CHAPTER 3

THE PSYCHONEUROLOGICAL INTERACTION IN TERMS OF THE CNA/SAM-AXIS

The aim of this chapter is to demonstrate the role of the central noradrenergic/sympatho-adrenomedullary axis (CNA/SAM-axis) in the behavioural functions and in behavioural disturbances. It also deals with the effects of psychological stress on the structure and functioning of the central noradrenergic system. It therefore represents the psychoneurological component of the psychoneuroimmunological interaction in terms of the CNA/SAM-axis. A wealth of experimental results gives credence to the importance of the CNA/SAM-axis in behaviour and the following paragraphs will provide some of the evidence, first in animals, and then in man. In an attempt to restrict the volume of work, more emphasis is placed on the psychoneurological interaction as evidenced from results and observations in humans, while animal studies are dealt with in a fairly concise way. The chapter is finally summarised in a heuristic model, depicting the central noradrenergic systems, their projections to other cerebral structures, their interactions with other neuroregulatory networks, their more specific cerebral effects and functions, as well as their relatedness to behavioural functions and psychiatric disorders.

CNA = central noradrenergic; SAM = sympathoadrenomedullary; NA = noradrenaline.

Introduction

The aim of Chapters 3 and 4 is to illustrate the psychoneuroimmunological interaction in terms of the first of the two major stress axes, i.e. the CNA/SAM axis. This chapter demonstrates the important role of the CNA/SAM-axis (central noradrenergic/sympathoadrenomedullary-axis) in behaviour and shows how emotional distress, as well as eustress, impacts on the structure and function of the central nervous system noradrenergic (CNA) neurons – with further long-term behavioural consequences. It therefore deals with the psychoneurological aspects of psychoneuroimmunology.

The layout of this chapter is as follows

3.1 The psychoneurological interaction in animals

3.2 The psychoneurological interaction in man

3.3 The bidirectional interaction between the psychological functions and the CNA/SAM-axis

3.4 Summary and heuristic model of the bidirectional interaction.

The distribution and projections of the CNA system, as well as its functions and interactions are shown in Figure 3.6. Figure 3.6 presents the final summary of the chapter and is given at the end of the chapter. However, a minimised version of it is also presented on the next page (Figure 3.1). There are two important reasons for showing the smaller scale version now and the larger scale version at the end. The first reason is that it is much easier to read the chapter having seen the overall distribution and functions of the system. The end of the chapter is, however, its rightful place and the larger, that is, easier to read version will thus be inserted there. The second reason is for the benefit of the reader not interested in the details of the interactions. The scheme on its own will, in such a case, provide enough information to verify the pervasiveness of the bidirectional influence between the noradrenergic system and the behavioural functions without having to read the fine details of the text.

Figure 3.1 is shown on the next page and its legend on the following page.

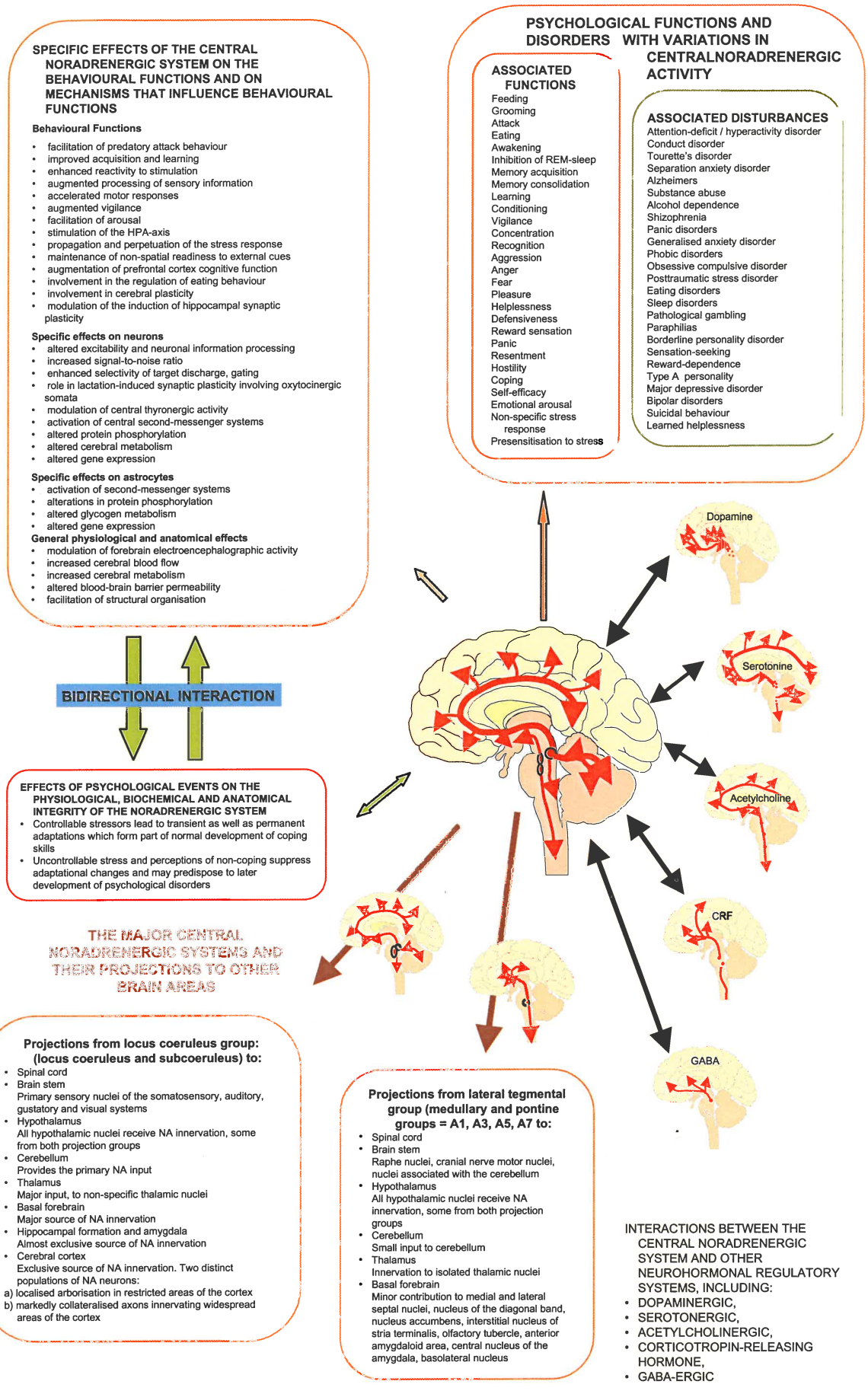


Figure 3.1: A heuristic model of the psychoneurological relationship in terms of the central noradrenergic system

Legend to Figure 3.1

Figure 3.1: A heuristic model of the psychoneurological relationship in terms of the central noradrenergic system.

[Figure 3.1 shows the structure-functional relationship of the CNA system. In the bottom left sector the two major divisions of the central noradrenergic (CNA) system with their projections are depicted. The top-left sector shows the specific effects of the noradrenergic influence. The top- right depicts the behavioural functions and disorders associated with variations in CNA activity and the bottom-right the interactions between the CNA system and other neuroendocrine modulatory systems. In the middle-left the bidirectional influence between structure and function is shown.]

3.1 The psychoneurological interaction in animals

Results from a multitude of publications confirm the existence of a link between the CNA/SAM-axis and the behavioural functions in animals. Studies on the association focus largely on adverse conditions and emotions, such as stress, fear, anxiety, and aggression. Hardly any animal studies have been performed in an attempt to examine the psychoneurological interaction during positive emotional states or to define the behavioural aspects in more discriminatory terms. This is partially due to problems involved in defining and categorising behavioural functions and dysfunctions in animals to the extent possible in man. Psychoneurological studies in animals are, however, of interest as the findings may sometimes be extrapolated to related clinical conditions in humans. Such studies are further relevant as they support the concept of a role for perception in the psychoneurological interaction. However, the most valuable contribution of animal studies is that certain processes and manoeuvres such as the measurement of central nervous system transmitters and activities, as well as direct neural manipulations, can be performed which are, for logistic and ethical reasons, not possible in man. Results from animal studies have opened a window into our understanding of the noradrenergic-related neurological mechanisms that underlie the behavioural functions and dysfunctions in man. Such noradrenaline-related mechanisms include processes involved in a) memory and memory impairment, b) fear, anxiety, aggression, stress, c) presensitisation to fear, to anxiety, to aggression and to stress, d) distortion of sensory and time perception, e) regulation of eat, sleep and drink, f) learned helplessness, g) traumatic recall/flashbacks of aversive events, as well as h) conditioning and failure to eliminate conditioned responses. It is easy to see how results from such experiments may be extrapolated to a number of psychopathological phenomena in man. A discourse on the feasible extrapolations is beyond the purpose of this writing. The aim of this section, which deals with the psychoneurological interaction in animals, is to provide the necessary evidence for this interaction in terms of the CNA/SAM-axis, and to resist the temptation to needless elaboration.

A major part of our knowledge on the psychoneurological interaction in animals is, as was previously mentioned, derived from experiments that involved activation of the central stress response. It is generally known that activation of the central stress response is almost without exception associated with an increase in central noradrenergic (CNA) activity. During periods of acute stress the CNA-activity can generally be measured as an increase in central noradrenaline release (CNA-release) and/or an increase in tyrosine hydroxylase production. However, continuous or excessive central noradrenaline release, as a result of chronic or inescapable stress, may lead to the situation where CNA-production is unable to keep up with CNA-release. It has been postulated that the resultant central noradrenergic depletion may be the cause of the chronic stress-induced behavioural alteration known as "learned helplessness" (1). The term "learned helplessness", as described by Seligman originated from experiments in which animals were subjected to uncontrollable shock. Learned helplessness in animals is by many considered to be a convincing laboratory model for depression in humans. This is based on the fact that the first six DSM-IV criteria for depression are seen in animals after uncontrollable, adverse experiences (2,3). Under such circumstances the stress-induced increase in noradrenergic neuron activity would be reflected as a decrease in CNA-content and/or an increase in MHPG, i.e., the major noradrenaline metabolite or even changes in the anatomical aspects of the CNA system. The effect of acute, as well as chronic stress on the various CNA parameters can be found in an excellent review by Bremner, *et al,* 1996 (4) that summarises the stress-induced alterations of CNA parameters in the cerebral cortex and in subcortical areas such as the hippocampus, the amygdala, the thalamus, and the hypothalamus.

Rapid activation of the central noradrenergic (CNA) system (locus coeruleus), as occurs during any episode of marked emotional arousal, is generally paralleled by simultaneous activation of the peripheral noradrenergic system, i.e., the SAM-axis (5). The synchronous activation of the locus coeruleus-CNA system and the peripheral SAM-axis would lead to the expression of central noradrenergically-induced behavioural alterations, and peripheral stress effects through the SAM-axis.

A considerable functional link exists between the peripheral part of the CNA/SAM-axis, i.e., the sympatho-adrenomedullary-axis (SAM-axis) and the behavioural functions. Due to the simultaneous activation of the locus coeruleus-central noradrenergic system and the SAM-axis, observations of hyperactivity of the latter are often equated with hyperactivity of the central noradrenergic (CNA) system. It is also known that wrong interpretations of some of the peripheral effects such as severe cardiac palpitations may have severe implications for the emotional stability. A discussion of alterations in the adrenomedullary noradrenaline:adrenaline ratio in major depressive states is deferred to the part dealing with the interaction in humans.

The peripheral so-called sympathetic effects are, as is well known, the result of direct stimulation by the sympathetic neurons, enhanced by the actions of circulating adrenomedullary hormones such as adrenaline and noradrenaline. The concomitant increase in activity in peripheral SAM-axis, at the time of emotions-associated CNA hyperactivity, involves neural structures such as the amygdala, descending projections from the locus coeruleus to the brainstem, as well as the nucleus paragigantocellularis (6,7). The effects of general activation of the peripheral sympatho-adrenomedullary system, (SAM-system) commonly known as the *alarm* or the *fight-or-fight* reaction, are summarised in Figure 3.2. Although it is by now common knowledge that these effects occur in man, the initial experimental results were all derived from animal experimentation (8).

The peripheral SAM-axis effects, as summarised in Figure 3.2, are determined by the type of adrenoceptor involved and the concentration of the transmitter substance. This is generally known and as such does not warrant further discussion at this point in time.

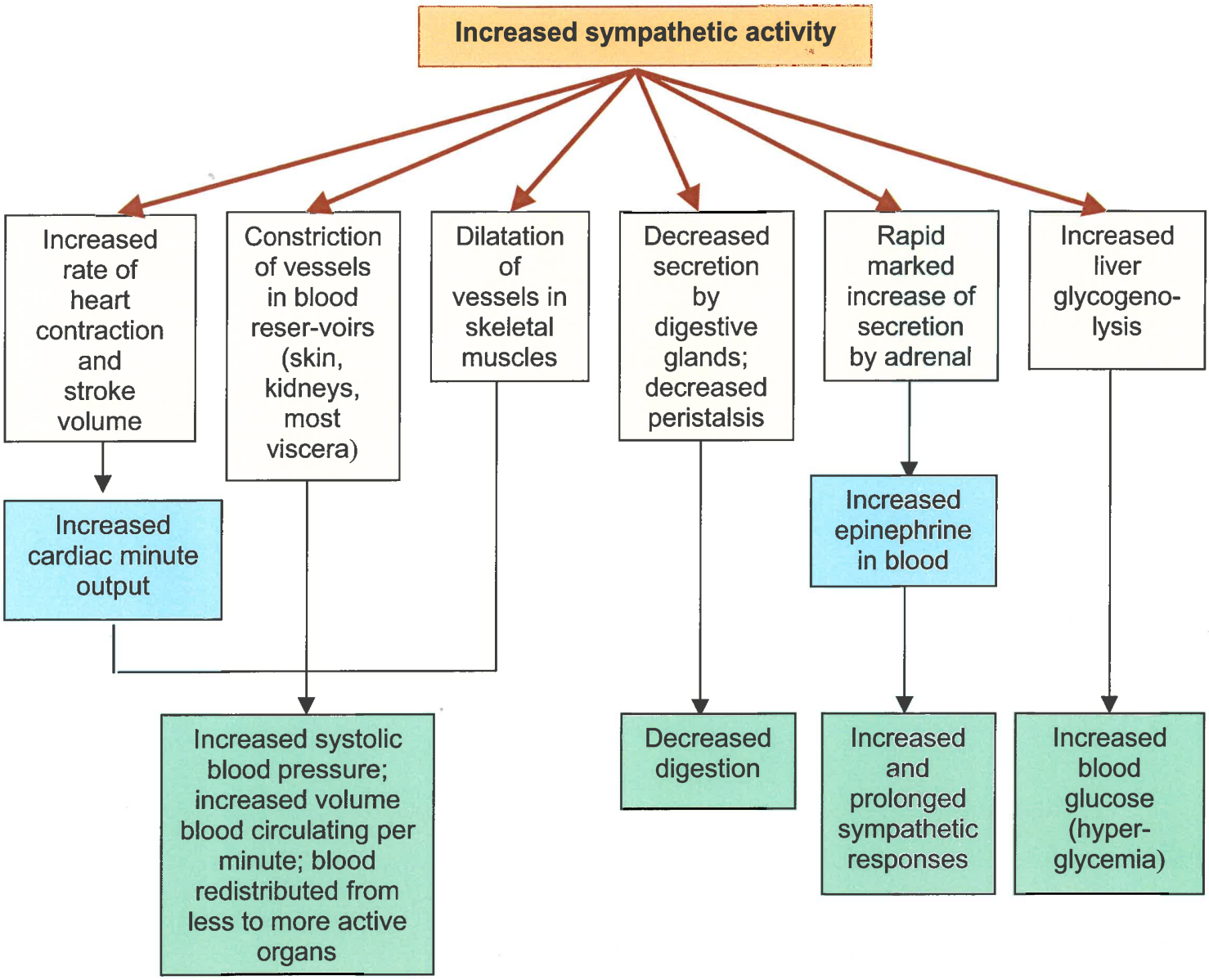


Figure 3.2 : Peripheral effects of general activation of the SAM-axis.

As in the case of the peripheral adrenergic effects, the effects of the central noradrenergic (CNA) system also depend on the postsynaptic receptor involved. These central noradrenergic receptor effects can be summarised by saying that postsynaptic beta-adrenoceptor and presynaptic alpha-2-adrenoceptor effects are generally of an inhibitory nature, while excitatory effects are commonly associated with alpha-1-adrenoceptor stimulation. As such beta-stimulation has been implicated on the ability to concentrate on the task at hand, while inhibiting the influence of irrelevant information, and alpha-1 activation with arousal, the transition from sleep to wakefulness, and the augmentation of registering sensory information about the environment. Impairment of the latter is said to have a bearing on the symptoms of dissociation, which is a characteristic of several behavioural states (4).

Published findings in support of the existence of an association between the central noradrenergic (CNA) system and specific behavioural functions in animals include

- defensive and/or aggressive behaviour upon noradrenergic infusion into subcortical areas (10)
- increases in the firing rates of locus coeruleus neurons upon real or perceived threats (11,12)
- significant increases in locus coeruleus activity, defensive behaviour as well as blood pressure and heart rate, upon exposure to potentially dangerous elements (13)
- fear and anxiety-related behaviour upon stress-induced increases in locus coeruleus activity (14)
- fear and anxiety-related behaviour upon pharmacologically-induced increases in the firing of locus coeruleus neurons, or increases in noradrenaline secretion (11,15,16)
- suppression of locus coeruleus firing rate and noradrenaline release during rest, sleep, white noise, feeding and grooming (17,18,19,20)
- the noradrenergic modulation of amygdalar functions and by implication of the influence of emotion on memory formation (21)
- the promotion of waking and the inhibition of REM-sleep (22) by noradrenaline

- higher levels of the enzymes involved in noradrenaline production in rats bred to attack (23)
- a role for noradrenaline in both the initiation and termination of food intake (24)
- the role for noradrenaline in pathways involved in pleasurable or reward sensation (23)

It has been shown that chronic stress can facilitate locus coeruleus activity through presensitisation - probably through suppression of the central alpha-2-adrenoceptor inhibitory function (4). It is suggested that the results of this presensitisation of animals, as a result of earlier stressful life events, might be extrapolated to human panic disorders, the post-traumatic stress syndrome (PTSD) and the acute combat stress reaction (ACSR) (25). The concept of presensitisation by the central stress response concurs with the finding that childhood abuse in humans would appear to presensitise the individual to the development of combat-related post-traumatic stress disorders in adulthood (26).

It is undeniable that perception does influence the outcome of the psychoneurological interaction. Conceptualisation of the word perception is, however, somewhat problematic when applied to animals. Anxiety is said to be an example of an animal behavioural function that can be seen as a perception-related phenomenon. This in view of the fact that the anxiety response in animals has in the past been described as a maladaptive fear response, i.e., a fear response in the absence of an appropriate virtual threat (27). Examples of the association between anxiety and increased activity of the CNA/SAM-axis were referred to earlier.

The role of perception in the interaction between the behavioural functions and the CNA system is further evident from the results of experiments on conditioned fear in animals. Central noradrenergic activity is said to be involved in this type of reaction where the fear response is provoked by means of a conditioned stimulus (28,29). A great deal of factual information on the interaction between the behavioural functions and the CNA/SAM-axis has, in fact, been derived from this type of experiment and some of the insight obtained from such animal studies contributed to our understanding of the underlying neurological

mechanisms of a number of psychological disturbances in man. Noteworthy results, from animal conditioning experiments, showed the following

a. Increased locus coeruleus activity during fear conditioning, but not during reward conditioning (11)

b. Overactivity-induced noradrenaline depletion of CNA contents to strengthen the response to contextual cues, but to inhibit the fear response to explicit cues (30)

c. The amygdala to be involved in the role of the CNA/SAM-axis in the development of conditioned responses, and perhaps more specifically, fear and anxiety related responses (4), in that

- the amygdala discriminates between noxious or rewarding as opposed to neutral experiences, and as such rules between stimulation and non-stimulation of the CNA activity
- the amygdala is instrumental in the peripheral expression of the conditioned fear response where noradrenaline appears to act through the central nucleus of the amygdala
- the amygdala is involved in the extinction, or stress-induced CNA-modulated non-extinction, of the conditioned response (the extinction of a conditioned response, upon exposure to the conditioned stimulus alone, entails the suppression of subcortical areas such as the amygdala, by cortical areas)
- noradrenaline release in the amygdala is said to help integrate the sensory aspects of experiences pertaining to conditioning as such influences modulate the conditioned emotional response
- amygdalar lesioning prevents the acquisition of conditioning, both in response to specific cues and to context

d. Pathways between the CNA system and the hippocampus to be involved in the neurological processes of conditioned responses (4, 9),in that

- hippocampal lesioning does not abolish the acquisition of fear-related responses to cues, but does interfere with the acquisition of conditioned emotional responses to context (noradrenaline is involved in the role of the hippocampus in conditioning related to spatial context)

- noradrenaline release in the hippocampus may help to integrate the various aspects of a new experience which contributes to the recall of the original aversive events
- the hippocampus, under the influence of the CNA system, may contribute to the stress-induced extinction failure of conditioned fear responses

e. A role for the CNA system in the modulation of the acquisition and retention of memory, in the attentional component of memory storage, in the age-related deficits in working memory and in memory retrieval or recall such as in trauma-related flashbacks (4, 9).

The information described above is derived from experiments in animals where the perception of adverse circumstances, induced through the process of conditioning, lead to alteration of central noradrenergic activity. It is easy to imagine how some of the psychoneurological interactions described may relate to psychological dyshomeostatic phenomena, including traumatic recall of combat-related post-traumatic disorders, the failure to eliminate conditioned emotional responses in patients with phobic anxieties by repeated exposure to the phobia inducing stimuli, as well as the cognitive impairment associated with panic disorders.

The link between the CNA/SAM-axis system and the behavioural functions, as for interactions between other physiological systems and the behavioural functions, are often best observed in situations perceived as extreme by either the body or the mind. It is clear from previous paragraphs that the extreme conditions referred to in the previous sentence are, where animal experimentation is concerned predominantly of an aversive rather than a pleasurable nature. The physiological changes which occur as a result of adverse psychological conditions or perceptions - especially those experienced chronically and perceived as uncontrollable - are seen as maladaptive, and often as incompatible with normal functional integrity. Such changes are peripherally expressed in symptoms like the stress-induced triad consisting of intestinal ulcers, atrophy of lymphoid tissue and hypertrophy of the adrenal glands, as well as cardiovascular, immunological and other abnormalities (the immunological stress-induced alteration of the two main stress axes

are discussed in Chapters 4 and 5). Central nervous system symptoms and even death may also occur. This in contrast to the positive, pro-adaptive neurological effects ascribed to acute activation by mild, intermittent, controllable stressors or by states of eustress. Despite the negative association between chronic, uncontrollable stressful situations and the adverse effects on physiological, as well as psychological well- being, it appears imperative that the neurological system be able to undergo favourable stress-induced anatomical, biochemical and/or physiological adaptations in order to meet novel psychosocial and environmental demands. Anatomical, biochemical and functional alterations have indeed been shown to occur in the brain of animals under certain conditions. Some such changes are seen in Table 3.1. In compliance with the context of this chapter, the changes listed in the table are limited to those pertaining to the central noradrenergic system.

Table 3.1: Modulation and modification of the central noradrenergic system by environmental and psychosocial influences (stress adaptation and presensitisation)

1.	Stress induced increases in synthesis, content, turnover, and release of noradrenaline. Increased production of NA results from ↑ tyrosine hydroxylase (TH) mRNA. The *c-fos* is stimulated by CRF and NA	31,32, 33,35,36, 37,38
2.	Firing rates of NA neurons of the locus coeruleus are increased by controllable stressors	39
3.	Multiple exposures to the same moderate controllable stressor lead to presynaptic axonal sprouting and an increase in cortical noradrenergic innervation which in turn lead to a decrease in receptor reactivity as a result of decreased β-adrenoceptor density (receptor down regulation)	40,41,42, 43
4.	Prolonged exposure to severe uncontrollable stress leads to a decline in cerebral NA concentration, NA release and tyrosine hydroxylase activity (stress presensitisation)	32,44,45, 46

5.	Prolonged severe stress causes retraction of degeneration of cerebral noradrenergic fibres (stress-induced cerebral damage)	40
6.	Intermediate stress with different stressors leads to an increase in central noradrenaline turnover but no presynaptic adaptations. This is dependent on previous stress-induced facilitation	31,32,33, 47
7.	Suppression of NA release, loss of noradrenergic innervation and decreased noradrenaline content in the frontal cortex are associated with uncontrollable stress-induced behavioural abnormalities	48,49,32, 50,51
8.	Chronic stress leads to degeneration of NA neurons in the rat cerebral cortex	52
9.	Chronic restraint stress decreases noradrenaline transporter binding sites in the amygdala, hypothalamus and locus coeruleus	53
10.	Stress exposure is associated with augmentation of the firing rate in the locus coeruleus with concomitant increase in the release and turnover of NA in relevant cerebral areas that receive noradrenergic projections	4,9
11.	Stress-induced noradrenaline secretion modulates gene transcription	4

Examples of the modulation and modification of the CNA system, shown in Table 3.1 provide corroboration that psychosocial and environmental influences are indeed instrumental in alterations of the neurological, and in this case CNA, system. Negative effects of stressors on the CNA/SAM-axis would appear to be fairly well documented. A negative influence, particularly well illustrated, is the previously described presensitisation of the neonatal noradrenergic system as a result of early exposure to unfavourable psychosocial influences. The fact that this type of neonatal presensitisation

of the noradrenergic system can predispose to the development of fear and anxiety related psychological disorders in adult life is supported by the results from both animal and human studies. Despite the general impression of the negativity of stressor endurance, it is well known that behavioural adaptation to stressors may eventually occur and that such experiences would often lead to the enhancement of appropriate coping skills. It is thus conceivable that relatively permanent neurological changes would constitute part of an adaptational process to moderate experiences or stressors. As such it would then form part of the development of coping strategies in response to a specific external or internal condition. Such central, and perhaps peripheral, nervous system alterations may potentially be major converting factors, whereby psychological stressors, erstwhile considered moderately uncontrollable, could be rendered perceptionally controllable. The plausibility of such an adaptational role for stress in the CNA/SAM-axis-psychological interaction would be argued further at a later stage.

In conclusion it can be said that animal experiments provide ample physical evidence for the interaction between the noradrenergic system and the behavioural functions. Such evidence, in view of the invasive nature of the experimental procedures, is unlikely to be derived from human experimentation or human observations. One major disadvantage of applicable animal research, however, is the inability to investigate the neurological-behavioural interaction in terms of a finer discrimination between the various psychological phenomena. The following number of paragraphs will attempt to deal with such aspects in man.

3.2 Psychoneurological Interaction in Man

In the previous section undeniable physical evidence was presented for the psychoneurological interaction in terms of the CNA/SAM-axis system. The aim of the present writing is to endorse the existence of the proposed interaction by documenting some of the associations reported to exist in humans between the behavioural functions and the CNA/SAM-axis.

Although the pathways and mechanisms of action were largely unknown, the central noradrenergic system has long been associated with behavioural functions such as arousal, vigilance, concentration, memory, fear, anxiety, aggression, hostility, agitation, resentment, pleasure, alertness, vigilance, arousal, as well as with enhanced activity of the peripheral sympathetic nervous system. (55,56,57). Evidence for some of these associations in animals were provided in the previous section that dealt with animal experimentation.

Identifying the physiological mechanisms underlying the different behavioural functions has always been problematic. During recent times at least some of the mysteries concerning this mind-body link, i.e., the pathways and mechanisms that have a bearing on psychological processes, were solved. The research involved in exploring the psychoneurological interaction is, however, still confounded by many factors - not least of it the interdisciplinary nature of the field. In animals the physical confirmation of the psychoneurological interactions are generally obtained by means of rather invasive experimental procedures. In man a major part of the relevant research has to rely on indirect assessments as major invasive experimental procedures are not possible in humans. These confounding factors are also applicable when examining the mind-body link in terms of the CNA/SAM-axis. Alterations in central noradrenergic functions are assessed, predominantly, by indirect measures such as a) changes in peripheral adrenergic activity, as reflected by factors such as heart rate and blood pressure, b) plasma catecholamine and catecholamine metabolite levels, c) urinary catecholamine and catecholamine metabolite levels, as well as 24hr excretion of the 3-methoxy-4-hydroxyphenyl-glycol (MHPG) metabolite, d) adrenergic receptor expression on circulating blood cells, e) post-mortem CNS receptor determinations, f) pharmacological modulation of the noradrenergic system by agonists and antagonists, and g) noradrenaline spill-over rates. As for all indirect assessments, each of these techniques poses certain potential errors in the estimation of central noradrenergic activity. With the development of newer neurological procedures, more innovative techniques are becoming available. A discussion of the merits and disadvantages of such techniques is, perhaps, beyond the scope of this writing. However, one fact that should always be kept in mind is that

chronically high levels of catecholamines may not reflect the stimulation state as receptor down regulation may occur.

Clinical research is often a continuance or in pursuit of indications derived from animal experiments. Although the picture is still far from complete, noradrenergic neural mechanisms and pathways involved in the expression of the behavioural functions are rapidly being identified. A great deal of insight into the noradrenergic effects on the psychological make-up of man is deduced from the connections between the CNA-system and other parts of the brain whose roles are known. It is, for instance, now known that the locus coeruleus-noradrenergic system stimulates the mesocortical and mesolimbic dopaminergic systems that in turn innervate the prefrontal cortex and nucleus accumbens, respectively (58,59,60,61,62,63). As such noradrenaline is involved in anticipatory and other cognitive functions, as well as with functions related to motivation, reinforcement and reward. It is of interest to note that the central noradrenergic system is also involved in the regulation of the prefrontal cortex in a more direct way. This implicates a far-reaching role for the noradrenergic system in the control of the behavioural functions as the prefrontal cortex is known to be involved with most of the higher cognitive functions such as the elaboration of thought. Dysregulation or impairment of the functional integrity of the prefrontal cortex has in the past been associated with behavioural problems such as augmentation of working memory and attention regulation, behavioural inhibition, schizophrenia-like symptoms and attention-deficit/hyperactivity disorder symptomatology (64). Some of these abnormalities are also connected to CNA/SAM-system dysfunction. Pharmacological intervention studies, by means of agonists and antagonists, indicate a favourable effect for noradrenaline on the prefrontal cortex when acting on presynaptic alpha-2-adrenoreceptors, and a detrimental effect when acting on alpha-1-adrenoceptors. It is further suggested that the prefrontal cortex needs the noradrenergic input for optimal functional integrity, but that excessively high levels of adrenergic activity, as with severe emotional stress, may suppress its activity and allow subcortical structures to take over the regulation of the required behavioural responses at a faster rate (64). One could perhaps hypothesise that this biphasic effect might be related to the well-known enhancement of cognitive abilities

seen with moderate increases in central noradrenergic activity as opposed to attention fixation with excessively high noradrenergic activity.

Two other important connections between the locus coeruleus-noradrenergic system and other cerebral areas are that with the amygdala and with the hippocampus. The link with the amygdala is important for information retrieval and emotional analysis pertaining to a stimulus (65,66,67). A very intricate neuroanatomical interaction exists between the hippocampus and the central noradrenergic system. This is further complicated by the fact that central noradrenaline can exert its effects on the hippocampus through presynaptic alpha-2-autoreceptors, through postsynaptic alpha-1-adrenoceptors, as well as through beta-adrenoceptors, and is therefore able to inhibit, to stimulate or to facilitate hippocampal neuronal activity (68). Bidirectional influences between the central noradrenergic and central serotonergic neurons have been identified and both neural systems are involved in similar hippocampus-related cognitive and affective functions (68). Their effects, as seen later, may however, often be of an opposing nature.

A connection of major importance with regard to the interaction between the behavioural and the physiological functions is that between the central noradrenergic system and the paraventricular nucleus. The connection comprises a positive, reverberatory feedback loop of activation between the central corticotrophin-releasing neurons and the locus coeruleus noradrenergic neurons and thus between the CNA/SAM-axis and the corticopin releasing hormone/ hypothalamo-pituitary-adrenal axis (CRH/HPA) (55). It is often, through this positive feedback association, that many of the behavioural phenomena find expression. This multi-faceted interaction is, however, a further confounding factor in identifying the primary neurological impairment of related behavioural dysregulations. More about that later in this chapter.

Undeniable evidence exists for the role of the noradrenergic system in learning (69). However, it is as yet not possible to define its exact role in learning behaviour. This despite a vast amount of work on the role of the CNA/SAM-axis in processing and integration of sensory and motor information. In view of the multiple influences of the

noradrenergic system on the rest of the central nervous system, including those on the amygdala, hippocampus and cortex, it is obvious that the CNA system must have at least strong indirect effects on learning behaviour. The connections between the CNA system, the amygdala and the hippocampus were referred to earlier in this chapter. The amygdala and hippocampus are known to be important for implicit, as well as explicit emotional memory, respectively. Strong evidence for noradrenergic involvement in learning and information retention in humans comes from pharmacological experiments and clinical studies where drugs with pro-catecholaminergic actions were shown to enhance learning and retention, and drugs with the opposite effect, seemed to impair such processes (69). An interesting observation is that destruction of the locus coeruleus does not seem to have a major impact on the learning process (23). The involvement of the CNA system in neonatal learning has also been shown in a study where the system would appear to be essential for recognition through preferred tactile and odour identification (70).

Another interesting observation is the fact that peripheral adrenaline, secreted from the adrenal medulla in conditions of stress, is said to have a positive influence on memory, and by implication, on the learning process (71). A pathway by which peripherally secreted adrenaline in response to stress may exert its central nervous system influence is suggested in Figure 3.3. In this pathway circulating adrenaline is said to have an effect on the vagus nerve, which would influence the nucleus tractus solitarius (NTS), which then, in turn, would stimulate the noradrenergic neurons of the locus coeruleus, which have widespread connections with the amydala and hippocampus - two structures intimately associated with learning and memory.

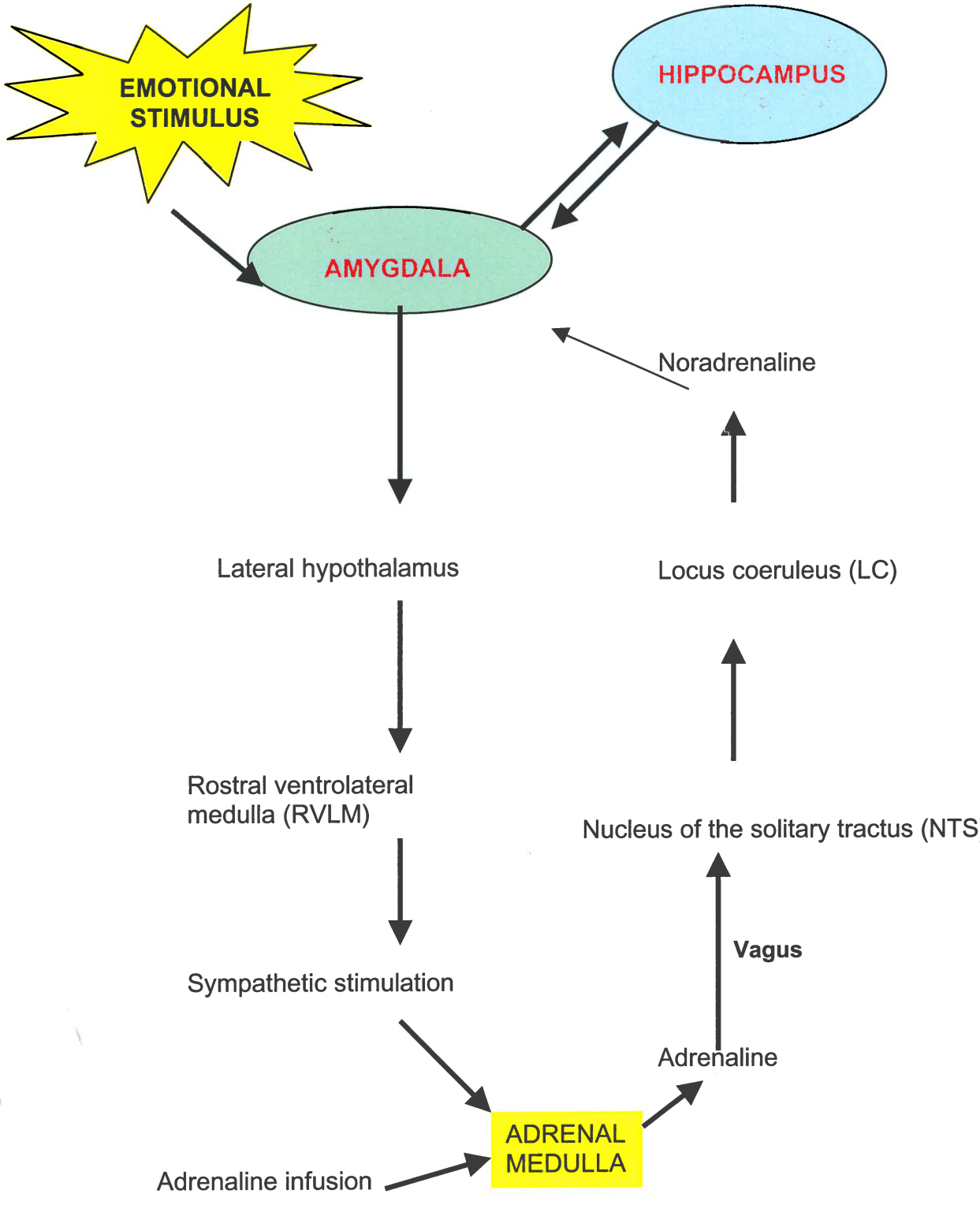


Figure 3.3: The influence of stress-induced peripheral adrenaline secretion on learning [Figure 3.3 shows how an emotional stimulus will activate the sympathetic nervous system, that in turn will increase adrenaline release. Adrenaline, through its effect on the vagus nerve, would lead to activation of the noradrenergic system of the locus coeruleus, which would facilitate the learning processes by the amygdala and hippocampus.] Adapted from (71).

In humans, in contrast to animals, it is possible to define the psychoneurological interactions in terms of more specific aspects of the behavioural functions. Unfortunately, research on this psychoneurological interaction in man, as for animal research, is focused largely on the interaction under adverse conditions, or in individuals with some or other psychological imbalance. Learning and sometimes personality, constitute two of the few behavioural phenomena studied in relation to the CNA/SAM-axis system that do not pertain to adverse environmental or psychosocial conditions, or do not involve a dysregulation of some or other psychological function.

It is fairly predictable that researchers should have tried to find a correlation between personality and the noradrenergic system. This is especially true where the Type A behavioural pattern is concerned, which, according to Friedman and Rosenman (72), conforms to the following:

- reliable components : loud voice, quick speech, enhanced psychomotor activity, tension of facial muscles
- attitudes and emotions : hostility, impatience, anger, aggressiveness
- motivational aspects : achievement motivation, competitiveness, leaning towards success and ambition
- evident or open behaviour: hyperactivity, alertness, celerity, work involvement
- cognitive aspects: control and attributional style

The above behavioural characteristics of the Type A person, in combination with the association of high blood pressure in this type of personality, would in itself be suggestive of high central and peripheral noradrenergic activity. This association is supported by a significant number of publications. There are, indeed, strong indications to suspect Type A personalities to have fast-activation-slow-recovery type psychological profiles (73). Of interest is the fact that this type of personality would appear to display the noradrenergic hyperactivity, as evidenced by cardiovascular and neurohormonal traits, during stress, as well as under basal conditions (74). It is possible that this may

contribute to the epidemiological findings of increased coronary risk. As mentioned earlier, examples of behavioural states associated with augmented noradrenergic activity include augmented vigilance, concentration ability, anger, aggression, irritability, restlessness, fear, anxiety, anticipation, certain perceptions and many others. The involvement of the adrenergic system in such behavioural states is confirmed by intravenous infusion of catecholamines and by symptoms seen in patients with tumours of the adrenal medulla. An increase in the activity of the CNA system, with concomitant hyperactivity in the peripheral sympathetic system (SAM-axis), has indeed been shown to occur in normal, healthy individuals in any situation where substantial emotional activation is present. Aggression is one of the emotions most often associated with noradrenergic function. Most of the evidence for a CNA/SAM-axis role in aggression is derived from peripheral catecholamine shifts. A change in the circulating noradrenaline: adrenaline (NA:A) ratio is a characteristic often seen in aggression, but may be found in many other states of emotion. One could with a fair amount of certainty say that a reduced NA:A ratio would probably refer to a greater HPA-axis involvement in an emotion as the stimulatory effect of the axis on adrenomedullary enzymes is a well-established fact. It is said that the "fight" sympathetic response, or active aggressive emotional display, is primarily associated with an increase in the NA:A ratio, and the "flight" or tense/passive/apprehensive emotional display of the fight-or-flight reaction, with a decrease in the NA:A ratio. The above assumption is supported by the findings of higher urinary noradrenaline levels in persons who are chronically irritable, resentful and angry, while a more significant increase in urinary adrenaline is said to be seen with generalised fearfulness and doubt (75). This may, again point toward an HPA-axis involvement as mentioned in the chapter dealing with the psychoimmunological interaction. Further support for a role of the noradrenergic system in aggression is derived from the aggression seen in normal animals treated with some drugs used to augment noradrenergic activity in depressive humans (76). Extrapolations to therapeutic implications are self-evident.

Temperament-related behaviours such as inhibition or aggression are known to be related to early childhood biological responses to social adversities. Based on results from a

sizeable number of investigators it is suggested (77) that autonomic reactivity in the so-called *easy child* is likely to be characterized by a high stimulus threshold and a quick return to baseline values (strong dampening). The difficult child, in contrast, is said to have a low autonomic threshold, slow return to baseline levels and a high predisposition for re-activation upon repeated stimulation (77). The individual contributions of the CNA/SAM-axis and the cholinergic system, respectively, to the altered autonomic balance are not clear. It is also not clear whether this psychobiological contrast between the easy and difficult child is to be ascribed to genetic differences or to early psychosocial preconditioning. The answer is probably to both. Similar presensitisation of the noradrenergic system to the combat-related stress syndrome has been described earlier in this chapter.

Most of the behavioural symptoms described in the last couple of paragraphs occurred in normal healthy individuals in reaction to the context of the situation, where the associated enhanced noradrenergic activity occurred as an acute change from baseline levels. It is, however, clear that the CNA/SAM-axis may very well be involved in a number of behavioural disturbances. The best substantiated indications for an association between noradrenaline and behavioural disorders are those pertaining to the fear and anxiety related disorders. Evidence supporting, as well as evidence refuting such a virtual relationship can be seen in Table 3.2, as adapted from recent reviews (4,9). References to the original authors can be found in the articles (4,9).

Table 3.2: Evidence for and against the involvement of the CNA/SAM-axis in fear and anxiety-related disorders (4, 9).

Disorder	**Supportive *vs* non-supportive publications**
1. Panic disorder	
Increased resting heart rate	5 vs 4
Increased resting blood pressure	1 vs 3
Increased resting heart rate in panic-prone patients	1 vs 1

Increased heart rate response to orthostatic challenge	1 vs 0
Increased heart rate during panic attacks	6 vs 2
Increased blood pressure during panic attacks	2 vs 2
Increased plasma noradrenaline	1 vs 5
Increased plasma adrenaline	2 vs 0
Increased resting urinary adrenaline and noradrenaline	2 vs 1
Increased plasma MHPG at baseline	0 vs 3
Increased plasma MHPG during panic attacks	1 vs 2
Decrease in lymphocyte β-adrenergic binding sites	1 vs 0
Decrease in basal activity of cAMP	1 vs 0
Decreased platelet alpha$_1$ binding sites (B_{max}) for clonidine	1 vs 1
Decreased platelet alpha$_2$ binding sites (B_{max}) for yohimbine	3 vs 2
Decreased platelet alpha$_2$ receptor affinity (K_D) for clonidine	0 vs 1
Decreased platelet alpha$_2$ receptor affinity (K_D) for yohimbine	1 vs 0
Decreased platelet alpha$_2$ (B_{max}) and (K_D) for [^{3}H] rauwolscine	0 vs 1
Reduction in panic anxiety with clonidine	4 vs 1
Blunted growth hormone response to clonidine	4 vs o
Increased plasma MHPG with yohimbine	5 vs 0

2. Posttraumatic stress disorder

Increased resting heart rate	5 vs 5
Increased heart rate and blood pressure response to traumatic slides and sounds	5 vs 0
Increased heart rate and blood pressure response to traumatic scripts	4 vs 0

Increased resting urinary noradrenaline	2 vs 2
Increased resting plasma noradrenaline	0 vs 1
Increased plasma noradrenaline in response to traumatic reminders	1 vs 0
Increased plasma adrenaline in response to traumatic reminders	1 vs 0
Increased startle reaction	1 vs 1
Decreased binding to platelet alpha$_2$ receptors	1 vs 0
Decrease in activity of cAMP	1vs 0
Decrease in platelet monoamine oxidase activity	1vs 0
Increase in PTSD and plasma MHPG with yohimbine	1vs 0
Differential effect of yohimbine on brain metabolism	1vs 0

3. Generalised anxiety disorder

Increased plasma noradrenaline	3 vs 1
Increased plasma adrenaline	2 vs 0
Increased plasma MHPG	2 vs 0
Increased monoamine oxidase activity	1 vs 0
Decreased platelet alpha$_2$ adrenergic binding sites	1 vs 1
Blunted growth hormone response to clonidine	1 vs 0
Behavioural and biological responses to yohimbine	0 vs 1

4. Phobic disorders

Increases in heart rate, blood pressure, plasma, noradrenaline and adrenaline with phobic stimulus in simple phobia	1 vs 0
Increased plasma noradrenaline in social phobia	1 vs 0
Blunted growth hormone reponse to clonidine in social phobia	1 vs 0

5.	**Obsessive-compulsive disorders**	
	Increased plasma noradrenaline	1 vs 0
	Increased plasma MHPG	1 vs 1
	Blunted growth hormone response to clonidine	1 vs 3

MHPG = 3-methoxy-4-hydroxyphenylglycol

The results from the studies referred to in table 3.2 almost uniformly support the assumption of increased noradrenergic activity during the attacks of patients suffering from panic disorders. Controversies still exist with regard to baseline activity, with some workers reporting raised levels, and others contradicting it. An increase in cerebral responsiveness is suggested, possibly involving alpha-2 receptor dysregulation. Similar results were found in the posttraumatic stress syndrome - again implicating alpha-2-receptor functional alterations. Indications from studies in patients with the generalised anxiety disorder also implicate the noradrenergic system, but it is unlikely that dysregulation of the central alpha-2-adrenoceptor be a major factor in the behavioural dysfunctioning. Although baseline catecholamine and catecholamine metabolite (MHPG) levels were seen to be augmented in phobic and obsessive-compulsive disorders, no conclusive results could be obtained by means of receptor agonist or antagonist studies. It is thus unlikely that the central noradrenergic system should represent the primary neurological impairment in either phobic or obsessive-compulsive disorders. The reason that the CNA/SAM-axis would appear to be strongly implicated as a primary contributor in panic and posttraumatic disorders, in contrast to that in the others, is suggested to be related to their direct pertainment to the stress response (9).

Examples of other associations between the CNA/SAM-axis and some defined behavioural functions and disorders in humans can be seen in Table 3.3.

Table 3.3: Examples of behavioural characteristics and psychiatric disorders associated with variations in noradrenergic activity.

Characteristic/disorders	Reference
Stress Link between central noradrenergic sympatho-adrenomedullary outflow and stress is an established fact (see text for further discussion)	78, 4, 9
Cognition Noradrenaline influences cognitive function through both alpha-1 and alpha-2 adrenoceptors	79
Sensation-seeking Possible association between noradrenergic dysregulation and sensation-seeking in youths with behavioural problems	80
Reward dependence Hypophysis that reward-dependent traits are partially determined by central noradrenaline	81
Pathological gambling A role is suggested for the central noradrenergic system as mediator of the selective attention trait of pathological gambling	82
Substance abuse Possible link between dopaminergic/noradrenergic dysfunction and substance abuse as well as antisocial behaviour	83
Alcohol dependence Changes in the levels of neurotransmitters such as NA	84

Conduct disorder	
Possible decreased NA-functioning (↓ production)	86 (p1072)
Attention-deficit hyperactivity disorder	
↓ adrenaline and ↓ noradrenaline in attention-deficit hyperactivity disorder	86 (p1064)
A multistage hypothesis as an update on the catecholamine hypothesis	93
Tourette's disorder	
Above normal NA-activity implicated by the effects of alpha-adrenergic agonists. May, however, merely reflect an indirect effect on dopaminergic activity	80
Paraphilias in males	
Monoamine hypothesis for paraphilias	94
Fear and anxiety-related disorders	
Extensive evidence for noradrenergic hyperactivity and alpha-2-adrenoceptor dysfunction.	See Table 3.2
Increased firing of locus coeruleus neurons associated with behavioural manifestations of fear	4, 9
Anxiety disorders	
Strong association between high NA-activity and anxiety.	86 (p576,612)
Dysregulation of the central NA-system with periodic activity bursts (General theory)	
Possible subsensitivity of alpha-2 receptors in anxiety disorders	
Proposed anatomical basis of anxiety and network of related brain regions involved in the genesis of anxious behaviour	95
Maladaptive reponses to stress in both the HPA-axis and SAM-axis (Review)	96

Post-traumatic stress disorder (PTSD)

Hyperactivity of at least the noradrenergic system	86 (p607)
Two different subgroups of PTSD; one with a sensitized NA-system, the other with a sensitised serotonergic system	97

Panic disorders

Increased sympathetic tone and central NA-activity implicated as contributing factors	86 (p583)
A functional neuro-anatomical/neurochemical model	98
Increased NA-reponsiveness in panic disorder without changes in baseline NA-function	9 and 4

Phobias

Adrenergic theory for social phobias - augmented secretion of central and peripheral NA and A and hypersensitivity to NA-stimulation	86 (p594)

Depression

Interaction between NA and serotonin a confounding factor in defining the exact role in mood disorders. The biogenic amine hypothesis: Mood disorders associated with heterogeneous dysregulation of biogenic amines such as NA. Decrease in central NA-activity, perhaps as a result of excessive alpha-2 receptor activation. NA activity varies depending on type, severity and phase.	86 (p139)
Higher sympatho-adrenal activity in major but not in minor depression. NA-activity related to HPA-axis activity.	99
The adrenergic-cholinergic imbalance hypothesis.	100
Serotonin-noradrenaline link hypothesis of affective disorders: a receptor-receptor interaction	101
Sympathetic nervous system activity is augmented in major depression	102

(Prolonged administration of desipramine leads to alpha-2 desensitisation and tricyclic antidepressants to reduced NA clearance)	
Depressed patients, especially melancholic and unipolar, excrete above normal amounts of NA and demonstrate subnormal biochemical and neuroendocrine responses to alpha-2 adrenergic agonists	103
Stronger link suggested between depressed states and adrenomedullary activation than depression and sympathetic system. This for unipolar as well as bipolar states	104
Hypothesis that stress-induced activity in the HPA-axis may be the cause of the abnormal noradrenergic activity of depression	105
Decrease in the NA transporter (NET) in the locus coeruleus neurons implicated in major depression	106
Results with non-psychotic major depressive disorder subjects indicate the HPA abnormality to be related to alpha-2 adrenoceptor dysfunction	107
Clinical improvement of melancholic/psychotic depressive illness after ECT-induced lowering of plasma noradrenaline	108
Abnormalities of alpha-2 and beta adrenoceptors in depression	109

Schizophrenia

Evidence from literature points towards an increase in the central noradrenergic activity and perhaps an alpha-2 receptor dysregulation, depending on severity and stage of affliction. In summary a) it is questionable whether NA alterations are primary to schizophrenia, b) abnormal NA-,metabolism of NA-response to stress may however be implicated in some patients and c) NA is without doubt involved in the modulation of dopamine (see dopamine hypothesis of schizophrenia)	86 (p464)
Hypothesis of multiple neurotransmitters involving complex circuitries. (Implicating a role for the NA-system)	110

Alzheimer's disease

Decrease in noradrenergic activity and decreased number of noradrenergic neurons in locus coeruleus	80 (p346)
Loss of NA neurons contributes to the development of the non-cognitive behavioural impairments of Alzheimer's disease	111

NA = Noradrenaline; 5-HT = 5-hydroxytryptamine (serotonin)

It is by now generally accepted that a dysregulation of the noradrenergic system is involved in the pathogenesis of mood disorders. Several references to this effect can be seen in Table 3.3. Patients with depressive disorders, especially melancholic unipolar subjects, are known to have higher levels of circulating noradrenaline levels than normal and to excrete greater amounts of catecholamine metabolites through their kidneys. Subsensitivity of the alpha-2 adrenoceptors is presumed to be involved in the exaggerated noradrenergic response to environmental and psychosocial stimuli. However, noradrenergic dysfunction is unlikely to be the sole, or perhaps even the major, neurological impairment in mood disorders. This statement may very well be debatable as results from studies on the alpha-2 and beta-adrenoceptors seem to indicate a central role for the central noradrenergic (CNA) system in depression. A variety of other neurohormonal disturbances have, however, also been implicated in depression. Of special interest, with regard to the mood disorders, are the findings of co-existing dysregulations in the CNA/SAM-axis with that in other neurohormonal systems. Some of them are referred to in Table 3.3, and a few examples of such coupled dysregulations will briefly be discussed in the following paragraphs.

- Concomitant dysregulation in both the CNA/SAM-axis and the CRH/HPA-axis is said to occur in severe depression (99). This is a major confounding factor in the search for the primary causative factor. In view of the reverberating positive feedback loop known to exist between the two axes, the primary disturbance may be either a) a disturbance in a common denominator to both axes, b) high sympatho-adrenal (SAM) tone as a result of sustained stimulation by glucocorticoids and/or opioids, i.e.,

augmented SAM-axis activity secondary to high HPA-axis activity, or c) a primary noradrenergic hyperactivity with a resultant secondary hyperactivity in the CRH/HPA-axis, due to the positive feedback interrelationship between the two systems (99). A simultaneous dysregulation in the two axes could, whatever the primary disturbance, lead to the exacerbation of a number of their respective behavioural effects and may, depending on the magnitude and equilibrium shift of the response, have other far reaching psychological effects. This in view of the similarity, and subtle, yet important, differences in their behavioural effects. It is important to note that simultaneous hyperactivation of the noradrenergic and HPA-axes is in no way limited to mood disorders. The stress-induced co-activation of the two systems is well known, but co-activation in other conditions or situations, such as anxiety-related disorders (112), panic- related disorders (96) and the Type A personality pattern (74), has also been reported. It might very well be that the co-activation represents a mere reflection of the activation of the generalised stress response.

- Another co-existing neurohormonal disturbance involving the central noradrenergic system that has been implicated in the mood disorders is that with the central serotonergic system. Approaches to this interrelationship differ, but the neuroanatomical interconnections and functional bidirectional influences between the two systems had already been described more than twenty years ago (113). The original *Serotonin/Noradrenaline Link Hypothesis of Affective Disorders* (114), has, however, been revised, and more recent evidence (115) indicates the serotonin-noradrenaline interaction to be a receptor-receptor interaction which involves alteration in the adrenergic beta-receptor density and second messenger activity. *The Serotonin/Noradrenaline Link Hypothesis of Affective Disorders* implicates the multi-component beta-adrenoceptor system to be an integrative/amplification/adaptation system for behavioural functions such as mood, sleep, arousal and pain perception, as well as for neuroendocrine and autonomic regulation. As such this system is suggested to serve an adaptational function against excessive sensory input. Dysregulation of the system is then hypothesised to predispose to depressive disorders (115).

- The coupled noradrenaline-serotonin dysregulation hypothesis as cause of mood abnormalities has also been implicated in various other approaches (105,114). We shortly refer to the implied role of the noradrenergic-serotonergic system as seen by supporters of the plea for a simpler classification model for psychiatric disorders According to this approach it is reasoned that the majority of common psychiatric disorders, excluding psychotic illnesses, are based on two major symptom dimensions, that is, depression-related symptoms and anxiety-related symptoms (116). This in view of the ideology that a simpler model of psychological illness would facilitate our integrative understanding of the subject. Overlapping of symptoms is said to occur as a result of the presence of social factors associated with each symptom dimension and to the fact that depression and anxiety, two reciprocally related phenomena, both relate to reward and punishment, respectively. Functional alterations in the central noradrenergic and central serotonergic systems are in turn implicated in the aetiology for both the symptom dimensions, i.e., depression and anxiety. A biosocial model for common mental disorders, based on this two-sided biological approach, and with further refinement based on three social factors, i.e., vulnerability, destabilisation and restitution, is suggested (116). Should this biosocial view of behavioural dysfunctioning be correct, the noradrenergic-serotonergic interaction would be a major biological factor in the majority of behavioural disturbances. As in the case of the CNA/SAM-CRH/HPA-axes interrelated dysregulation, the noradrenergic-serotonin coexisting dysregulation has also been implicated in several other psychiatric disorders, including the impulse-control disorders (92), alcohol-related changes in behaviour (85), the generalised anxiety disorder (96) and many more.
- A concomitant cholinergic-adrenergic shift is described in the *adrenergic–cholinergic imbalance hypothesis* of depression where the cholinergic–adrenergic balance is said to be involved in the regulation of drive and mood (100) .The hypothesis is derived from the integration of the knowledge on noradrenergic activity in mood disorders, the observation of depressiogenic and antimanic properties of cholinomimetics, and the acute euphoriant effects of anticholinergic agents. The idea of a co-operative connection or influence between the sympathetic and cholinergic systems with regard

to the behavioural functions is also being considered by others and a concept of synergism of sympathetic and parasympathetic activity has been described (117).

- Various other types of neurohormonal shifts, coexisting with alterations in the CNA/SAM-axis, have been reported for a fairly wide spectrum of behavioural disturbances. Systems or substances in which a disturbance, co-existing with that in the central noradrenergic system, are known to occur, include gamma-aminobutyric acid, endogenous opioid peptides, serotonin, glutamine, thyronergic substances, neurohormonal substances belonging to the hypothalamo-pituitary-adrenomedullary (HPA) axis, as well as a number of other neuropeptides (84,96,110,107).

As bidirectional regulatory influences seem to exist between the CNA/SAM-axis and the majority of neurohormonal systems, it is not surprising to find changes in other neurohormonal factors or systems co-existing with that in the CNA/SAM-axis. It is important to note that the so-called neuropeptides also play an important regulatory role in both the central noradrenergic (CNA) and the peripheral sympatho-adrenomedullary (SAM) systems (118).

Another phenomenon that should perhaps be mentioned is the apparent association between the peripheral part of the CNA/SAM-axis and the behavioural functions, i.e., the proposed influence of sympatho-adrenomedullary (SAM) secretory activity on the psychological make-up. Despite the assumption that catecholamines cannot readily cross the blood-brain barrier, central behavioural effects have been reported in the presence of high circulating adrenaline levels. Published examples of this observation include

- Indications from experimental work show that drugs that affect peripheral, rather than central catecholamine levels will attenuate memory retention. An example of this was referred to earlier in this chapter.
- The reported importance of adrenomedullary activity in the symptoms of both mixed and pure mania (119).
- The increase in the circulating adrenaline:noradrenaline (A:NA) ratio in unipolar depression, which points towards a strong adreno-medullary involvement (99).

- The emotional effects, sometimes mimicking psychogenic anxiety attacks, seen in patients with adrenomedullary tumours (120).
- The psychological effects of catecholamine infusion into the peripheral circulation (71).

Several possible explanations can be volunteered in an attempt to explain the above-mentioned association between the behavioural functions and conditions where the major disturbance appears to be peripheral, rather than central. Due to the influence of the locus coeruleus on sympathetic outflow, as well as the dependence of the adrenal medulla on stimulation by preganglionic sympathetic fibres, it would be absurd to interpret a mere increase in circulating adrenaline (A) and noradrenaline (NA), without A:NA-ratio alterations, as an indication of adrenomedullary involvement in the behavioural functions. An explanation for the changed ratio may possibly be the augmentation of adrenomedullary function secondary to the secretory activity of the adrenal cortex. This in view of the commonly known role of the adrenocortical hormones in changing the A:NA ratio of the circulating catecholamine pool and *vice versa* (121). However, the most feasible explanation would seem to be the alteration of central noradrenergic function through an indirect effect of circulating adrenaline. This could be accomplished by circulating adrenomedullary derived adrenaline, influencing the transmission along vagal afferents to the tractus solitarius, which in turn could activate the locus coeruleus , giving rise to the CNA-induced changes in behaviour. A schematic presentation of this was given earlier in this chapter (Figure 3.3).

The coexistence of disturbances in more than one neurohormonal system just described stresses the fact that any hypothesis trying to describe a behavioural syndrome as a *too-little* or a *too-much of one specific neurotransmitter* is bound to be incomplete. This statement, especially with regard to the CNA/SAM-axis, is substantiated by the multiple anatomical-physiological interactions between the noradrenergic and other neurotransmitter/ neurohormonal systems. It would appear that one could at best arrive at a decision on the type of neurohormonal shift typical for a specific behavioural disturbance or, in some instances, at a decision on the primary disturbance. In view of the

widespread connections of the noradrenergic system, as well as the adrenoceptor alteration repeatedly shown in association with variations in behavioural functions, one cannot summarily rule out the possibility of a disturbance in this system as the primary factor in a number of psychological disturbances. It is, however, unlikely that diagnoses, based on such potential neurohormonally-defined patterns, would be possible without considering the psychosocial environment as well as the perception, self-efficacy and coping characteristics of the individual. But then again it should be remembered that coping and self-efficacy influence and are influenced by CNA structure and function.

3.3 The bidirectional interactions between psychological functions and the CNA/SAM-axis

It is not always easy to distinguish between cause and effect with regard to the psychoneurological interaction. It is likely that the interaction may be of a continuously reverberating nature, rather than a simple bidirectional interaction. For this reason no distinction was made in the previous two divisions of this chapter between the CNA's effect on the mind or the mind's effect on the CNA. It is, however, now indisputable and well documented that the physiological-anatomical integrity of the brain can be a determinant of mind and that the mind can affect the body in a variety of ways. This is especially true in the case of the CNA/SAM-axis where the fight or flight reaction occurs in response to cognitive or emotional arousal as discussed earlier in the chapter. The effects of both acute and chronic stress can further influence the CNA/SAM-axis in ways that could, in turn, influence the psychological disposition and even cause or predispose the individual to psychological disorders by changing the structural characteristics.

The decision between cause or effect is less problematic in some cases – especially in situations where deliberate psychological therapeutic interventions are employed in order to bring about physiological and other somatic effects. Examples of what can perhaps be seen as primarily mind-on-body influences are the results obtained by a number of biofeedback interventions, the practice of certain Eastern philosophies, the effects of suggestions made under surgical anesthesia, the effects of hypnosis and possibly that of

cultural healing and psychotherapy. In general terms volumes can be written about the influence of mind-over-body. Linking the impact of psychological factors to specific neural mechanisms is however a different matter altogether. Examples of some of the above in terms of the CNA/SAM-axis are discussed in a writing by Rossi (122), as summarised in the following paragraph. The reader is referred to his writing for the references to the original publications on which the examples in this paragraph are based.

Examples of the CNA/SAM-axis modulation by the mind, discussed by Rossi (122), include phenomena like hypnosis, unconscious learning during surgical anesthesia, coping, and some of the effects derived from practices based on Eastern philosophies. Rossi sees hypnosis as a prime example of the influence of mind-over-body. Many of the effects of therapeutic hypnosis are said to be secondary to sympathetically induced blood flow alterations. Control of sympathetic system-induced circulatory control by the mind is already known to form the basis of a variety of biofeedback therapies. Effects thus obtained through hypnosis include the curing of headaches, the control of blushing, breast enlargement, amelioration of bruises, induction of sexual arousal and erection, curing of warts and dermatitis, production of inflammatory reactions, amelioration of congenital ichthyosis, as well as the control of the alarm response, hypertension, Raynaud's disease, coagulation and the immune response. The second type of examples of physiological-modulation, i.e., noradrenergic system-modulation by the mind, discussed by Rossi, is unconscious learning during surgical anesthesia. This is reported to influence the outcome of the surgical procedure as well as the postoperative recovery. This in response to suggestions made while under the influence of anesthesia and augmented by peripheral administration of adrenaline. Coping under stress is yet another example described in association with the CNA/SAM-axis. Coping, where stress is seen as a challenge, in contrast to non-coping where stress is seen as a threat, is said to be characterised by activation of predominantly the CNA system, while the central activation of both stress axes is said to occur during non-coping. This noradrenergic dominance during coping may perhaps be extrapolated to motivation as the differentiation of the response to stress into the perception of challenge or threat corresponds to Selye's description of eustress and distress, as well as to Abraham Maslow's deprivation motivation as opposed to stress

motivation. The relationship between CNA/SAM-axis activation and coping just mentioned seems illogical in view of the degree of emotional arousal expected. A perhaps more acceptable relationship between coping and noradrenergic activity was reported by Albert Bandura (123) in patients experiencing some kind of phobia where an inverse relationship is said to exist between the sense of coping (sense of self-efficacy) and the catecholamine levels.

Another mind-over-body effect, which involves the noradrenergic system, is the control of consciousness by means of the practises associated with Eastern philosophies. Many examples exist, some of them generally known and others beyond the common knowledge of the average Westerner. They would not be discussed at this point. Enough to say that a link was shown between such practices and central noradrenergic activity.

The examples of the influence of the mind over the CNA/SAM-axis thus far mentioned, are just some of a number of generally well known phenomena. Perhaps lesser known or accepted is the fact that behaviour or psychological reactivity in response to perceptions can have a more permanent impact on, not only cerebral function but also cerebral structure. Some such examples were previously shown under the results from animal experimentation.

The next couple of paragraphs are intended to show that the higher neurological centers are a) more than the hardware where environmental and psychosocial demands are recognised, b) more than the sites from where appropriate or inappropriate behavioural reponses are initiated, c) and more than the structures which, in the presence of functional or structural abnormalities, can give rise to alteration in psychological functionality. It is meant to show that the neural structures are, in fact, also the target organs of perceptions with regard to novel or stressful environmental and psychosocial situations or influences. As such the psychological make-up and experiences would serve as response modifiers of cerebral structure and function. It is suggested that such modifications may then, if successful, form the basis for psychological adaptation or, in the case of maladaptation, for presensitisation to future behavioural disturbances. The discussion, in accordance

with the intent of this chapter, is confined to facts pertaining to the CNA/SAM-axis and the magnitude and depth thereof limited in conformance to the aim of the chapter, that is, to provide the necessary evidence in support of a bidirectional psychoneurological interaction in terms of the CNA/SAM-axis.

The old argument of *nurture* versus *nature* is well known. Under this misconception of posing the one against the other, it was argued that behaviour is determined either by environmental factors, by genetic factors, or by a combination of the two. This type of reasoning was based on the believe that gene expression is autonomous and that the effects of psychological influences on the neurological system are independent of the genome. The realization that the brain can adapt to environmental and psychosocial influences by changing the variable expression of genes (124), brings about a dramatic change in our perspective with regard to behaviour. By taking the potential effect of hormones and neurological transmitters on the genetic variability into account, it becomes obvious that psychologically-induced changes in the neurohormonal profile of an individual can lead to a type of remodeling of neural structure and function, which in itself would have an influence on behaviour. Such neural alterations may either be transient or permanent. It has indeed become conceivable how environmental conditions, as well as internal conditions such as stress, fear, anxiety, trauma, happiness, contentment, or even just the perception of psychosocial conditions, can lead to a shift in behavioural disposition - ranging from adaptation to the stressor, to presensitisation to a stressor, to neurotransmitter imbalances, to psychological disorders and even to neuronal atrophy. One could surmise that the primary aim of such an adaptational capacity would be situated in the psychological development of the individual.

Modification of the neural structures by internal and external environmental influences is nothing new and forms part of the early developmental, as well as of all postnatal learning processes. It is highly likely that such modifications occur throughout the individual's normal life span. Examples of this were given in Table 3.1, where the destructive nature of uncontrollable stress, as well as the developmentally advantageous effects of controllable stress were presented. The suggested cellular and sub cellular

mechanisms through which the noradrenergic system contributes to this implied neural plasticity is beyond the aim of this writing, but can be found in a recent text (125), that deals, amongst others, with the role of the adrenergic system in central and peripheral plasticity, in genetic diseases, as well as with potential gene therapy. Some interesting findings are discussed where behaviour is used to analyse the role of the various aminergic receptors. Most of the experimental evidence discussed were, however, derived from work on lower invertebrata.

Evidence derived from higher vertebrata and from man is available to support the validity of the results from lower invertebrata. It would appear that not only the neurons, but also the central nervous system astrocytes and other structures are involved in the adaptational modification of the noradrenergic system by the psychological experiences. It is also known that noradrenergic activity in the brain has many effects over and above that of membrane potential alterations. Such activities include the activation of second messenger systems in post-synaptic neurons which in turn leads to metabolic alterations and to changes in the responsiveness to incoming stimuli, effects on oncogene expressions, astrocyte modification, blood-brain barrier permeability alterations and more. The specific influences of noradrenergic activity on cerebral function and structure, as well as the effects of sympathetic activation, are shown in Figure 3.3. Such changes are often characterised by a considerable time lag between stimulation and the actual alterations. As such they are postulated to be involved in, or to act as trigger mechanisms for long term adaptive modifications (126). Examples of such non-transmitter functions and modifications of the CNA in response to stressors include

- the noradrenaline/c-AMP-mediated release of glucose and lactate from astrocyte glycogen stores (127) and the exacerbation of the process by stress (128) with subsequent attenuation by repeated exposure to the same stressor (129).
- synthesis and release of growth factors from astrocytes upon noradrenaline release (130).
- the expression of oncogenes such as *c-fos* in neurons (131).
- the role of the central noradrenergic system in developmental cortical plasticity

(132).

- the role of the central noradrenergic system in morphological plasticity and recovery from cortical lesions (133).
- the structural changes in astrocytes upon stress-induced noradrenergic secretion (135).
- transient acute stress-induced beta-adrenergic-mediated increases in cerebral perfusion and energy consumption (136).
- prolonged (chronic) stress-induced decreases in cerebral blood flow (137).
- the apparently beta-adrenoceptor-mediated regional increases in blood-brain barrier permeability (138,139) in response to stress.

Other examples of the psychosocial influence on the central noradrenergic structure and function are available. Certain emotional influences on the CNA/SAM-axis that are of significance to the dissertation as a whole, are those that are in turn involved in the development of a sense of self-efficacy and coping. Although many neural networks are probably involved, a role for the noradrenergic system is suspected – over and above the reference to that effect on earlier pages. It is, however, virtually impossible to embark on a reasonable discussion on the link between such psychological phenomena and the biological alterations, in terms of either the possibility of psychological adaptation or psychopathological development, without reference to the CRH/HPA system. The discussion on such potential implications will therefore be deferred to Chapter 5, which deals with the psychoneurological interactions in terms of the CRH/HPA-axis.

The previous paragraphs focused on the influence of the psyche on the CNA/SAM-axis. The reversed influence, i.e., the role of the CNA/SAM-axis in the psychological disposition, was discussed throughout the first two sections of this chapter. In concordance with the aim of this chapter, as part of a minor subdivision of the study, an in-depth discussion of any one aspect was avoided. The need for a detailed, meticulously executed review of noradrenergic involvement across the spectrum of behavioural functions and disorders has, however, become patently clear. What is, in fact, suggested is a reversed perspective with the focus on one neurohormonal system across the

psychological spectrum, rather than on all neurohormonal aspects of one psychological disturbance. The results of such a study could have marked implications with regard to the relatedness of various psychological phenomena and perhaps to diagnostic criteria. An example of a possible unexpected relatedness may, for instance, be that between impulse-control and bipolar disorders (92) where related CNA system alterations have been shown.

In an attempt to understand the pervasiveness of the influence of the CNA/SAM-axis on behaviour – and thus to see its importance in the psychoneuroimmunological interaction, its behavioural and specific functions were summarised. This is presented as Figure 3.4.

Figure 3.4, i.e., the functions of the CNA-system and the peripheral SAM-system, is inserted on the next page with the legend to Figure 3.4 following on the subsequent page.

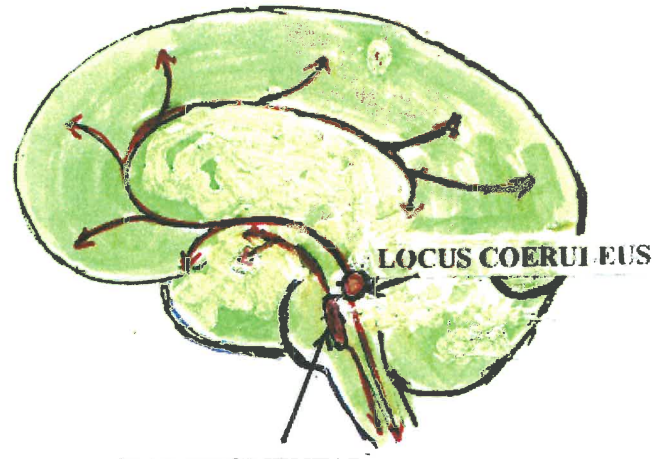
SPECIFIC FUNCTIONS OF THE CNA-SYSTEM.

Behavioural functions
Facilitation of predatory/attack behaviour
Enhanced anxiety-related behaviour
Improved acquisition and learning
Enhanced reactivity to stimulation
Augmented sensory information processing
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 clues
Augmentation of cognitive functions of prefrontal cortex
Regulation of eating behaviour
Involved in cerebral plasticity
Modulates the induction of hippocampal synaptic plasticity

Specific effects on neurons
Changes excitability and information processing
Increases signal-to-noise ratio
Enhances target selection
Role in lactation-induced synaptic plasticity
Modulates central thyronergic activity
Activates central second messenger systems
Alters protein phosphorylation
Alters metabolism & gene expression

Specific effects on astrocytes
Activation of second messenger systems
Alters protein phosphorylation and glycogen metabolism
Alters gene expression

General physiological and anatomical effects
Modulation of forebrain electroencephalographic activity
Increases cerebral blood flow and metabolism
Increases blood-brain barrier permeability
Facilitation of cerebral structural organization



LATERAL TEGMENTAL
NORADRENALINE SYSTEM

SPECIFIC FUNCTIONS OF THE SAM-AXIS

Adipose tissue-----lipolysis (β-AR)
Adrenal medulla---secretion of catecholamines
Eye----------contraction radial muscle (α-AR)
relaxation ciliary muscle (β-AR)
Gall bladder----------relaxation (β-AR)
Heart----------increased cardiac output (β-AR)
Hair follicle----------contraction (α-AR)
Kidney----------increased blood pressure (α/β-AR)
Lacrimal glands----increased secretion (α-AR)
Liver----------increased blood sugar
Lungs----------bronchodilation (β-AR)
Pineal gland---------increased melatonin (β-AR)
Thyroid----------increased secretion
Micturition----------inhibited
Blood vessels-------vasoconstriction (α-AR)
Gastrointestinal-----delayed emptying (α/β-AR)

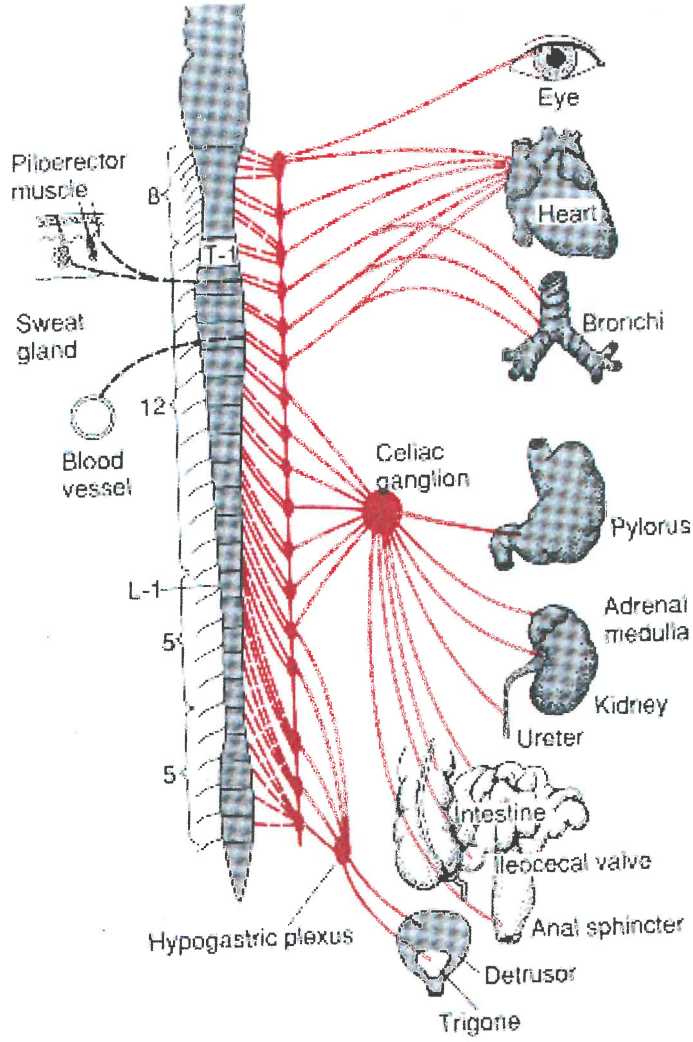


Figure 3.4 Functions of the CNA-system and the peripheral SAM-system

Legend to Figure 3.4

Figure 3.4: Functions of the CNA-system and the peripheral SAM-system.

(Compiled from 125, 126, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 149, 150, 151, 152)

[Figure 3.4 shows that the peripheral SAM-axis functions are, in general, to gear the body for action. The central noradrenergic (CNA) system seems, to a degree, to mirror these peripheral functions as the major behavioural effects are that of cerebral activation and increased adaptational plasticity. The specific effects on neurons, glial cells, blood flow and blood-brain barrier permeability underlie most of the behavioural functions and once again are mostly of an excitatory nature. It is easy to imagine how overexpression of these functions can lead to psychopathology.]

It is perhaps necessary to remind ourselves that the central noradrenergic system forms a major part of the ascending reticular activation system which consists of neuromodulatory networks such as the noradrenergic, serotonergic, cholinergic, histaminergic and dopaminergic systems (140). These networks are involved in the regulation of functions such as sleep, awakening, arousal, attention and wakefulness. The multiple projections from these neuromodulatory networks to various brain areas hint at the pervasiveness of their influence. This, in addition to the interconnectedness between the different neuromodulatory networks, and their regulation by the CRH system, emphasise the total integration of neural functions. The central role of the central nervous system CRH neurons and projections and their role in the integration of the stress response are discussed in Chapter 5.

3.4. Summary of the psychoneurological interactions in terms of the CNA/SAM-axis: A heuristic representation of the psychoneurological role of the system

The aim of this chapter was to demonstrate the bidirectional interaction between the psychological and biological aspects in terms of the central noradrenergic/ sympathoadrenomedullary axis. It therefore represents the psychoneurological part of the psychoneuroimmunological interaction as reflected by the CNA/SAM-axis. The first part dealt with evidence of the psychoneurological interaction in animals and the second part with that in man. Both confirmed the existence of a pervasive bidirectional psychoneurological interaction. The advantage of animal research is that the collection of certain types of physical evidence as well as experimental procedures considered unethical in man, are permissible in animals. Disadvantages do, unfortunately, also exist in animal experimental work - such as the problem of finer discrimination between certain psychological phenomena, as well as the legitimacy of extrapolation of the results to humans. However, a considerable bank of information exists which was originally derived from animal experimentation and eventually confirmed in man by indirect measures. It is clear that the functional and structural integrity of the CNA/SAM-axis has an influence on a multitude of behavioural functions and that many psychological disorders are characterised by abnormalities of the system. The psychological disposition

can, in turn, alter, not only the functionality of the CNA/SAM-axis, but also the biochemical and structural aspects as well as the genetic expression. Changes in the system as a result of controllable stressors can be seen as necessary adaptational processes, i.e., a form of noradrenergic plasticity. Stressors perceived as uncontrollable could, however, give rise to biological alterations that may cause, or predispose to psychopathology. It speaks for itself that the CNA/SAM-axis does not operate in isolation, or perhaps even as the major determinant of the behavioural functions mentioned, but as part of a large multiple receptor network. The major function of the CNA would in fact appear to be that of a neuromodulatory system which, through its projections to various areas of the brain, can influence the specific functions of those areas. The fact that the CNA system can exert an influence on other neuromodulatory systems such as the serotonergic, dopaminergic, cholinergic and other, is indicative of its diverse and pervasive influence on the behavioural functions. One would therefore expect concurrent, related or compensatory changes in interacting neural networks. Such a situation would make the identification of the primary neuromodulatory disturbance associated with a specific psychological function or disturbance extremely problematic. Several such concomitant alterations of the CNA system with other neuromodulatory systems were discussed. The interaction between the psycho- and the neurological can further not be described as simply bidirectional, but rather as a circuitry of reverberating influences. The continuation or discontinuation of mutual influences are probably determined by the nature of the feedback. This type of interaction where an emotional experience causes alteration in the physiological/anatomical integrity of the noradrenergic system, that in turn predisposes to shifts in the psychological disposition, which then lead to further functional or structural changes, makes coping, as well as adaptational sense.

The chapter is summarised in Figures 3.5 and 3.6. Figure 3.5 summarises the psycho-neurological interactions. Figure 3.6 shows the major central noradrenergic systems, their projections to other cerebral areas, neuromodulatory systems that interact with the noradrenergic system, the specific and psychological functions and disorders associated with the central noradrenergic system, as well as the bidirectional interaction between the psychological and the neural elements.

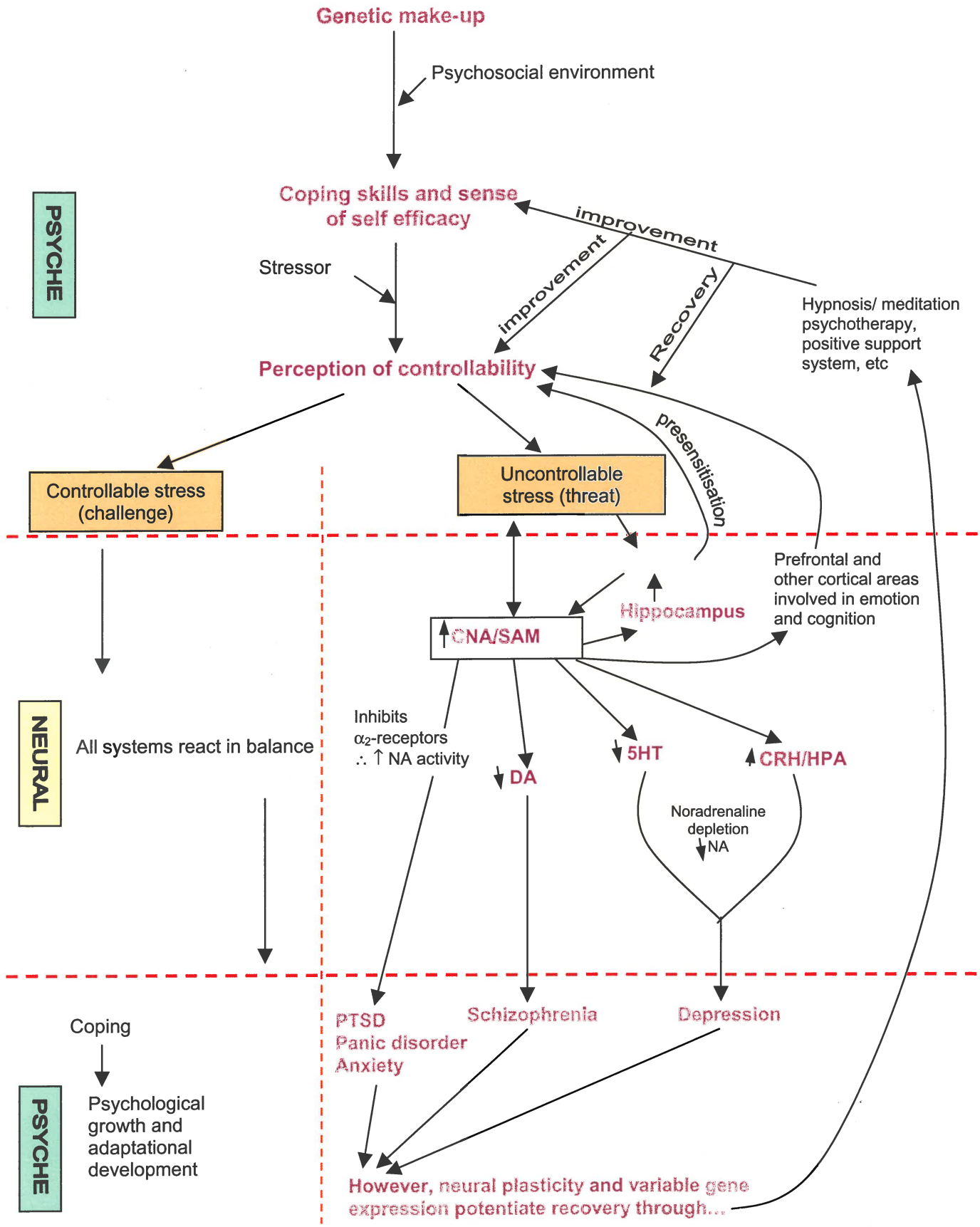


Figure 3. 5: Heuristic representation of the psychoneurological interactions in terms of the CNA/SAM-axis

Legend to Figure 3.5

Figure 3.5: A heuristic representation of the psychoneurological interactions in terms of the CNA/SAM-axis

[Figure 3.5 shows how the psychosocial environment acts in concert with the genetic make-up to produce an individual with specific coping skills and sense of self-efficacy. These qualities contribute to a large extent to the individual's perception of control in the face of stressors. Should a stressor be perceived as controllable all systems will react in balance and the end result would be a sense of coping, as well a psychological growth and adaptational development. Should the individual perceive the stressor as uncontrollable several events could take place – none of them mutually exclusive. The noradrenaline reserves of the brain may be depleted which could give rise to depression. Inhibition of the alpha-1adrenoceptors could give rise to conditions such as the post-traumatic stress syndrome, panic disorders or anxiety. Involvement of dopamine may lead to schizophrenia. It should be stressed that this was a scheme which evolved from studying the central noradrenaline system and therefore merely a representation of facts pertaining to the CNA/SAM-axis.]

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 thyronergic 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 organisation

BIDIRECTIONAL INTERACTION

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 skills
- Uncontrollable stress and perceptions of non-coping suppress adaptational changes and may predispose to later development of psychological disorders

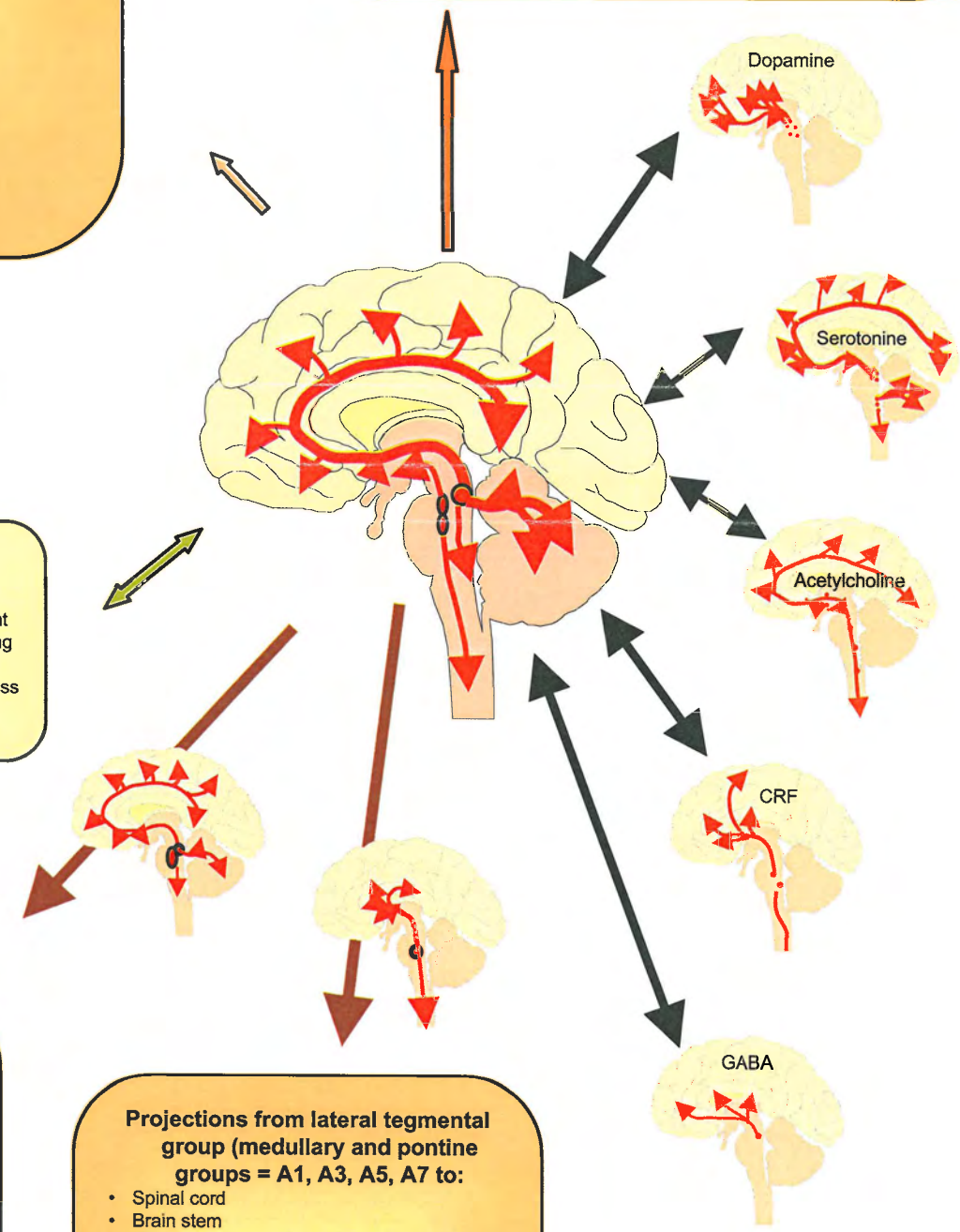
PSYCHOLOGICAL FUNCTIONS AND DISORDERS WITH VARIATIONS IN CENTRALNORADRENERGIC ACTIVITY

ASSOCIATED FUNCTIONS

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

ASSOCIATED DISTURBANCES

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



THE MAJOR CENTRAL NORADRENERGIC SYSTEMS AND THEIR PROJECTIONS TO OTHER BRAIN AREAS

Projections from locus coeruleus 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, some from both projection groups
- 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
  Almost exclusive source of NA innervation
- Cerebral cortex
  Exclusive source of NA innervation. Two distinct populations of NA neurons:

a) localised arborisation in restricted areas of the cortex
b) markedly collateralised axons innervating widespread areas of the cortex

Projections from lateral tegmental 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 to cerebellum
- Thalamus
  Innervation to isolated thalamic 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 of the amygdala, basolateral nucleus

INTERACTIONS BETWEEN THE CENTRAL NORADRENERGIC SYSTEM AND OTHER NEUROHORMONAL REGULATORY SYSTEMS, INCLUDING:

- DOPAMINERGIC,
- SEROTONERGIC,
- ACETYLCHOLINERGIC,
- CORTICOTROPIN-RELEASING HORMONE,
- GABA-ERGIC

Figure 3.6: A heuristic model of the psychoneurological relationship in terms of the central noradrenergic system

Legend to Figure 3.6.

Figure 3.6: Central noradrenergic system in psychoneurological context.

[The figure illustrates the two major central noradrenergic systems, i.e., the locus coeruleus and the lateral tegmental groups of noradrenergic neurons (middle of diagram). It shows their projections to other cerebral areas (left bottom-half of picture), the neuromodulatory systems which interact with the noradrenergic system (right bottom-half), the specific mechanisms through which noradrenergic activity influences cerebral function (specific functions) (top-left), the psychological functions and disorders associated with the central noradernergic system (top-right), as well as the bidirectional interaction between the psychological and the neural elements (middle-left).]

In view of the multidisciplinary, integrative nature of the writing, the topic was dealt with in a fairly synoptic manner and a host of supporting evidence, as well as in-depth debating, had to be omitted from the chapter. The writing of a number of review articles that could considerably contribute to our understanding is suggested, including (tentatively suggested titles)

- The role of cerebral plasticity in the acquisition and extinction of adverse psychological patterns and psychiatric disorders
- Variable gene expression and psychological behaviour
- The mind-body paradigm in terms of the ascending reticular activating system neuromodulatory network.

In conclusion it can be said that the CNA/SAM-axis most likely exerts its diverse and pervasive influence on the behavioural functions predominantly through its role as a major neuromodulator. Behavioural influences can, in turn, alter the functional and anatomical integrity of the CNA/SAM-axis, depending on the perception of the controllability of the situation. As perception of controllability is dependent on alterable factors, such as coping skills and degree of self-efficacy, and, in view of the enduring plasticity of the CNA system, as well as the variability of the gene expressions, one could assume the possibility of psychosocial correction of similarly induced adverse neural structure and function. Surely, this must present a case for changing the argument of *nurture versus nature* into a plea to *nurture nature*.

This chapter demonstrated the psychoneurological interaction in terms of the CNA/SAM-axis. It showed that the central noradrenergic system primarily serves as neuromodulator and in this capacity acts in concert with all other modulator systems to set the psychological tonus. The next chapter will deal with the neuroimmmunological interactions in terms of the CNA/SAM-axis.

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