosis and other mental disorders. At any rate, it appears very clear that an autonomic and vegetative input to the LC noradrenergic network in brain can probably influence anxiety disorders in several ways and that autonomic dysfunction or vulnerabili-

ty, via central neurotransmitter systems such as the LC network, may thus precipitate panic attacks.

B. Depression

Although the putative significance of a vegetative input to brain noradrenergic systems seems less clear in affective disorder than in anxiety disorders, some comments may seem warranted. First, most if not all pharmacological, antidepressant treatments as well as electroconvulsive treatment seem with repeated administration to interfere with brain NE systems, as one, presumed common denominator of action (for review see, e.g., Svensson 1983). Second, most depression-prone patients are clearly sensitive to continued stress, which may even precipitate depressive episodes. Third, a number of depressive patients also display anxiety. Consequently, from the above review follows that peripherally or internally generated stress responses in brain, as elicited by autonomic or visceral dysfunction or disorder, may via the LC system contribute to the precipitation of a depressive episode, particularly if combined with intense and prolonged, externally generated sensory load. Perhaps depression in a biological sense can be viewed as an inability to cope, involving an exhausted defense reaction capability, and thus capacity for survival. Clearly, the slow development of a depression cannot be directly related to the minute-to-minute, or even second-to-second, adjustment of the LC system in monitoring the external versus the internal environment. Yet, in the vicious circle of stress the LC may represent a pivotal system and, at any rate, a concomitant peripheral vegetative disorder influencing brain NE systems may clearly contribute to the development of mental fatigue in this way. In other words, the vegetative state in a depression-prone, psychiatric patient can clearly never be ignored and the present physiological data strongly support this classical contention.

C. Schizophrenia

Although pharmacological evidence profoundly implicates brain dopamine-containing neuronal systems as a prime target site for antipsychotic drug action, certain functional characteristics of the LC noradrenergic system in brain make it still quite interesting in relation to psychotic symptomatology. In schizophrenia there is frequently a problem in the discrimination of sensory, environmental stimuli in terms of their attributed significance. The purported function of the LC (see Foote et al. 1983), which involves a sensory biasing rôle in behavior, would thus suggest that the functional state of the LC system could influence psychotic symptomatology, including associated anxiety or fear reactions. The demonstrated profound peripheral, vegetative input to the LC is in this respect of considerable interest (cf. above). In addition, a reduced capacity to discriminate significant from insignificant stimuli from the external environment may also apply to some stimuli from the internal, vegetative environment. In particular, such endogenously generated regulatory stimuli for the LC, which do not reach the level of cognitive recognition, such as fluctuations in blood pressure, bowel contractions, etc., are quite interesting in this regard. One might thus speculate that in schizophrenia such stimuli may represent a peripheral source for intensified alarm reactions or, perhaps even the triggering of a defence reaction (cf. above) with overt, aggressive behavior in a paranoid patient, without any rational, external triggering stimulus. The often strange and even aggressive reaction to touch, i.e., cutaneous, sensory stimuli, which also cause activation of the LC network in brain, may represent a similar phenomenon. One can thus conceive how poorly discriminated signals from both the external and the internal, vegetative environment, fed into the same central LC system, might add to confusion or ambivalence in the patient, as regards the ultimate, global orientation of behavior, particularly since it appears as if internal, autonomic signals of salient nature even in the normal individual overrides the significance attributed to external, environmental stimuli (cf. above).

Psychopharmacological implications

The information presented thus provides new physiological insights with bearing on the question of how vegetative stimuli or dysfunction can influence behavior, the mental state and psychiatric symptomatology and disorders. It follows that psychoactive drugs may, accordingly, influence brain function not only by means of their direct central actions, but also indirectly by means of peripheral cardiovascular or vegetative actions. Thus psychopharmacology seems to have been given a new dimension, which deserves further attention in experimental research and drug development.

The locus coeruleus noradrenergic system may represent a pivotal neurotransmitter system in brain as regards psychosomatic symptomatology and disorder (Wålinder and Svensson 1983), since it has both efferent connections to centers for autonomic control as well as a significant afferent vegetative input. Consequently, pharmacological manipulation of the system will not only interfere with its proposed behavioral function but will, in all probability, also affect autonomic and visceral functions in a complex manner. The beneficial effect of antidepressants in enuresis may be of interest within this context, in addition to their well-known ameliorating action in panic attack disorder, perhaps related to a stabilizing action on brain NE systems (Svensson and Usdin 1978).

Several pharmacologically-induced abstinence reactions are characterized by mental symptoms of arousal, alarm or anxiety concomitant with significant vegetative dysfunction, as, for example, seen in the classical opiate withdrawal reaction and in the ethanol abstinence reaction, with elevated sensitivity to external sensory stimuli. The present review underlines the vicious circle of stress mechanisms that may prevail under these circumstances. Probably, the demonstrated beneficial action of clonidine in such drug-induced abstinence reactions (Björkquist 1975; Gold et al. 1978; for review see Svensson 1986) may in part, as indicated by Aghajanian (1978), be related to its direct and potent inhibitory action on the LC noradrenergic network in brain (Svensson et al. 1975), an effect which accordingly may also be significant for its ameliorating action in anxiety disorders (Svensson et al. 1978; Hoehn-Saric et al. 1981; Liebowitz et al. 1981), including panic attack disorder.

Consequently, it may be that one, common physiological denominator of action for centrally acting α_2-adrenoceptor agonists in disorders as diverse as anxiety diseases, schizophrenia (Freedman et al. 1982), drug-induced abstinence reactions, and developing, essential hypertension with central overreactivity (see Svensson 1985), may reside in inhibition of brain NE systems, such as the LC network,

and an ensuing reduction in stress responses such as the triggering of the defense reaction.

Concluding remarks

Thirty years after Marthe Vogt's original findings indicating NE as a neurotransmitter in brain, it appears that we are beginning to understand the overall physiological function of the largest central NE system, originating in the LC. Its behavioral implication in vigilance reactions to sensory, environmental stimuli, particularly if characterized by novelty or fear, coupled with a peripheral input allowing the same neurotransmitter system in brain to monitor salient stimuli from the internal, vegetative environment, clearly suggests a neurobiological integrative function for the system, ultimately serving the purpose of facilitating accommodation of the individual with the environment, i.e., to cope. Its many physiological similarities with major parts of the peripheral sympathetic nervous system, which subserve a similar biological function, underline this notion. From the present results emerges the notion that external, sensory information thus seems to be processed against a background of peripheral, vegetative information by means of the LC system in brain. Moreover, such internal vegetative stimuli appear, as judged by some of our experimental results, to influence and partly override the influence of external environmental information as regards the global orientation of behavior. Consequently, it appears now understandable in a direct physiological sense how autonomic vulnerability or visceral dysfunction may precipitate or aggravate mental symptoms and disorder. Since the LC responds to salient stimuli from the external or the internal environment within seconds, the proposed integrative rôle of this central neurotransmitter system must be quite important for the initiation of biological and behavioral responses secondary to such stimuli and, ultimately, for survival.

Generally, neither sympathectomy nor LC lesions have been found to imply serious danger for life in experimental animals, living in the protective confines of the laboratory, with no necessity to struggle for food, no requirement to escape from enemies and no danger of hemorrhage. As pointed out by Cannon (1932), we might thus easily draw the inference that the sympathetic system is only of minor importance for survival. However, as he also showed, when exigencies arise, a sympathectomized animal is unable to preserve the constancy of its internal environment and will ultimately die. The lack of normal fear responses to threatening stimuli in LC-lesioned monkeys (cf. introduction) implies an analogous conclusion as regards this central NE network. In other words, it is here suggested that a dysfunctioning or degenerating LC system in brain implies a severe shortcoming for the individual as regards the possibility of preserving the mental homeostasis, integrity or balance under the conditions of real life. Given the biologically integrative function of the LC which, as outlined, has to be assumed, such a central shortcoming must ultimately impair the overall ability of the individual to maintain the internal stability and constancy of the organism (cf. Claude Bernard 1878). In accordance with this notion, acute selective pharmacological depletion of brain NE has been found associated not only with behavioral disruption but also with reduction in body temperature, effects which were both antagonized by restoration of brain NE but not by peripheral injection of NE (Svensson 1971).

The degeneration of the LC system with old age may, consequently, explain some of the symptomatology seen in the elderly patient, such as exaggerated fatigue by a novel environment as well as increased distress by vegetative dysfunction, which in these patients easily seems to distort the reliability and efficiency of feature extraction from external, sensory stimuli. One might argue that the two pontine LC nuclei represent only a tiny fraction of the billions of neurons in the immensely complicated, mammalian CNS and, hence, the purported functional rôle of the LC as well the consequences of its degeneration may appear overboard, albeit logical. However, very few neurotransmitter systems in brain seem to share the unique morphological characteristics of the LC system in its wide-spread innervation throughout the neuroaxis. In addition, we know the gross functional deficits associated with degeneration of another tiny brain region containing catecholamine neurons, the substantia nigra, as encountered in Parkinson's disease. Thus, a dysfunctioning LC system in brain may very well imply serious consequences for the individual as outlined.

On balance, the demonstration a of profound vegetative input to the LC seems to provide a missing link in the ongoing transformation of psychiatry into a biological discipline. In fact, it is tempting to suggest that we may now even conceive some experimental exploration of certain psychoanalytical theories. For example, the emerging significance of brain NE system for the development of brain function during early infancy, i.e., the neurotrophic rôle of NE in the postnatal development of the cerebral cortex and the shaping of brain by experiential factors (Felten et al. 1983; O'Shea et al. 1983), may in conjunction with the here documented input from, e.g., the intestines to the LC allow a direct experimental analysis of a neurobiological basis for presumed early generation of neurotic behaviors. Consequently, the now available information may allow a narrowing of the cleft between analytical and biological psychiatry.

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