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General Discussion

In this thesis the results were presented of studies that were designed to provide more insight in the role of the central nucleus of the amygdala (CEA) in the adaptation to environmental demands. The experiments were performed in several situations, in which rats react either directly to aversive stimuli or to an expected (conditioned) aversive stimulus with distinct behavioral responses accompanied by diverse patterns of autonomic and neuroendocrine alterations. CEA activity was influenced by either electrolytical lesioning or neurochemical manipulation during different stages of the conditioning process: either before or after the learning session. Changes in behavioral, autonomic, and neuroendocrine components were determined during acquisition and retention and compared to changes in sham-operated controls. The experiments lead to a general model of CEA function in adaptive responses. The major finding of the studies is a differential involvement of the CEA in the expression of various stress responses as determined during unconditioned and conditioned environmental challenges; some of the measures are likely to be influenced directly by neuronal output from the CEA, whereas the CEA affects other output systems only indirectly, but failure to alter certain patterns occurs as well. It will be argued that the expression of the various autonomic and neuroendocrine components of the unconditioned stress response as induced via CEA mechanisms are crucial in determining the extent of conditioning.

12.1 Brief Summary of the Results

The present studies and extensive literature (e.g. 3, 31, 33, 38, 40, 41, 69) allow the conclusion that the CEA is involved in the expression of various physiological and behavioral components of the stress response. Lesioning of the CEA completely abolishes the occurence of parasympathetic output both during acquisition and retention (Chapters 2, 4, 5 and 7). This involvement in parasympathetic output is not restricted to stress conditions.

Conditioned stress-independent parasympathetically mediated responses like the cephalic phase of insulin release are blocked by CEA damage as well (Chapter 3). Conversely, electrical stimulation of the CEA in a variety of species leads to parasympathetic activation [1, 14, 38, 42, 45]. These results indicate that the CEA is a crucial part of the neural circuitry involved in parasympathetic output. Indeed, neuroanatomical tracing studies showed a direct, peptidergic innervation of the dorsomedial medulla, particularly of the nucleus ambiguus, dorsal motor nucleus of the vagus and the nucleus of the solitary tract [16, 64, 68, 73]. These areas are considered to be responsible for the organization of the vagal responsiveness.

A response that is consistently affected by CEA manipulation is the behavioral passivity, i.e., immobility, mostly accompanying the vagal responses (Chapter 4, 5 and 7). The attenuation of stress-immobility by CEA lesioning is thought not to be causally related to parasympathetic outflow. It is only observed in situations in which the animal has a free choice between active and passive strategies of coping to the already known stressor (Chapters 2 and 5). On the other hand, active behavioral coping concomittant with cardiac sympathetic responses are not altered by CEA lesioning (Chapter 2, 4, 5, 6 and 7). CEA manipulation affects active shock avoidance acquisition leading thus to an exception of the above rule (Chapter 6).

Finally, neuroendocrine parameters like plasma catecholamines, corticosterone and prolactin responses to stressors are attenuated only during acquisition, and not during retention (Chapters 7 and 8). This emphasized the importance of the complex in learning of behavioral and neuroendocrine responses.

A major point of discussion regarding the function of the CEA is the question to what extent the effects mentioned above are directly due to CEA manipulation or to indirect influences. This issue will be discussed in relation to the suggested role of the CEA in learning and memory processes.

12.2 Role of the CEA in the Learning Process

Several reports support the involvement of the CEA in learning and memory processes (for a review see: 37, 65). The present thesis also shows evidence that CEA functioning is related to learning and memory. Conditioned parasympathetically derived responses disappear both in pretraining (learning) and posttraining (memory) lesioned animals. In contrast, pretraining lesioned animals, and not posttraining ones, show amnesia during exposure to conditioned situations leading to immobility, passive shock avoidance, or defensive burying. The behavioral amnesia is accompanied by an absence of the physiological stress responses (Chapters 4, 5, 6 and 8). Memory deficits found after destruction of the CEA are interpreted as being primarily due to either emotional changes (loss of fear) or cognitive failures [15, 51, 58, 59]. The learning tasks in which the CEA affects learning and

memory are characterized by emotio
of neuroendocrine correlates [9].
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For example, peripheral epinephrin
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excluded that direct amygdalo-cortica
memory processes [43].

12.3 Role of the CEA in the Neuroend

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memory are characterized by emotional feelings, and accompanied by elevated plasma levels of neuroendocrine correlates [9]. McGaugh stated that these expressions of the unconditioned stress response are of importance in amygdaloid related learning processes. For example, peripheral epinephrine enhances retention by modulating the release of norepinephrine in the CEA [47, 55]. Short-term adrenalectomy produces deficits in passive avoidance retention of inescapable footshock. Epinephrine or norepinephrine given immediately after learning normalizes passive avoidance behavior [7, 8, 19]. Furthermore, memory-enhancing effects of peripherally administered corticosterone [20, 39] and prolactin [23] are reported. Prolactin in particular is known to affect conditioning, but not retention of emotional learning tasks. Findings in this thesis demonstrate that CEA lesioning attenuates the rise in neuroendocrine responses during acquisition (Chapter 7). On the basis of these observations it may be hypothesized that the CEA is particularly involved in eliciting an autonomic and neuroendocrine state during acquisition that is optimal for long-term storage of the experience. This neuroendocrine and autonomic state affects memory functions via feedback action to the brain [5, 18, 54]. However, on the basis of connectivity of the basolateral and lateral nuclei, and to a lesser extent also the CEA [10, 66, 67] it cannot be excluded that direct amygdalo-cortical connections are also of importance in learning and memory processes [43].

12.3 Role of the CEA in the Neuroendocrine State

The proposed role for the CEA in learning and memory processes raises the question by which way the input-output system(s) of the CEA are involved in this neuroendocrine and autonomic state. As mentioned in paragraph 12.1, the CEA is thought to be directly involved in the organization of parasympathetic output to stressful and nonstressful challenges as demonstrated with the bradycardia and the cephalic insulin response. Indeed, during retention, the CEA is selectively involved in parasympathetic outflow and passive behavioral components without affecting other conditioned stress responses.

An important candidate of eliciting neuroendocrine output are central monoaminergic mechanisms. The CEA is reciprocally connected with norepinephrine containing cell bodies in the locus coeruleus (LC) [21, 70, 74]. The CEA may contribute to the activation of LC neurons. This may then lead to a stress-induced increase in noradrenergic activity in several brain areas involved in autonomic and neuroendocrine output like the hypothalamus and bed nucleus of the stria terminalis (BNST) [2, 3, 25, 63]. Furthermore, the CEA innervation of serotonergic and dopaminergic containing cell groups in the brainstem have been implicated in several autonomic and neuroendocrine stress responses [3]. This opens the possibility that the CEA output in relation to unconditioned stress primarily consists of a general activation of central aminergic mechanisms which leads to secondary activation. However, a direct

pathway between the CEA and the hypothalamic paraventricular nucleus (PVN) has been described as well [32, 48]. Feldman et al. [26] have shown that during exposure to ether stress, circulating levels of corticosterone show increases independent of this direct pathway. Electrical stimulation of the CEA has, however, been shown to elicit changes in plasma corticosterone via the direct pathway to the PVN [26]. This suggests that activation of this direct pathway may depend on the nature of stress, and probably on individual characteristics of the rat's behavior as well.

12.4 Role of the CEA in Behavioral Responses

Immobility responses are abolished both during acquisition and retention (Chapters 4, 5, 6 and 7). Because this runs parallel to the effects of the CEA on the vagal response, this may suggest a direct involvement of the CEA in passive behavioral output as well. However, the precise amygdaloid efferents involved in the expression of these behavioral components are still a matter of discussion. LeDoux et al. [45] stated that the immobility response is elicited via a monosynaptic connection to the periaqueductal gray. Fear-potentiated startle is another behavioral response, influenced by CEA activity. The CEA projects via the caudal part of the ventral amygdalofugal pathway to the nucleus reticularis pontis caudalis, a nucleus in the startle pathway [17]. McDonald [52] demonstrated that the lateral part of the CEA shares common features on cytoarchitecture, histochemistry and hodology with striatal areas. On the basis of these findings it is suggested that the CEA can be considered as a modified extension of the striatum. In addition, the projections of the basolateral nucleus of the amygdala (BLA) to the CEA and from the BLA to striatal areas originate in the same region of the BLA [53]. This extensive interface between the amygdala and extrapyramidal motor system is considered to be very important for generating behavioral responses to environmental stimuli [56]. Cools and colleagues attributed a key role to mesolimbic noradrenergic mechanisms in the nucleus accumbens that serve as a link between the limbic (amygdala) and extrapyramidal neurons (for a review see: 13). An interesting phenomenon is that abolishment of immobility is particularly observed in those situations in which the animal has a free choice between active and passive coping strategies (Chapter 2 and 5). These findings suggest that the role of the CEA in the expression of stress-related behaviors is not absolute, but is restricted to certain aspects of strategy choice.

Most interestingly, active behavioral components are not affected by CEA manipulation (Chapter 5). An exception is the active shock avoidance acquisition. It is attenuated following CEA damage, but only during the first day of conditioning (Chapter 6). The mixed character of this response, consisting of both acquisition and retention aspects, makes this result difficult to interpret. Moreover, in this experiment, shock punishment is always followed by an escape response, supporting the view that the CEA is not involved in active behavioral

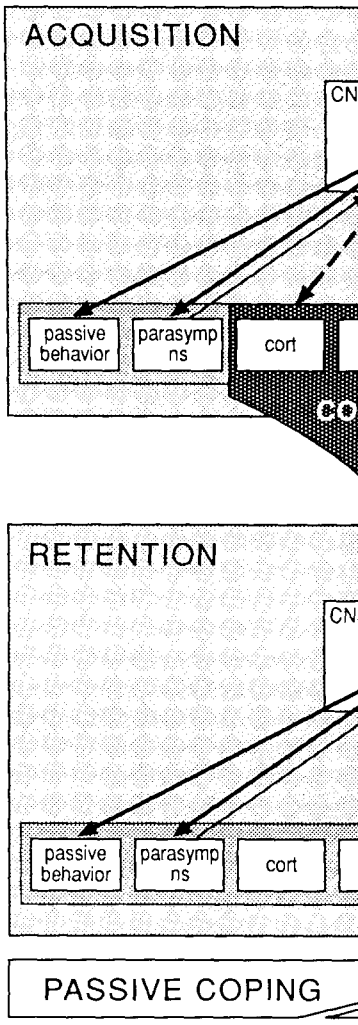

Fig. 1
A schematic representation of CEA functioni
Abbreviations: CEA = central amygdala; CNS
E = epinephrine; NE = norepinephrine; prl =

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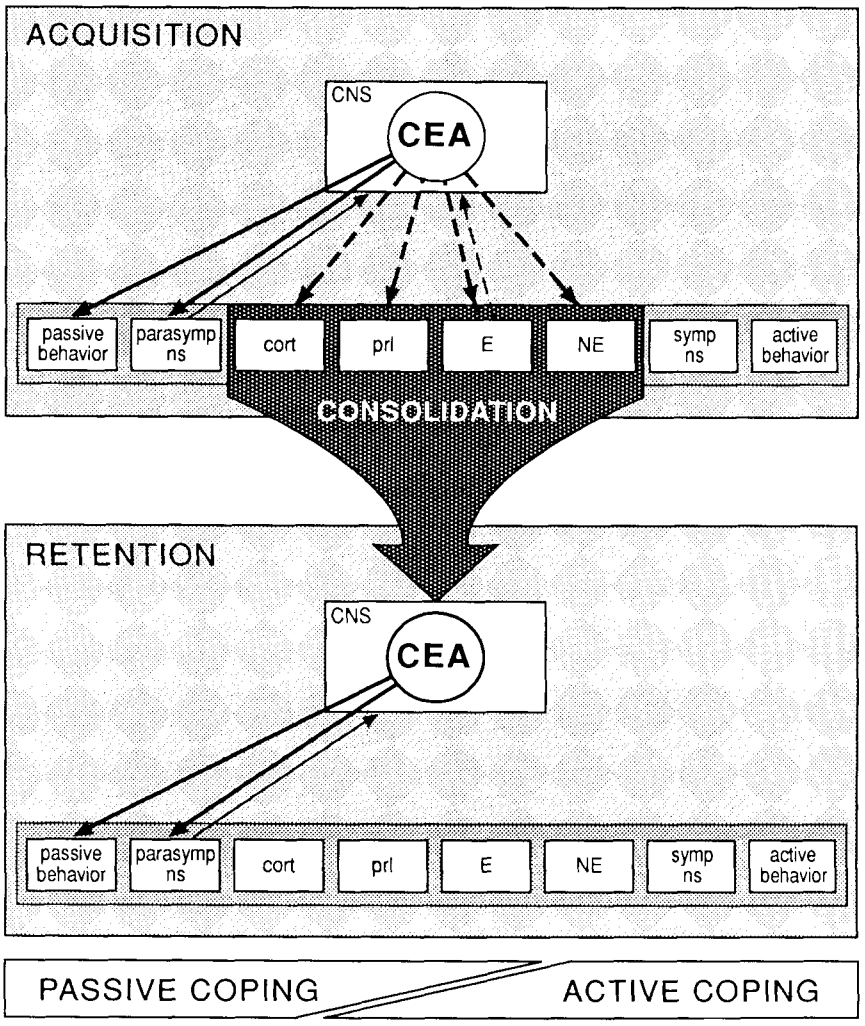

Fig. 1
A schematic representation of CEA functioning. For a detailed description see text.
Abbreviations: CEA = central amygdala; CNS = central nervous system; cort = corticosterone; E = epinephrine; NE = norepinephrine; prl = prolactin.

strategies per se. Taken together, these findings suggest that the CEA is unequivocally involved in the expression of behavioral output systems: only the passive component of the behavioral stress response can be changed by CEA manipulation, without affecting most active behavioral components.

12.5 A Model of CEA Functioning

Summarizing the discussion so far, it can be concluded that the CEA is directly involved in the induction of parasympathetic output via its monosynaptic connections to the dorsomedial medulla. In contrast, other effects such as neuroendocrine responses are considered to be indirect effects due to activation of central aminergic mechanisms. Although a direct involvement of the CEA in the PVN and adrenocortical output cannot be excluded [32, 48]. Thirdly, immobility is also considered to be elicited by CEA activity. The autonomic and neuroendocrine state during acquisition, which is elicited by the CEA, is thought to be of importance in the conditioning process of the aversive experience (Fig. 1).
The suggested mechanisms are thought to be attributed to the CEA proper. Electrolytical lesioning of the CEA destructs both cell bodies and fibers of passage. Thus one cannot exclude that damage to the fibers crossing is causing a functional deficit rather than the destruction of cell bodies in the CEA. However, results from both ibotenic acid lesions and chemical manipulation studies are generally consistent with the electrolytical lesioning studies [69], suggesting that the observed effects are primarily due to destruction of CEA neurons.

12.6 CEA Involvement in the Passive Coping Strategy

The observation that the CEA directly affects parasympathetic activity concomittant with immobility, whereas sympathetic outflow and active behavioral components remain unaffected, indicate that the CEA is predominantly involved in processes of passive coping (Chapter 6). Studies in psychogenetically selected rat lines, considered as models for active and passive coping, are consistent with these findings. Independent of the used selection criterion (e.g. high blood pressure, aggression, active avoidance learning, emotionality etc.), in the selected lines of rodents, coping strategies are coupled to a set of comparable autonomic and neuroendocrine responses [5]. The Roman low-avoidance (RLA/Verh) rats preferentially adopt a passive strategy in response to novelty or to a conditioned emotional stressor (Chapters 10 and 11)[5]. This passive type of coping to environmental challenges is accompanied by a parasympathetic response and a stimulated adrenocortical system,

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reflected in high plasma levels of adrenocorticotropin (ACTH) and corticosterone (Chapters 10 and 11)[5, 29]. In contrast, increases in parasympathetic output are not observed in Roman high-avoidance (RHA/Verh) counterparts in response to stressful challenges that require a passive kind of coping. In addition, the adrenocortical system is less activated in these animals [29]. A selective activation of the CEA in the RLA/Verh, and not in the RHA/Verh rats, both during acquisition and retention is considered to underly the distinct pattern of behavioral, autonomic and neuroendocrine stress responses (Chapters 10 and 11). This role is consistent with the results by Henke [35], who reported differences in multiple unit activity in the CEA during restraint stress between both lines.
Norepinephrine infusion into the CEA elicits a bradycardiac response [57]. Noradrenergic antagonists administered in the CEA inhibit classical heart rate conditioning in the rabbit as originally described by Kapp [28]. Blockade of the central norepinephrine metabolism by L-deprenyl (a monoamine oxydase B inhibitor) has been shown to prevent vagally mediated stress-induced gastric pathology [30]. In addition, a pilot study shows that norepinephrine infusion into the CEA evokes corticosterone release under resting conditions. These findings altogether suggest that norepinephrine release in the CEA may be involved in the induction of the unconditioned stress response during acquisition. It was proposed in Chapter 11 that the induction of unconditioned neuroendocrine responses by amygdaloid norepinephrine may underly the enhancement of memory storage as suggested by McGaugh and colleagues [37, 46, 47, 55]. Genetic differences in emotionality may determine to what extent central noradrenergic, serotonergic, and dopaminergic systems are activated by several types of stress possibly by activation of the CEA. RLA/Verh rats show an increased metabolism of norepinephrine and serotonin in the hypothalamus after unconditioned stress, whereas RHA/Verh rats display an opposite effect on serotonin utilization [24]. In the Maudsley strain, the LC is more activated in "emotionally nonreactive" than in "emotionally reactive" rats in response to stress. The "nonreactive" line is characterized by low sympathetic and sympatho-adrenal responses [4]. The differential activation of central aminergic systems may be the underlying mechanism of the substantial stress levels of plasma ACTH, corticosterone, and prolactin observed in the RLA/Verh, and not in RHA/Verh rats. Furthermore, activation of the CEA by norepinephrine release in this area may cause an additional activation of the pituitary adrenocortical axis probably via the direct connection to the PVN.
Peptidergic manipulation studies indicate a predominant involvement of the CEA in passive coping as well. Activation of the CEA is thought to depend on tonic influences of the vasopressinergic and/or oxytocinergic receptive system(s) in the CEA. A possible involvement of these peptidergic mechanisms in the CEA in interaction with aminergic transmission in cognitive processes has been suggested by behavioral and neurochemical studies [6, 44]. In Chapters 9 and 10, the role of the vasopressinergic V1a and oxytocin receptor in the CEA has been studied under stressfree and during conditioned emotional stress conditions. Stimulation of V1a receptors results in an enhancement of CEA activity, reflected in parasympathetic and adrenocortical output, and an increase in behavioral

passivity. In contrast, oxytocin receptor activation, elicited by local administration of oxytocin and high doses of vasopressin, inhibits CEA outflow (Chapters 9 and 10). The effects of vasopressin via V1a activation may be mediated by a release of dopamine in the CEA [71]. Indeed, preliminary results show that dopamine is also involved in activation of CEA output systems. An important issue that remain to be encovered is whether or not vasopressin shows this inverse U-shaped response curve under physiological conditions. The idea that vasopressin induces passive coping is only true if under physiological stress conditions vasopressin exclusively binds to V1a receptors, and not to oxytocin receptors.

Findings in this thesis indicate fundamental differences in vasopressinergic and/or oxytocinergic function in the CEA between both lines. Local infusion of vasopressin and oxytocin exclusively affects CEA output systems in the RLA/Verh rats, without eliciting changes in the RHA/Verh rats (Chapter 10). This assumes differences in amygdaloid AVP and OXT receptor densities between both lines. Furthermore, vasopressinergic innervation of the CEA, but also of the lateral septum is more dense in genetically-selected passive coping animals in comparison with active coping animals [11]. The origin of the vasopressinergic input to the CEA is not yet elucidated. It may arise from cells in the BNST [22]. Numerous AVP-positive cell bodies have been localized in the BNST [72]. Compaan et al. [12] have demonstrated that the brain of selected lines of mice predominantly showing passive coping contain more AVP-positive cell bodies in the BNST than active coping ones. Oxytocin innervation in the brain is known to originate exclusively from the PVN [22]. It may be hypothesized that the BNST-CEA connection via vasopressin may play a key role in determining whether active or passive types of coping are activated in response to environmental challenges.

12.7 Role of the CEA in Stress Pathology and Adaptation

One of the main conclusions of the present thesis is the observation that the CEA is not uniformly involved in the expression of several physiological and behavioral stress responses. Thus, malfunctioning of the CEA may lead to selective disturbances of autonomic, neuroendocrine and behavioral balances that may underly several pathological manifestations. The involvement of the CEA in the development of vagally mediated gastric ulceration is one of the best studied amygdaloid related pathologies. Gastric ulceration can be aggravated by electrical and chemical stimulation of this area [34, 36], whereas lesioning or chemical blockade of the CEA inhibits this gastric pathology to immobilization [33, 60-62]. Furthermore, in spontaneous hypertensive (SHR) rats a stress experience is characterized by a relative decline in arterial blood pressure; lesioning of the CEA has been shown to prevent this effect [27]. Markgraf and Kapp [49, 50] showed that digitalis treated rabbits developed a

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cardiac pathology of a bradyarrhythmic nature when tested in a classical conditioning paradigm; lesioning of the CEA prevented the occurence of this arrhythmia. In contrast, electrical stimulation of the CEA induces the occurence of arrhythmia. The present experiments also found some anecdotical evidence for the involvement of the CEA in the development of bradyarrhythmias that occur in relation to unavoidable social or nonsocial stressors. After infusion of the low dose of AVP (20pg), one of the animals showed a transient arrhythmia. Ten minutes after termination of the infusion, heart rate suddenly dropped from 353 to 176 beats per minute. In addition, the variation of the heart rate increased considerably. This may suggest that peptidergic mechanisms in the CEA may play a crucial role in the development of cardiac pathology of a bradyarrhythmic nature.

The involvement of the CEA in stress pathology has been restricted to acute, short-term processes. Consequences of chronic dysfunction of the CEA on the development of diseases like arteriosclerosis and hypertension, cardiac failure, depression, and consequences on the functioning of the immune system have received little attention so far; studying the role of the CEA during the whole lifespan may be essential in the understanding of the etiology of these diseases.

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