The central noradrenergic system: an overview

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Abstract

The central noradrenergic system belongs to a group of brainstem neuromodulatory systems previously referred to as the ascending reticular activating system. In this article a heuristic model is presented of the central noradrenergic system depicting the major projections to other cerebral areas, its interactions with other neuromodulatory systems, mechanisms through which it can influence cerebral function, as well as the major functions and disorders associated with alterations in central noradrenergic activity. It is not the aim of this paper to provide fine detail on the various aspects, but rather to provide a concise overview where structure and function, as well as the interactions with other systems are brought together. The contents of the paper are summarized in a diagram.

Key words: Central noradrenergic system; Neuromodulatory; Brainstem

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Introduction

The majority of central noradrenergic neurons are situated in the brainstem where they form part of the brainstem neuromodulatory systems. The brainstem neuromodulatory systems include cell groups such as the noradrenergic neurons, the dopaminergic neurons, the cholinergic neurons and the serotonergic neurons. The cell bodies of the ascending projections of these systems were erstwhile seen as part of the ascending reticular activating system.[1] In wider context the brainstem neuromodulatory systems form part of the cerebral arousal system that includes a) the brainstem arousal systems (the reticular formation, the brainstem cholinergic, noradrenergic, dopaminergic and serotonergic systems), b) the thalamocortical activating system, c) the hypothalamic arousal systems and d) the basal forebrain wake and sleep promoting systems.[2] The primary functions of the brainstem neuromodulatory systems are that of modulation and regulation of the activity levels of other CNS systems where they increase or decrease activity levels of other neurons and synchronize or desynchronize other systems. As part of the brainstem arousal systems these systems overlap in function, but differ in their contributions under various conditions and in specific waking behaviours.[2] The importance of the brainstem neuromodulatory systems'

influence on higher brain centers is perhaps best illustrated by the fact that the cerebral cortex is unable to maintain consciousness without stimulatory influences from the brainstem modulatory systems.[3] Their effects on the behavioural functions are further demonstrated by the many psychiatric disturbances associated with malfunctioning in one or more of the brainstem neuromodulatory systems. Typical of these neuromodulatory systems is the vastness of their postsynaptic connections on other cerebral structures and the fact that they often propagate their impulses to the rest of the CNS through volume transmission where the neurotransmitters are released into the extracellular fluid[4] – both mechanisms that vastly increase the scope of their influences.

The heuristic model presented in this overview focuses on the central noradrenergic system, a system generally associated with cortical activation, increased cerebral responsiveness to stimuli, an increase in the rate at which the brain processes information and the ability to focus attention on relevant and ignore irrelevant incoming information. The content of this text is summarized in Figure 1.

Location of the central noradrenergic system, its major projections and its connection with the peripheral sympathetic nervous system
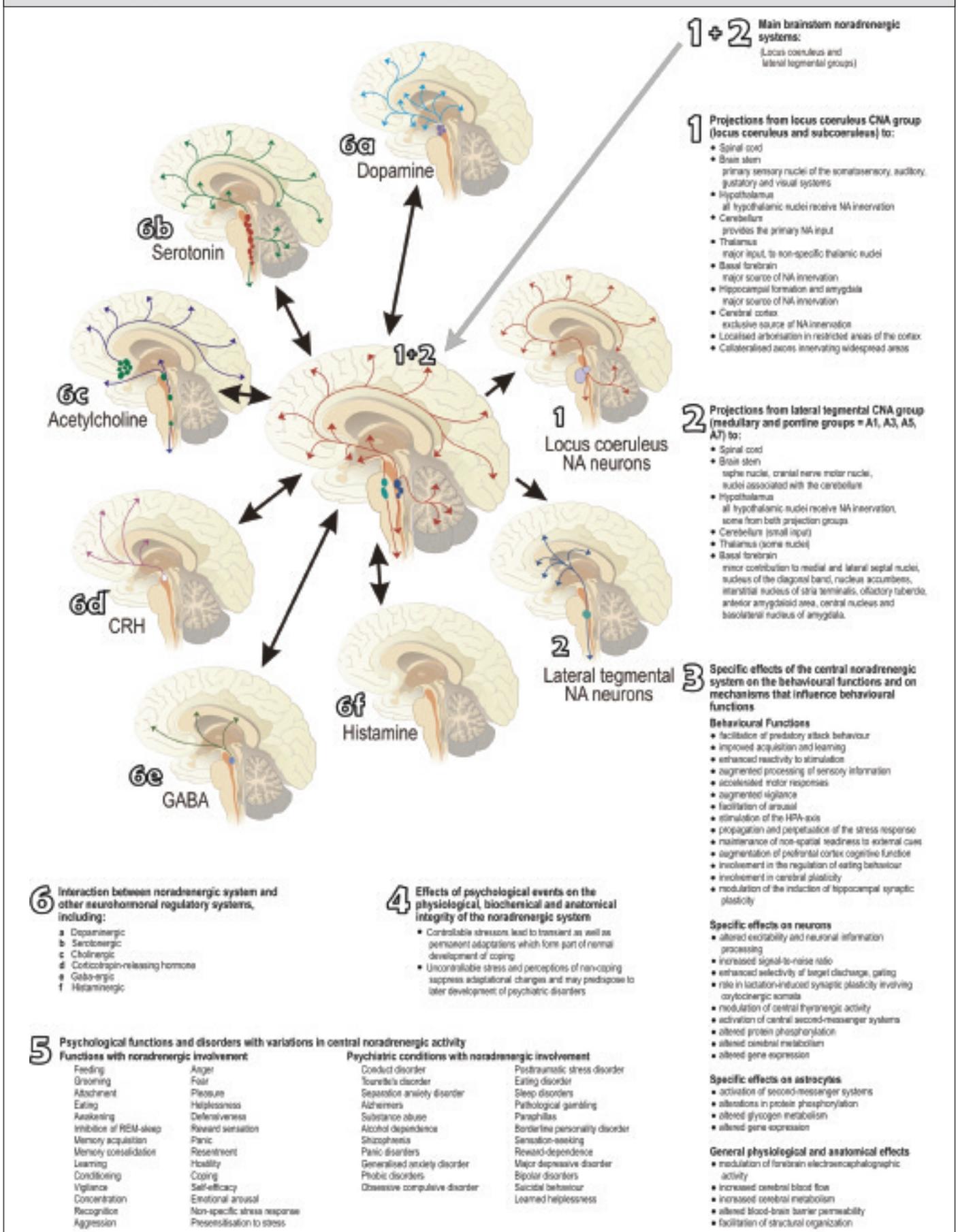
The sympathetic nervous system and the adrenomedullary system are collectively referred to as the sympathoadrenomedullary system or SAM-axis, while the central noradrenergic system is often simply referred to by its abbreviation, i.e., the CNA system. The central noradrenergic

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Figure 1: The brain stem noradrenergic systems.
The diagram shows the two major brain stem noradrenergic systems (1&2), their projections to other CNS structures (1&2), specific effects of the noradrenergic systems on cerebral structure and function (3), the influence of psychological events on the noradrenergic system (4), functions and disorders associated with noradrenergic activity (5) and other brain stem neuromodulatory systems with which the central noradrenergic system interacts (6).

1 + 2 Main brainstem noradrenergic systems:
(Locus coeruleus and lateral tegmental groups)

1 Projections from locus coeruleus CNA group (locus coeruleus and subcoeruleus) to:
- Spinal cord
- Brain stem
  primary sensory nuclei of the somatasensory, auditory, gustatory and visual systems
- Hypothalamus
  all hypothalamic nuclei receive NA innervation
- Cerebellum
  provides the primary NA input
- Thalamus
  major input, to non-specific thalamic nuclei
- Basal forebrain
  major source of NA innervation
- Hippocampal formation and amygdala
  major source of NA innervation
- Cerebral cortex
  exclusive source of NA innervation
- Localised arborisation in restricted areas of the cortex
- Collateralised axons innervating widespread areas

2 Projections from lateral tegmental CNA group (medullary and pontine groups = A1, A3, A5, A7) to:
- Spinal cord
- Brain stem
  raphe nuclei, cranial nerve motor nuclei, nuclei associated with the cerebellum
- Hypothalamus
  all hypothalamic nuclei receive NA innervation, some from both projection groups
- Cerebellum (small input)
- Thalamus (some nuclei)
- Basal forebrain
  minor contribution to medial and lateral septal nuclei, nucleus of the diagonal band, nucleus accumbens, interstitial nucleus of stria terminalis, olfactory tubercle, anterior amygdaloid area, central nucleus and basolateral nucleus of amygdala.

6a Dopamine
6b Serotonin
6c Acetylcholine
6d CRH
6e GABA
6f Histamine

1 Locus coeruleus NA neurons
2 Lateral tegmental NA neurons

3 Specific effects of the central noradrenergic system on the behavioural functions and on mechanisms that influence behavioural functions

Behavioural Functions
- facilitation of predatory attack behaviour
- improved acquisition and learning
- enhanced reactivity to stimulation
- augmented processing of sensory information
- accelerated motor responses
- augmented vigilance
- facilitation of arousal
- stimulation of the HPA-axis
- propagation and perpetuation of the stress response
- maintenance of non-spatial readiness to external cues
- augmentation of prefrontal cortex cognitive function
- involvement in the regulation of eating behaviour
- involvement in cerebral plasticity
- modulation of the induction of hippocampal synaptic plasticity

Specific effects on neurons
- altered excitability and neuronal information processing
- increased signal-to-noise ratio
- enhanced selectivity of target discharge, gating
- role in lactation-induced synaptic plasticity involving oxytocinergic somata
- modulation of central thyrinergic activity
- activation of central second-messenger systems
- altered protein phosphorylation
- altered cerebral metabolism
- altered gene expression

Specific effects on astrocytes
- activation of second-messenger systems
- alterations in protein phosphorylation
- altered glycogen metabolism
- altered gene expression

General physiological and anatomical effects
- modulation of forebrain electroencephalographic activity
- increased cerebral blood flow
- increased cerebral metabolism
- altered blood-brain barrier permeability
- facilitation of structural organization

6 Interaction between noradrenergic system and other neurohormonal regulatory systems, including:
- a Dopaminergic
- b Serotonergic
- c Cholinergic
- d Corticotropin-releasing hormone
- e Gaba-ergic
- f Histaminergic

4 Effects of psychological events on the physiological, biochemical and anatomical integrity of the noradrenergic system
- Controllable stressors lead to transient as well as permanent adaptations which form part of normal development of coping
- Uncontrollable stress and perceptions of non-coping suppress adaptational changes and may predispose to later development of psychiatric disorders

5 Psychological functions and disorders with variations in central noradrenergic activity

Functions with noradrenergic involvement

Feeding	Anger
Grooming	Fear
Attachment	Pleasure
Eating	Helplessness
Awakening	Defensiveness
Inhibition of REM-sleep	Reward sensation
Memory acquisition	Panic
Memory consolidation	Resentment
Learning	Hostility
Conditioning	Coping
Vigilance	Self-efficacy
Concentration	Emotional arousal
Recognition	Non-specific stress response
Aggression	Presensitisation to stress

Psychiatric conditions with noradrenergic involvement

Conduct disorder	Posttraumatic stress disorder
Tourette's disorder	Eating disorder
Separation anxiety disorder	Sleep disorders
Alzheimers	Pathological gambling
Substance abuse	Paraphilias
Alcohol dependence	Borderline personality disorder
Schizophrenia	Sensation-seeking
Panic disorders	Reward-dependence
Generalised anxiety disorder	Major depressive disorder
Phobic disorders	Bipolar disorders
Obsessive compulsive disorder	Suicidal behaviour
	Learned helplessness

system and the peripheral noradrenergic system are generally thought of as two separate systems sharing the same major neurotransmitter. Yet, activation of the central noradrenergic (CNA) neurons, as occurs during any period of marked emotional arousal, is generally paralleled by simultaneous activation of the peripheral noradrenergic (sympathetic nervous) and adrenomedullary systems.[5] Symptoms of sympathetic hyperactivity are also often equated with an increase in central noradrenergic activation. However, scientific recognition of a direct influence of the central noradrenergic system on peripheral sympathetic nervous system activity is not well documented in the literature. There are, nonetheless, indications that a direct link does exist. The concomitant increase in activity of the SAM-axis, at times of emotion-associated CNA hyperactivity, is said to involve neural structures such as the amygdala, the ascending reticular activating system, descending projections from the central noradrenergic nuclei to the brainstem and spinal cord, posterior hypothalamic control areas, as well as the nucleus paragigantocellularis.[6,7] It has also been shown that cerebral-derived noradrenaline can have a sympatho-excitatory role in the regulation of preganglionic neurons of, at least, the thoracolumbar spinal cord, and that some of the effects of centrally-produced noradrenaline on peripheral sympathetic function may be mediated through spill-over of noradrenaline from the subcortical areas into the plasma.[8,9] In short, common observations as well as scientific evidence support the notion of a sympatho-excitatory role for the central noradrenergic system.

The two major divisions of the brainstem noradrenergic system and their projections to the rest of the CNS are depicted in the middle-right side of the diagram (1&2). The cell bodies of the central noradrenergic neurons are situated in the pons and medulla. The major groups are a) the locus coeruleus and subcoeruleus found near the floor of the fourth ventricle and b) those located in the lateral parts of the medullary reticular formation and in nuclei associated with cranial nerves such as the solitary nucleus and dorsal motor nucleus of vagus.[3,10] Ascending and descending fibers from these major sites of origin innervate virtually the whole cerebral cortex, the brainstem, the thalamus and hypothalamus, limbic forebrain structures, as well as the cerebellum and spinal cord. The locus coeruleus nuclei (locus coeruleus = meaning blue spot) are responsible for almost the entire output to the cerebral cortex, while the lateral reticular formation neurons provide the output to the spinal cord.[10]

Interaction with other neuromodulatory systems

The brainstem noradrenergic system, as previously mentioned, forms part of what was generally referred to as the ascending reticular activation system (ARAS). The neuromodulatory aminergic systems interact in a complex way – as yet not completely understood.[1] Several reviews and other publications are available that endorse the fact that the neuromodulatory substances directly or indirectly influence the release of each other. Examples include the interaction between noradrenaline and serotonin[11], the effect of noradrenaline on dopamine release[12], the interactions between corticotropin-releasing hormone (CRH), noradrenaline and serotonin[13], the regulatory influence of noradrenergic neurons on GABA-ergic neurons and histaminergic neurons[14], and many others. In addition, several

higher brain centers each receive modulatory inputs from a number of brainstem neuromodulatory systems[15] – yet another way of functional cooperation between these systems. Some of the interacting neuromodulatory systems are depicted in Figure 1, No 1.

The individual neuromodulatory systems show hemispheric asymmetry in their widespread projections to higher cerebral areas. For instance, the noradrenergic projections to the right hemisphere are more prominent than those to the left hemisphere.[1] This phenomenon is speculated to play a role in handedness. It is also speculated that the asymmetrical distribution of noradrenergic projections could play a role in the observed association between handedness and the vulnerability to immune-related disturbances. The prevalence of disorders such as myasthenia gravis, asthma, hay fever, eczema, migraine, coeliac and Crohn's disease, as well as Hashimoto's thyroiditis is, for instance, significantly higher among left-handers than among right-handers.[16,17]

In addition to the interactions between the brainstem noradrenergic nuclei and other neurohormonal systems of the brainstem, noradrenergic neurons have a close interaction with the central corticotropin-releasing hormone system in the brainstem and elsewhere. A positive reverberating feedback mechanism is for instance known to exist between the noradrenergic neurons of the locus coeruleus and the central corticotropin-releasing hormone neurons.[18] Substances that stimulate the noradrenergic cell bodies will, in general, also stimulate CRH cell bodies, and inhibitory factors will suppress both systems.[18] Although the concept of a bi-directional stimulatory influence between the CRH and central noradrenergic systems is well established, to the extent that the sensitivity of a feed-forward loop between them has been proposed as an underlying cause of clinical depression, some uncertainty still exists – such as whether intermediates are involved in these bi-directional stimulatory actions.[19] The interactions between the central noradrenergic system and other neuroendocrine modulatory systems are depicted on the upper-left hand side of the diagram (6a-6f).

As interactions between the neurohormonal modulatory systems can lead to modulation of their respective influences on cerebral function and behavior it is impossible to imagine that a disturbance in one system, or for that matter medications that influence one system, could act in isolation from other systems. Many examples of co-dysregulation of these systems can, in fact, be found such as the co-dysregulation of serotonergic and noradrenergic function in depression and anxiety disorders[20], and the co-dysregulation of noradrenaline, serotonin, GABA, CRH, and glutamine in depression and epilepsy.[21] In most instances we are still far from absolute identification of the primary causative system. Nevertheless, the central noradrenergic system is by several theories postulated as central to a number of psychiatric disturbances. The best known theories are probably related to mood disorders, but others are also known, such as a recent theory (based on the fact that the central noradrenergic system influences both the nigrostriatal dopaminergic and basalocortical cholinergic systems) postulating that the activity of the noradrenergic system plays a central role in the progression of a number of neurodegenerative disorders including Parkinson's and Alzheimer's disease.[22]

Mechanisms of influence on cerebral and behavioural functions

Specific effects of the noradrenergic influence on cerebral function (Fig 1, No 3) can be seen in the bottom-right of the diagram.[1,23-36] The major noradrenergic influence would in general appear to be that of activation and facilitation. This is evident from effects such as an increase in cerebral blood flow, increased cerebral metabolism, and increased electroencephalographic activity, as well as augmentation of adaptational plasticity, arousal, and vigilance. It is, however, also known that excessive stimulation of the central noradrenergic system may give rise to adverse effects, not only on the structure and function of the noradrenergic system itself, but also on other brain structures and activities.[18,24,37,38]

There has lately been much interest in the differences between gene expression during wakefulness and gene expression during sleep and it is known that the central noradrenergic system can play a modulating effect on gene expression. It would appear that the activity of the central noradrenergic system during wakefulness contributes to neuronal transcription in favour of synaptic potentiation and to counteracting cellular stress, while its inactivity during sleep could play a permissive role in the increase in brain protein synthesis.[39] The central noradrenergic system would appear to be most active in the presence of novel, interesting, stimuli in order to make the rest of the brain more responsive to such stimuli and to speed-up information processing.[4]

The influence of noradrenergic activity on behavioural functions is evident from both animal and human studies. Most of the evidence derived from animal experiments was obtained by subjecting animals to stressful situations. In conditions of severe uncontrollable stress, the reaction known as ''learned helplessness'' can be observed. This reaction has been described as the animal model of depression in humans and is associated with complete depletion of central noradrenaline stores.[40,41,42] Descriptions of the effects of acute as well as chronic stress on central noradrenergic activity in brain areas such as the cerebral cortex and on subcortical areas including the hippocampus, the amygdala, the thalamus and the hypothalamus, can be found in excellent reviews by Bremner et al.[37,38] Acute stress exposure is, for instant, known to be accompanied by a transient increase in the firing rate of neurons of the locus coeruleus and an increase in the release and turnover of noradrenaline at the cerebral projections areas of the noradrenergic neurons. Chronic stress exposure, on the other hand, leads to more permanent changes in the firing rate of locus coeruleus neurons. Presensitization of the central noradrenergic neurons leads to exaggerated stress responses e.g., increased noradrenaline release upon re-exposure. Excessive stimulation may, however, deplete the noradrenergic supply resulting in the typical behavioural pattern of helplessness.[37] Both excessive noradrenaline secretion due to previous sensitization, and depletion due to excessive stimulation, can lead to psychiatric disturbances.

Major functions of the noradrenergic system

Noradrenaline has a widespread influence on central nervous system functioning (See Figure 1, No 5). Alterations in central noradrenergic activity has been reported to take place during several behavioural phenomena, including defensive/aggressive behaviour[43], perception of a threat[44,45],

observation of potentially dangerous situations,46 during fear and anxiety[47-50], during feeding and grooming[51-53]. with various other types of emotion[50], during waking and inhibition of REM sleep[54], in attacking personalities[55], upon initiation, as well as termination, of food intake[56], in experiencing rewards and other pleasurable sensations[55], as well as during arousal, concentration, increased vigilance, memory consolidation, attention, learning, agitation, aggression, resentment, recognition, and emotional analysis pertaining to a stimulus.[18,23,57-61] The influence of the noradrenergic system on the amygdala and the hippocampus is said to be important for processes like conditioning[37,38,44], extinction failure of the conditioned response, memory retention and memory retrieval.[37,38] The fact that noradrenergic involvement is reported for such a wide scope of functions is not at all surprising when one considers that it's primary function comprises the modulation of the activity of other neurons, that it does this in cooperation with other neuromodulatory systems, and that its activity level is in turn influenced by many other systems and signals.

Disorders associated with alterations in central noradrenergic activity

Psychiatric disturbances in which involvement of the noradrenergic system is implicated are listed in Figure 1 (No 5). Over the years abnormal noradrenergic activity has been implicated in many disturbances, some marked by co-dysregulation of other systems and others not. Abnormal noradrenergic activity has for instance been implicated as a major feature in all forms of stress[18,37,38,62], in variations in cognitive function[25], sensation-seeking[63], reward-dependence[64], pathological gambling[64], substance abuse[66], alcohol dependence[67,68], aggression[69,70], type A personality characteristics[71], borderline personality disorder[72], suicidal behaviour[73,74], eating disorders[75], impulse control disorders[76], conduct disorders[69], ADHD[69,77], Tourette's disorder[63], paraphilias in males[78], fear and anxiety disorders[37,38,69,79,80], posttraumatic stress disorder[81,96], panic disorder[37,38,69,82], phobias[69], depression[37,69,83-92], schizophrenia[69,93] and Alzheimer's disease.[63,94] Fear and anxiety is almost universally associated with activation of the central noradrenergic system. Central noradrenergic activity in the panic disorder, posttraumatic stress disorder, generalized anxiety disorder, phobic disorders and obsessive-compulsive disorders has been reviewed by Bremner et al[38], and it would appear that the highest activity is seen in panic disorders and the posttraumatic stress syndrome, i.e., those disorders where the stress response is most directly implicated.

It is not always easy to distinguish between cause and effect with regard to the psychoneurological interaction. What is of great interest is the fact that emotions and perceptions can alter, not only the transient physiological processes, but also the more permanent biochemical and structural characteristics of the brain – including that of the central noradrenergic system. This modification of neural structures by the internal and external environment is nothing new and forms part of the early learning processes.[95] However, it is known that this plasticity persists throughout life and that the central noradrenergic system can be involved in the plasticity of other systems. A role for the noradrenergic system has, amongst others, been described in developmental cortical

plasticity[96], morphological plasticity during recovery from cortical lesions[97], the expression of oncogenes in neurons,98 prolonged changes in cerebral perfusion[99,100], structural changes in astrocytes upon stress-induced noradrenaline secretion[101] and noradrenaline-induced changes in blood-brain barrier permeability.[102,103] A detailed discussion on persisting alterations in central noradrenergic structure and function, or alterations in other brain areas due to a noradrenergic influence, is beyond the scope of this writing, but these phenomena are postulated to be involved in, or to act as trigger for long-term adaptive modification.[24] However, more permanent adverse alterations due to modulation of gene transcription are also known to occur and it was shown that it can even be induced by negative psychosocial influences.[37,38] An overview of the long-term consequences and the structure-function changes of the noradrenergic system in response to controllable and uncontrollable stressors can be found in an excellent writing by Heuter.[24] In summary it can be said that changes in the noradrenergic system as a result of controllable stressors can be seen as necessary adaptational processes, i.e., as a form of noradrenergic plasticity. In contrast, stressors perceived as uncontrollable would give rise to anatomical and functional alterations that could cause or predispose to psychopathology (Figure 1 No 4).

Conclusion

Due to its abundant terminations on other central nervous system neurons, the fact that it can propagate impulses through volume transmission and the fact that it interacts with other neuromodulatory systems of the brainstem, activation of the central noradrenergic system has widespread effects on cerebral functioning and on behavior. There can be no doubt that optimal understanding of these neuromodulatory influences and interactions will lead to a much better understanding of many behavioural functions and dysfunctions.

Acknowledgements

References

1. Windhorst U. Bilateral organisation of the brain. In: Gregor R, Windhorst U, eds, Comprehensive Human Physiology, Vol 1. Berlin: Springer-Verlag; 1996:1137-1160.

2. Jones BE. Arousal systems. Frontiers Biosci 2003;8:438-451.

3. Nolte N. Organization of the brainstem. In: The Human Brain. An introduction to its functional anatomy. St Louis Missouri: Mosby Inc, 1999:254-282.

4. Bear M, Connors BW, Paradiso MA. Neuroscience: Exploring the brain. 2nd ed. Baltimore: Lippincott Williams & Wilkins; 2001.

5. Grant SJ, Huang YH, Redmond DE. Benzodiazepines attenuate single unit activity in the locus coeruleus. Life Sci 1980;27:2231.

6. Aston-Jones G. Behavioural functions of locus coeruleus derived from cellular attributes. Physiol Psychol 1986;13:118-126.

7. Aston-Jones G, Shipley MT, Chovet G, Ennis M, van Bockstaele E, Pieribone V, Shiekhatter R. Afferent regulation of locus coeruleus neurons: Anatomy, physiology and pharmacology. Prog Brain Res 1991;88:47-75.

8. Lambert GW. Paring down on Descartes: a review of brain noradrenaline and sympathetic nervous function. Clin Exp Pharmacol Physiol 2001;28(12):979-982.

9. Esler MD, Lambert GW, Ferrier C, Kaye DM, Wallin BG, Kalff V, et al. Central nervous system noradrenergic control of sympathetic outflow in normotensive and hypertensive humans. Clin Exp Hypertension 1995;17(1-2):409-423.

10. Holets VR: Anatomy and function of noradrenaline in the mammalian brain. In: The Pharmacology of Noradrenaline in the Central Nervous System. Oxford: University Press; 1990:1-27.

11. Svensson TH. Brain noradrenaline and the mechanisms of action of antidepressant drugs. Acta Psych Scand Suppl, 2000;402:18-27.

12. Srinivasan J, Schmidt WJ. Functional recovery of locus coeruleus noradrenergic neurons after DSP-4 lesion: effects on dopamine levels and neuroleptic induced-parkinsonian symptoms in rats. J Neural Transmiss 2004;111(1):13-26.

13. Feldman S, Weidenfeld J. Involvement of endogenous glutamate in the stimulatory effect of norepinephrine and serotonin on the hypothalamo-pituitary-adrenocortical axis. Neuroendocrinology 2004;79(1):43-53.

14. Stevens DR, Kuramasu A, Erikson KS, Selbach O, Haas HL. Alpha 2-adrenergic receptor-mediated presynaptic inhibition of GABAergic IPSPs in rat histaminergic neurons. Neuropharmacology 2004;46(7):1018-1022.

15. Stone EA, Lin Y, Ahsan R, Quartermain D. Gross mapping of alpha 1-adrenoceptors that regulate behavioural activation in the mouse brain. Behav Brain Res 2004;152(2):167-175.

16. Geschwind N, Behan PO. Left-handedness: Association with immune disease, migraine, and developmental learning disorder. Proc Natl Acad Sci USA 1982;79:5097-5100.

17. Geschwind N, Galaburda AM. Cerebral lateralization: Biological mechanisms, associations, and pathology. Cambridge, MIT Press, 1987.

18. Chrousos GP, Gold PW. The concept of stress and stress systems disorders. JAMA 1992;267:1244-1252.

19. Dunn AJ, Swiergiel AH, Palamourchouk V. Brain circuits involved in corticotropin-releasing factor-norepinephrine interactions during stress. Ann NY Acad Sci 2004;1018:25-34.

20. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depression and Anxiety 2000;12(suppl 1):2-19.

21. Jobe PC. Common pathogenic mechanisms between depression and epilepsy: an experimental perspective. Epilepsy & Behav 2003;4(suppl 3):S14-S24.

22. Marien MR, Colpaert FC, Rosenquist AC. Noradrenergic mechanisms in neurodegenerative diseases: a theory. Brain Res Brain Res Rev 2004;45(1):38-78.

23. Leon M. Catecholaminergic contributions to early learning. Adv Pharmacol 1998;42:961-964.

24. Huether G. The central adaptation syndrome: Psychosocial stress as a trigger for adaptive modifications of brain structure and brain function. Prog Neurobiol 1996;48:569-612.

25. Arnsten AF, Steere JC, Jentsch DJ, Li BM. Noradrenergic influences on prefrontal cortical cognitive function: Opposing actions at postjunctional alpha 1 versus alpha 2 adrenergic receptors. Adv Pharmacol 1998; 42:764-767.

26. Partonen T. Possible pathophysiological mechanisms regulating food intake in seasonal affective disorder. Med Hypotheses 1996;47(3):215-216.

27. Huang QH, Takaki A, Arimura A. Central noradrenergic system modulates plasma interleukin-6 production by peripheral interleukin-1. Am J Physiol 1997;273:R731-738.

28. Witte EA, Marrocco RT. Alteration of brain noradrenergic activity in

rhesus monkeys affects the alerting component of overt orientating. Psychopharmacol 1997;132(4):315-323.

29. *Dratman MB, Gordon JT. Thyroid hormones as neurotransmitters. Thyroid 1996;6(6):639-647.*

30. *Arnsten AF, Steere JC, Hunt RD. The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical significance for attention-deficit hyperactivity disorder. Arch Gen Psychiatry 1996;53(5):448-455.*

31. *Berridge CW. Modulation of forebrain electroencephalographic activity and behavioural state by the locus coeruleus - noradrenergic system: Involvement of the medial septal area. Adv Pharmacol 1988;42:744-748.*

32. *Hasselmo ME, Linster C, Patil M, Cekic M. Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. J Neurophysiol 1997;77(6):3326-3339.*

33. *Katsuki H, Izumi Y, Zorumski CF. Noradrenergic regulation of synaptic plasticity in the hippocampal CA1 region. J Neurophysiol 1997;77(6):3013-20.*

34. *Michaloudi HC, Mjboudi M, Poulain DA, Papadopoulos GC, Theodosis DT. The noradrenergic innervation of identified hypothalamic magnocellular somata and its contribution to lactation-induced synaptic plasticity. J Neuroendocrinol 1997;9(1):17-23.*

35. *Rorig B, Sutor B. Regulation of gap junction coupling in the developing neocortex. Mol Neurobiol 1996;2(3):225-249.*

36. *Bhatia SC, Saha S, Manchanda SK, Nayar U. Role of midbrain ventro-lateral tegmental area (VLTA) adrenergic mechanisms in facilitation of hypothalamically-induced predatory attack behaviour. Indian J Exp Biol 1997;35(4):332-337.*

37. *Bremner JD, Krystal JH, Southwick SM, Charney D. Noradrenergic mechanisms in stress and anxiety. I Preclinical studies. Synapse 1996;23:28-38.*

38. *Bremner JD, Krystal JH, Southwick, Charney DS. Noradrenergic mechanisms in stress and anxiety. II. Clinical Studies. Synapse 1996;23:39-51.*

39. *Cirelli C, Tononi G. Locus coeruleus control of state-dependent gene expression. J Neurosci 2004;24(23):5410-5419.*

40. *Petty F, Kramer G, Wilson L, Chae Y-L. Learned helplessness and in vivo hippocampal norepinephrine release. Pharmacol Biochem Behav 1993;46:231-235.*

41. *Seligman EP, David L, Rosenhan. Depression and suicide. In: Abnormality. WW Norton and Company Inc; 1998:246.*

42. *Bloom FE, Lazerson A. Emotions: The highs and the lows of the brain. In Brain, Mind and Behaviour. 2nd edition. NY: Freeman and Company; 1996:231.*

43. *Barret JA, Shaikh MB, Edinger H, Siegel A. The effects of intrahypothalamic injections of norepinephrine upon affective defense behaviour in the cat. Brain Res 1987;426:381-384.*

44. *Rasmussen K, Jacobs BL. Single-unit activity of locus coeruleus neurons in the freely moving cat II. Conditioning and pharmacological studies. Brain Res 1986;371:335-344.*

45. *Rasmussen K, Morilak DA, Jacobs BL. Single-unit activity of locus coeruleus neurons in the freely moving cat I. During naturalistic behaviors and in response to simple and complex stimuli. Brain Res 1986;371:324.*

46. *Levine ES, Litto WJ, Jacobs BL. Activity of cat locus coeruleus noradrenergic neurons during the defense reaction. Brain Res 1990;531:189-195.*

47. *Grant SJ, Redmond DE. Neuronal activity of the locus coeruleus in awake Macaca arctoides. Exp Neurol 1984;84:701-708.*

48. *Redmond DE jr. New and old evidence for the involvement of a*

brain norepinephrine system in anxiety. In: Phenomenology and Treatment of Anxiety. Spectrum Pub;1979. pp 153-201.

49. *Redmond D, Huang Y. New evidence for a locus coeruleus norepinephrine connection with anxiety. Life Sci 1979;25:2149-2162.*

50. *Abercrombie ED, Jacobs BL. Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats II. Adaptation to chronically presented stressful stimuli. J Neurosci 1987;7:2844-2848.*

51. *Aghajanian G. Tolerance of locus coeruleus neurons to morphine and suppression of withdrawal response by clonidine. Nature 1978;276:186-188.*

52. *Foote SL, Aston-Jones G, Bloom FE. Impulse activity of locus coeruleus neurons in awake rats is a function of sensory stimulation and arousal. Proc Natl Acad Sci 1980;USA, 77:3033-3037.*

53. *Aston-Jones G. Behavioural function of locus coeruleus derived from cellular attributes. Physiol Psychol 1986;13:118-126.*

54. *Rosenzweig MR, Leiman AL, Breedlove SM. Biological rhythms, sleep and dreaming. In: Biological Psychology. Massachusetts: Sinauer Ass Inc; 1999. 300-406.*

55. *Bloom FE, Lazerson A. Emotions: The highs and the lows of the brain. In: Brain, Mind and Behaviour. NY: WH Freeman & company; 1996:208-237.*

56. *Bloom FE, Lazerson A. Homeostasis: Maintaining the internal environment. In: Brain Mind and Behaviour. NY: WH Freeman and Company; 1996:399.*

57. *Le Doux J. Once more with feeling. In: The Emotional Brain. London: Phoenix Paperback, 1999:267-303.*

58. *Donovan BT. Humors, Hormones and the Mind. An approach to the understanding of behaviour. London: MacMillan Press,1988:159-208.*

59. *Arnsten AF. Catecholamine regulation of the prefrontal cortex. J Psychopharm 1997;11(2):151-162.*

60. *Sakanaka M, Shibasaki T, Lederis K. Distribution and efferent projections of corticotropin-releasing factor-like immunoreactivity in rat amygdaloid complex. Brain Res 1986;382:213-238.*

61. *Bloom FE, Lazerson A. Learning and memory. In: Brain, Mind and Behavior. NY: WH Freeman and Company; 1996:261.*

62. *Kopin IJ, Eisenhofer G, Goldstein D. In: Chrousos GP, Loriaux DL, Gold PW, editors. Mechanisms of physical and emotional stress. NY and London. Plenum Press; 1988:11-23.*

63. *Gabel S, Stadler J, Bjorn J, Shindledecker R, Bowden CL. Sensation seeking in psychiatrically disturbed youth: relationship to biochemical parameters and behavior problems. J Am Acad Child Adol Psychiatry 1994;33(1):123-129.*

64. *Garvey MJ, Noyes R jr, Cook B, Blum N. Preliminary confirmation of the proposed link between reward-dependence traits and norepinephrine. Psychiatry Res 1996;65(1):61-64.*

65. *Bergh C, Eklund T, Sodersten P, Nordin C. Altered dopamine function in pathological gamling. Psychol Med 1997;27(2):473-475.*

66. *Gabel S, Stadler J, Bjorn J, Shindledecker R. Homovanillic acid and dopamine-beta-hydroxylase in male youth: relationships with paternal substance abuse and antisocial behavior. Am J Drug Alcohol Abuse 1995;21(3):363-378.*

67. *De Witte P. The role of neurotransmitters in alcohol dependence: animal research. Alcohol 1996;319 (Suppl)1:13-16.*

68. *Clayton CJ, Hicks RE. Ethanol, monoamines, and affect. J Neur Transm Gen Sect 1994;98(3):169-195.*

69. *Kaplan HI, Sadock BJ, Grebb JA. Synopsis of Psychiatry 7th edition. Behavioural Sciences. Clinical Psychiatry. Baltimore: Maryland, Williams and Wilkins, 1994.*

70. *Kavoussi R, Armstead P, Coccaro E. The neurobiology of impulsive*

aggression. *Psychiatr Clin North Am 1997;20(2):395-403.*

71. Williams RB jr, Suarez EC, Kuhn CM, Zimmerman EA, Schanberg SM. Biobehavioural basis of coronary-prone behavior in middle men. Part 1: Evidence for chronic SNS activation in Type A. *Psychosom Med 1991;53:517-527.*

72. Figueroa E, Silk KR. Biological implications of childhood sexual abuse in borderline personality disorder. *J Pers Dis 1997;11(1): 71-92.*

73. Arango V, Underwood MD, Mann JJ. Biological alterations in the brainstem of suicides. *Psychiatr Clin North Am 1997;20(3):581-593.*

74. Gilbert C. Major human cancers are preventable: psychological stimuli induce a dopamine-thyroid - immune efficient mechanism. *Psychiatr Clin North Am 1997;20(3):581-593.*

75. Pirke KM. Central and peripheral noradrenaline regulation in eating disorders. *Psychiatry Res 1996;62(1):43-49.*

76. McElroy SL, Pope HG jr, Keck PE jr, Hudson JI, Phillips KA, Strakowski SM. Are impulse-control disorders related to bipolar disorder? *Compr Psychiatry 1996;37(4):229-240.*

77. Pliszka SR, McCracken JT, Maas JW. Catecholamines in attention-deficit hyperactivity disorder: Current perspectives. *J Am Acad Child Adolesc Psychiatry 1996;35(3):264-272.*

78. Kafka MP. A monoamine hypothesis for the pathophysiology of paraphillic disorders. *Arch Sex Behav 1997;26(4):343-358.*

79. Krystal JH, Deutsch DN. Charney DS. The biological basis of panic disorder. *J Clin Psychiatry 1996;57((Suppl)10:23-31.*

80. Brawman-Mintzer O, Lydiard RB. Biological basis of generalized anxiety disorder. *J Clin Psychiatry 1997;58(Suppl)3:16-25.*

81. Southwick SM, Krystal JH, Bremner JD. Morgan CA, Nicolaou AL, Nagy LM, et al. Noradrenergic and serotonergic function in post-traumatic stress disorder. *Arch Gen Psychiatry 1997;54(8):749-758.*

82. Goddard AW, Charney DS. Toward an integrated neurobiology of panic disorder. *J Clin Psychiatry 1997;58(Suppl)2:4-11.*

83. Meas M, Minner E, Suy C, Vandervorst, Raus J. Coexisting dysregulations of both the sympathoadrenal system and hypothalamic-pituitary-adrenal-axis in melancholia. *J Neural Transm 1991;85:195-210.*

84. Fritze J. The adrenergic-cholinergic imbalance hypothesis of depression: A review and a perspective. *Rev Neurosci 1993; 4(1):63-93.*

85. Sulser F, Sanders-Bush E. The serotonin-norepinephrine link hypothesis of affective disorders: Receptor-receptor interactions in brain. *Adv Exp Med Biol 1987;221:489-572.*

86. Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC et al. Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Arch Gen Psych 1994;51(5):411-22.*

87. Potter WZ, Manji HK. Catecholamines in depression: An Update.

Clin Chem 1994;40(2):279-287.

88. Maas JW, Katz MM, Koslow SH, Swann A, Davis JM, Berman N, Bowden CL, Stokes PE, Landis H. Adrenomedullary function in depressed patients. *J Psych Res 1994;28(4):357-367.*

89. Dinan TG. Noradrenergic and serotonergic abnormalities in depression: stress-induced dysfunction? *J Clin Psychiatry 1996;57(Suppl 4):14-18.*

90. Klimek V, Stockmeier C, Overholser J, Meltzer HY, Kalka S, Dilley G, et al. Reduced levels of norepinephrine transporters in the locus coeruleus in major depression. *J Neurosci 1997;17(21):8451-8458.*

91. Mokrani MC, Duval F, Crocq MA, Bailey P, Macher JP. HPA axis dysfunction in depression: Correlation with monoamine system abnormalities. *Psychoneuroendocrinol 1997;22 (Suppl)1:S63-68.*

92. Kelly CB, Cooper SJ. Plasma noradrenaline reponse to electroconvulsive therapy in depressive illness. *Br J Psychiatry 1997;171:182-186.*

93. Carlsson A, Hansson LO, Waters N, Carlsson ML. Neurotransmitter aberrations in schizophrenia: New perspectives and therapeutic implications. *Life Sci 1997;61(2):75-94.*

94. Palmer AM. Neurochemical studies of Alzheimer's disease. *Neurodegeneration 1996;5(4):381-91.*

95. Schwartz JP. Development and plasticity. Overview. *Adv Pharmacol 1998;42:877-882.*

96. Marshall KC, Christie MJ, Finlayson PG, Williams LT. Developmental aspects of the locus coeruleus noradrenaline system. *Prog Brain Res 1991;88:173-185.*

97. Boyeson MG, Krobert KA. Cerebellar norepinhephrine infusions, facilitate recovery after sensorimotor cortex injury. *Brain Res Bull 1992;29:435-439.*

98. Vaccarino FM, Hayward MD, Lee MW, Harigan DJ, Duman RS, Nestler EJ. Induction of immediate early genes by c-AMP in primary cultures of neurons from rat cerebral cortex. *Molec Brain Res 1993;19:76-82.*

99. Bryan RMJ jr. Cerebral blood flow and energy metabolism during stress. *Am J Physiol 1990;259:H269-H280.*

100. Bryan RM, Lehmann RAW. Cerebral glucose utilization after aversive conditioning and during conditioned fear in rat. *Brain Res 1988;444:17-24.*

101. Stone AA, Ariano MA. Are glial cells targets of the cerebral adrenergic systems? *Brain Res Rev 1989;14:297-308.*

102. Nathanson JA. Adrenergic receptors in brain microvessels. *Trends Neurol Sci 1983;4:422-424.*

103. Ohata M, Takei HO, Fredericks WR, Rapoport SJ. Effects of immobilization stress on cerebral blood flow and cerebrovascular permeability in spontaneously hypertensive rats. *J Cereb Blood Flow Metab 1982;2:373-379.*