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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.

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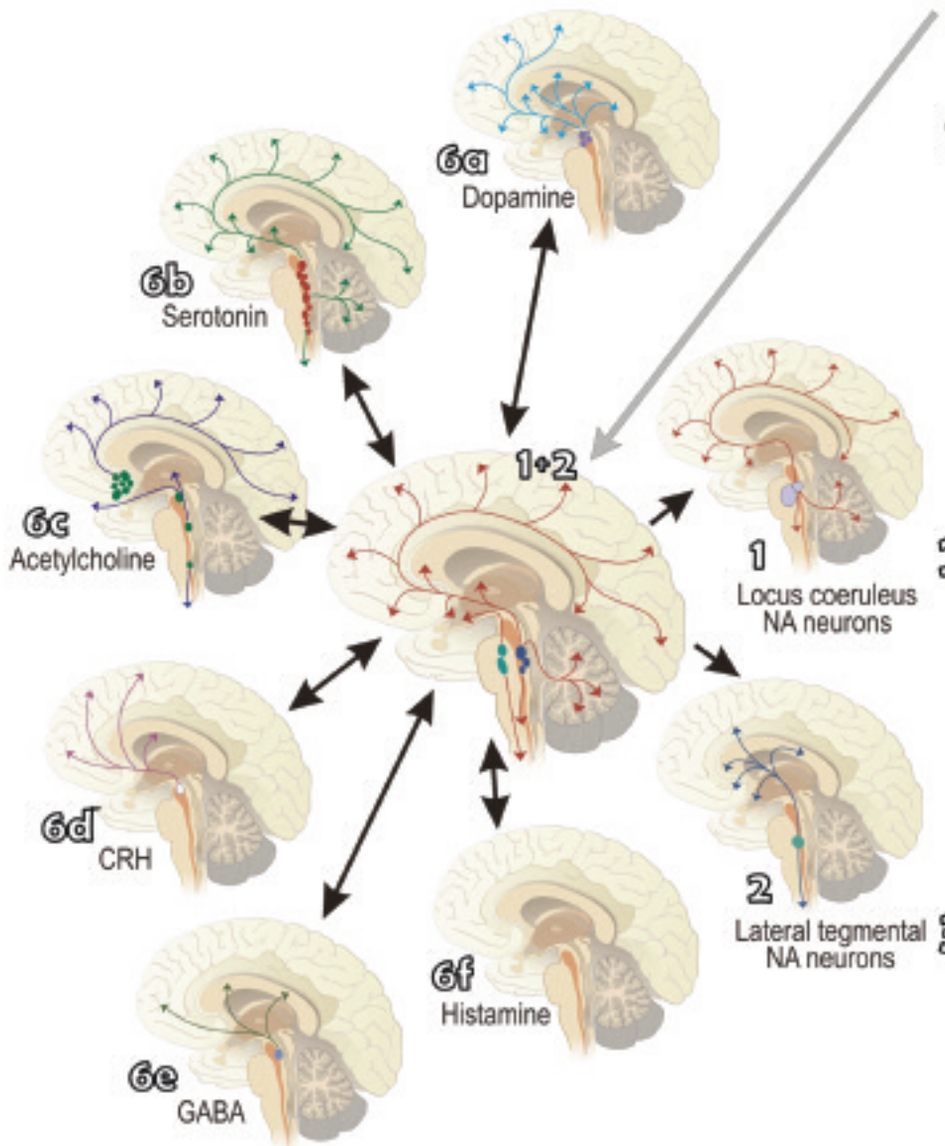
Location of the central noradrenergic system, its major projections and its connection with the peripheral sympathetic nervous system

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

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 somatosensory, 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.

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 thyrotropic 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
Shizophrenia	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.

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