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European Journal of Pharmacology 405 (2000) 225–234

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Role of corticotropin-releasing factor, vasopressin and the autonomic nervous system in learning and memory

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Accepted 28 June 2000

Abstract

Learning and memory are essential requirements for every living organism in order to cope with environmental demands, which enables it to adapt to changes in the conditions of life. Research on the effects of hormones on memory has focused on hormones such as adrenocorticotropic hormone (ACTH), glucocorticoids, vasopressin, oxytocin, epinephrine, corticotropin-releasing factor (CRF) that are released into the blood and brain following arousing or stressful experiences.

Most of the information have been derived from studies on conditioned behavior, in particular, avoidance behavior in rats. In these tasks, an aversive situation was used as a stimulus for learning. Aversive stimuli are associated with the release of stress hormones and neuropeptides. Many factors play a role in different aspects of learning and memory processes. Neuropeptides not only affect attention, motivation, concentration and arousal or vigilance, but also anxiety and fear. In this way, they participate in learning and memory processes. Furthermore, neuropeptides such as CRF and vasopressin modulate the release of stress hormones such as epinephrine. In turn, systemic catecholamines enhance memory consolidation. CRF and vasopressin are colocalized in neurons from the nucleus paraventricularis, which project to nuclei in the brainstem involved in autonomic regulation. The objective of this paper is to discuss the role of CRF, vasopressin, and the autonomic nervous system (ANS) in learning and memory processes. Both CRF and vasopressin have effects in the same direction on behavior, learning and memory processes and stress responses (release of catecholamines and ACTH). These neuropeptides may act synergistically or in a concerted action aimed to learn to adapt to environmental demands.

Keywords: Corticotropin-releasing factor (CRF); Vasopressin; Autonomic nervous system; Learning; Memory

1. Autonomic nervous system (ANS)

The parasympathetic nervous system consists of vagal efferents arising in the medulla oblongata of the brain stem, and synapsing in ganglia either embedded in the wall of or close to a wide variety of thoracic and abdominal viscera. The sympathetic nerves and the adrenal medullae together constitute the sympathetic division of the ANS. Epinephrine is released into the circulatory system from the adrenal medulla and norepinephrine by postganglionic sympathetic nerves in the synaptic cleft. A complex hierarchy of central nervous system elements determines neurosympathetic and adrenomedullary activity (Luiten et al., 1987). A number of discrete neuron populations originating from the nucleus tractus solitarius, ventrolateral medulla, parabrachial nuclei, hypothalamus (paraventricular nucleus) and limbic (amygdala, prefrontal cortex) regions project directly and/or indirectly to the sympathetic preganglionic neurons of the intermediolateral column located in the thoracic and lumbar segments of the spinal cord to determine sympathetic output. The level of plasma epinephrine following stimulation varies with the intensity of the stressor (De Boer et al., 1990). Only a small proportion of norepinephrine released from the nerves diffuses into the bloodstream. Nevertheless, circulating norepinephrine is a useful estimate of neurosympathetic activity which changes after exposure to challenging environmental stimuli (De Boer et al., 1990).

In general, exposure to a stressor induces tachycardiac responses. The sympathetic nervous system plays an important role in stress-induced tachycardia. In a well-established model to study the impact of emotional stress in rats (Fanselow, 1980), the conditioned fear test, we found that the other branch of the ANS, the parasympathetic nervous

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0014-2999/00/$ - see front matter
PII: S0014-2999(00)00556-2

system, is also activated. Conditioned fear was induced by forced exposure to an environment in which rats experienced inescapable footshocks the day before. Conditioned fear is accompanied by freezing behavior and associated with an increase in heart rate and catecholamines (Korte et al., 1990, 1992; Nijsen et al., 1998a, 2000b; Roozendaal et al., 1990; Wan et al., 1990). However, conditioned fear results in a less pronounced tachycardia than the exposure to the same cage in non-shocked controls. We found that exposure to the cage without prior shock experience merely leads to sympathetic activation, as evidenced by an increase in plasma catecholamines, whereas in conditioned fear rats, the parasympathetic nervous system is activated additionally. The latter finding was demonstrated by a lengthening in PQ interval, which can be derived from the electrocardiogram (Nijsen et al., 1998a,b, 2000a,b). The increase in PQ interval occurred almost immediately and reached its maximum well within 30 s after the start of conditioned fear, suggesting that neural rather than hormonal mechanisms underlie this effect.

1.1. Behavior

The one-trial learning passive avoidance test can be employed to study learning and memory processes (Ader et al., 1972). It makes use of a rodent's innate preference for a dark environment. In this test, the rat is placed on an illuminated platform connected to a dark box. Upon entrance to the box, the rat receives an electric footshock (learning trial). Retention of the aversive experience is tested various hours per day after the learning trial. The acquisition of new behavioral patterns, such as passive avoidance behavior, involves the adrenomedullary hormones, such as epinephrine and norepinephrine. Removal of the adrenal medulla blocks passive avoidance behavior, which can be restored by the administration of adequate amounts of epinephrine (Borrell et al., 1983a,b) This is an indirect effect of epinephrine. Epinephrine does not readily cross the blood–brain barrier, but it enhances memory consolidation by activating adrenoreceptors located peripherally on vagal afferents projecting to the nucleus of the solitary tract in the brainstem and from this region influencing other brain regions (McGaugh, 2000). Peripheral administration of amphetamine enhances retention of passive avoidance behavior (Kovács et al., 1979). For this effect, the adrenal medulla seems to be necessary. McGaugh et al., (1982) showed that the amphetamine effect is absent in adrenomedullectomized rats. In addition, blockade of β-adrenoceptor by propranolol effectively attenuates passive avoidance behavior (McGaugh et al., 1984). Post-training administration of epinephrine influences the retention of several types of learning tasks. Typically, inverted-U dose response effects were obtained: retention is enhanced by moderate doses and impaired by high doses (McGaugh et al., 1984). Furthermore, the presence of peripheral catecholamines appears to be essential for central effects of vasopressin on learning and memory processes (see paragraph on vasopressin).

Besides the sympathetic nervous system, the role of cholinergic systems in learning and memory processes have been widely accepted (Bartus et al., 1982). The cholinergic hypothesis of geriatric memory dysfunction has already been put forward by Bartus et al. (1982). Cholinergic blockade with scopolamine induces memory-deficient mice in a passive avoidance test (Tanabe et al., 1999) and memory-deficient rats in an eight-arm radial maze task (Fujiware et al., 1997).

2. Corticotropin-releasing hormone

2.1. Corticotropin-releasing factor (CRF), distribution and receptors

Most of CRF cell bodies are found within the amygdala, hypothalamus and bed nucleus of the stria terminalis (Foote and Cha, 1988; Merchenthaler et al., 1983; Sakanaka et al., 1987; Swanson et al., 1983).

Vasopressin- and CRF-containing parvocellular neurons from the nucleus paraventricularis project to the median eminence where the hormones are released into the portal system and transported to the anterior pituitary to stimulate adrenocorticotropic hormone (ACTH) release (Verbalis et al., 1986). CRF is the primary activator of the pituitary adrenal system. Vasopressin has a powerful synergistic action on CRF-induced ACTH secretion. During stress (insulin-induced hypoglycemia or immobilization), the vasopressin-containing subset of CRF neurons in the external zone of the median eminence is selectively activated (Whitnall, 1989).

A terminal field of vasopressin- and CRF-containing fibres from the nucleus paraventricularis also reaches nuclei in the brain stem involved in the regulation of the ANS (Merchenthaler et al., 1983; Sawchenko, 1987). Furthermore, CRF cell bodies are found within the amygdala, from which its fibres project to brain areas involved in autonomic function.

The sites of localisation of CRF receptors correspond well with the distribution of CRF-terminals in the brain (De Souza, 1995). Two types of CRF receptors are found in the rat brain: CRF_1 and CRF_2 (2α and 2β). The CRF_1 receptor has been found predominantly in the pituitary, suggesting a role in the regulation of the hypothalamus–pituitary–adrenal (HPA) axis; whereas both the CRF_1- and CRF_2 receptors have been localised in the cerebellum, cortex, olfactory bulb, dentate gyrus and subcortical areas (hypothalamus, amygdala, bed nucleus of the stria terminalis, hippocampus) that are known to play a role in the regulation of behavioral, neuroendocrine and autonomic responses (Chalmers et al., 1995; Dieterich et al., 1997; Grigoriadis et al., 1996; Primus et al., 1997). The $CRF_{2\alpha}$ receptor variant is primarily found in neuronal brain struc-

tures, whereas the $CRF_{2\beta}$ subtype is expressed in non-neuronal structures in the brain (choroid plexus and cerebral blood vessels) and in the periphery (cardiac and skeletal muscle, lung and intestine) (Grigoriadis et al., 1996; Lovenberg et al., 1995).

2.2. CRF and stress-induced autonomic responses

Acute or chronic stress has been reported to enhance the concentration of CRF and CRF mRNA in several brain areas, such as the nucleus paraventricularis, locus coeruleus, Barrington's nucleus and bed nucleus of the stria terminalis, whereas chronic stress reduced these levels in the dorsal motor nucleus of the vagus (Aguilera et al., 1997; Chappel et al., 1986; Herman et al., 1995; Imaki et al., 1991; Imaki et al., 1996). Furthermore, acute stress enhanced expression of c-*fos* mRNA in the nucleus paraventricularis, which was inhibited by α-helical CRF-(9–41), a non-selective CRF receptor type 1 and 2 antagonist (Imaki et al., 1995). On the contrary, stress-induced c-*fos* expression in the dorsal motor nucleus of the vagus was inhibited by intracerebroventricular (i.c.v.) CRF (Wang et al., 1996). These functional–anatomical studies suggest that stress-induced increases in endogenous CRF lead to activation of the nucleus paraventricularis, locus coeruleus, Barrington's nucleus and, bed nucleus of the stria terminalis and inhibition of neurons which activate the dorsal motor nucleus of the vagus, suggesting a stimulating action on the sympathetic nervous system and inhibitory action on vagal outflow during stress. This agrees with physiological studies of Fisher (1989), who reported that i.c.v. CRF significantly reduced the baroreflex gain. They concluded that CRF can act to suppress transmission and/or neurotransmitter release at the central nervous system terminals of afferent baroreceptor fibres, leading to activation of the sympathetic nervous system and withdrawal of the parasympathetic nervous system. This agrees with a study by Overton et al. (1990), who showed that blockade of only the sympathetic or vagal system could not prevent the CRF-induced increase in blood pressure and heart rate, suggesting that both sympathetic and parasympathetic nervous system are involved in CRF-induced cardiovascular responses. Evidence for sympathetic nervous system activation by exogenous CRF has been provided by several studies, which reported that i.c.v. administration of CRF results in stress-like increases in blood pressure, heart rate, plasma norepinephrine and plasma epinephrine, that were blocked by autonomic ganglionic blockade with chlorisondamine (Brown et al., 1982; Brown and Fisher, 1985; Diamant and De Wied, 1991; Fisher et al., 1983; Fisher et al., 1982; Grosskreutz and Brody, 1988; Korte et al., 1993; Overton et al., 1990; Overton and Fisher, 1991).

Endogenous CRF does appear to play a role in stress-induced responses, as i.c.v. administration of α-helical CRF-(9–41) has been demonstrated to attenuate stress-induced increases in heart rate, blood pressure, plasma epinephrine, defensive burying and freezing responses (Brown and Fisher, 1985; Brown et al., 1986; Cole and Koob, 1991; Kalin and Takahashi, 1990; Korte et al., 1994; Morimoto et al., 1993; Nijsen et al., 2000a). The stress-induced increase in plasma norepinephrine, however, was not affected by blockade of the endogenous CRF system (Brown and Fisher, 1985; Brown et al., 1986; Nijsen et al., 2000a). Yet, others have demonstrated that α-helical CRF-(9–41) can block the CRF-induced plasma norepinephrine and epinephrine response (Brown et al., 1985). So far, however, no conclusive evidence has been provided that the endogenous CRF system is involved in stress-induced elevations in sympathetic activity. We reported that in the conditioned-fear paradigm endogenous CRF merely reduces parasympathetic activation, but has no effect on the sympathetic nervous system per sé. CRF in the brain inhibits the conditioned fear-induced net increase in vagal outflow and thereby contributes to the tachycardiac stress response. This was demonstrated in a study using α-helical CRF-(9–41), which reduces the tachycardiac response by potentiating the increase in PQ interval due to conditioned fear (Nijsen et al., 2000a). An inhibition of sympathetic outflow cannot explain this effect, since α-helical CRF-(9–41) did not alter the sympathetic-adrenomedullary response, as indirectly evidenced by the absence of differences in plasma norepinephrine and epinephrine responses between the α-helical CRF-(9–41) and the saline-treated groups. The finding that the effect of i.c.v. infusion of by α-helical CRF-(9–41) on the heart rate and PQ response was completely blocked by pre-treatment of the rats with the peripherally acting muscarinic antagonist atropine methylnitrate, substantiates this notion.

2.3. CRF, effects on behavior

Anxiety has profound effects on learning and memory processes. Based on several behavioral effects, it was suggested that CRF enhances the anxiogenic nature of environmental stimuli. In an open field in which a pellet of food was placed in the centre, CRF reduces both the number of approaches to the food and the average amount of food consumed per approach. When animals experience the open field as a threatening environment, they will stick to the boundaries. High doses of CRF increase grooming behavior which often occurs in aversive situations (Britton, 1989). Besides anxiogenic effects, it has been suggested that CRF has arousal properties, which are also part of learning and memory processes (Kovács et al., 1977). I.c.v. CRF also decreases slow-wave sleep (Ehlers et al., 1986) and shortens pentobarbital-induced sleeping time in rats (Imaki et al. 1986), whereas administration of α-helical CRF-(9–41) reduces spontaneous waking (Chang and Opp, 1998). Studies with a CRF_1 antagonist, CRA1000 demonstrated that CRF mediates at least some effects on

arousal and attention through activation of the CRF_1 receptor. CRA1000 reverses the restraint stress-induced shortening of pentobarbital-induced sleeping time in rats, but has no effect on pentobarbital-induced sleeping in nonstressed animals (Arai et al. 1998). Performance in a variety of test situations varies with the level of activation or arousal in animals. A bell-shaped relation between arousal and performance was described (Hebb, 1966). Low doses of subcutaneously (s.c.) administered CRF were effective and moderate doses disrupt acquisition of one-way and two-way active avoidance behavior. Low doses of CRF s.c. facilitate passive avoidance behavior and high doses attenuate it.

It has been suggested that CRF_1 receptors are involved in the modulation of learning and memory processes. A CRF_1 receptor antagonist, CP-154,526 injected prior to training, impaired the induction of contextual fear conditioning (Deak et al., 1999). CRF_1 receptor knockout mice show impaired speed in acquiring a five-choice simultaneous discrimination, but eventually reach a level of accuracy comparable to that of wild-type mice. It is not clear whether the acquisition deficit is a learning deficit, or is confounded by impaired attention/arousal (Steckler et al., 1999). The presence of CRF_1 receptors in the hippocampus suggest a role in learning and memory processes. This notion is supported by electrophysiological data, which show that CRF induces a long-lasting enhancement of synaptic efficacy in the hippocampus (Wang et al., 1998).

3. Vasopressin and related neuropeptides

3.1. Vasopressin, synthesis and distribution

Synthesis of vasopressin precursors takes place predominantly in hypothalamic nuclei. In the hypothalamus, two vasopressinergic cell types can be distinguished: magnocellular and parvocellular neurons. Magnocellular neurons from the paraventricular and supraoptic nuclei produce vasopressin precursors that are transported to the posterior pituitary. From there, the release of vasopressin into the circulation can be elicited by stimuli such as osmotic variations, pressor changes and stress. Parvocellular neurons in the nucleus paraventricularis of the rat send a vasopressinergic projection to the hypophyseal portal system terminating in the median eminence area; vasopressin released by this route may be involved in the regulation of the pro-opiomelanocortin cell in the anterior pituitary.

Furthermore, there are abundant extrahypothalamic projections. One of the major sets of vasopressin neurons arises from the nucleus paraventricularis and projects to brain areas involved in autonomic regulation (see paragraph on CRF, distribution and receptors).

Two types of vasopressin receptors are found in the rat brain: vasopressin V_{1A} and V_{1B}. The localisation of vasopressin V_{1A} binding sites in the olfactory bulb, lateral septum, hypothalamus, bed nucleus of the stria terminalis, periaqueductal gray, hippocampus, nucleus tractus solitarius and spinal cord correspond well with the relative distribution of vasopressin-terminals in these brain areas (Barberis and Tribollet, 1996; Ostrowski et al., 1994; Tribollet et al., 1988). Cells which express vasopressin V_{1A} mRNA were found in the above-mentioned brain areas and in the nucleus paraventricularis, central nucleus of the amygdala, locus coeruleus, dorsal motor nucleus of the vagus and nucleus ambiguous (Ostrowski et al., 1994). The vasopressin V_{1B} binding site has been found only in the pituitary so far (Antoni, 1984), suggesting a role in the modulation of the HPA-axis. However, others reported that vasopressin V_{1B} mRNA is also expressed outside the pituitary, in those brain regions where vasopressin V_{1A} binding sites have been localised (Lolait et al., 1995; Saito et al., 1995). These findings raise the possibility that the vasopressin V_{1A}- and V_{1B} receptor may play a role in the regulation of the ANS.

3.2. Vasopressin and stress-induced autonomic responses

It has been reported that i.c.v. administered vasopressin enhances heart rate, blood pressure, renal sympathetic nerve activity, plasma norepinephrine and epinephrine in conscious rats under resting conditions, indicating that exogenous vasopressin enhances sympathetic nervous system activity (Nijsen, 1999; Rohmeiss et al., 1986; Zerbe and Feuerstein, 1985). In addition, many cardiovascular studies have demonstrated that vasopressin-induced tachycardiac and pressor responses can be blocked by the vasopressin V_{1A} or $V_{1A/1B}$ receptor antagonist in rats (Brattström et al., 1990; Matsuguchi et al., 1982; Nijsen, 1999; Rohmeiss et al., 1986; Vallejo et al., 1984). Chemical stimulation of the nucleus paraventricularis in conscious rats was associated with increases in heart rate, blood pressure, renal sympathetic nerve activity, plasma norepinephrine and epinephrine, which was completely blocked by intrathecally injected vasopressin V_{1A} receptor antagonist (Malpas and Coote, 1994; Martin and Haywood, 1992). These responses were not affected by intravenous administrations of vasopressin V_1 receptor antagonist $d(CH_2)_5Tyr(Me)$vasopressin, which suggests that plasma vasopressin is not the major mediator in the cardiovascular response. Others showed that electrical stimulation of the nucleus paraventricularis increased heart rate and blood pressure, associated with increased vasopressin release in the nucleus tractus solitarius/dorsal motor nucleus of the vagus area in rats (Landgraf et al., 1990; Pittman and Franklin, 1985). Administration of the vasopressin V_{1A} receptor antagonist in the nucleus tractus solitarius, dorsal motor nucleus of the vagus area reduced nucleus paraventricularis-stimulated pressor and tachycar-

diac responses. In vitro studies indicated that application of vasopressin on brain slices of the rat increases the spontaneous neural activity of the dorsal motor nucleus of the vagus, which can be completely blocked by a vasopressin V_{1A} receptor antagonist (Mo et al., 1992). These data suggest that exogenous vasopressin is able to activate vagal activity via binding on V_{1A} receptors in the dorsal motor nucleus of the vagus dorsal motor nucleus of the vagus area. Collectively, these findings suggest that sympathetic and vagal output are increased through an action of exogenous vasopressin on the vasopressin V_{1A} receptor.

The possible role for endogenous vasopressin in stress-induced responses is less clear than for CRF. Callahan et al. (1989) demonstrated that i.c.v. administration of the vasopressin V_{1A} receptor antagonist abolished the foot-shock-induced tachycardia in rats. We reported that i.c.v. infusion of a vasopressin $V_{1A/1B}$ receptor antagonist in freely moving rats reduces tachycardia, and tends to elongate the PQ interval during conditioned fear (Nijsen, 1999). These effects are probably not mediated by inhibition of sympathetic and/or adrenomedullary activity, since the vasopressin antagonist enhances rather than reduces the stress-induced plasma norepinephrine and epinephrine response. Taken together, these results indicate that vasopressin activity in vasopressin containing fibres to the autonomic centres is increased as a result of conditioned fear, and leads to inhibition of sympathetic and vagal outflow.

The above mentioned studies suggest that exogenous vasopressin activates the sympathetic and parasympathetic nervous system when centrally administered under resting conditions, resulting in an increase in blood pressure, heart rate, plasma norepinephrine and epinephrine. From stress research, it can be concluded that endogenous vasopressin may be involved in stress-induced tachycardia due to inhibition of sympathetic and parasympathetic activation.

The contradiction between the effects of exogenous and endogenous vasopressin, but also CRF (see previous paragraph) on the ANS can be explained by several reasons. Probably, the amount of CRF/vasopressin levels in the brain determines the outcome of the ANS. This is supported by many studies, which showed that the effects of exogenous CRF or vasopressin depend on the amount administered (Diamant and De Wied, 1993; Dunn and Berridge, 1990; Stepniakowski et al., 1991; Versteeg et al., 1979). Another factor is the state of arousal of the animals. It is possible that the outcome of CRF or vasopressin during stress interacts with stress-induced release of other neuropeptides. It has already been demonstrated that vasopressin interacts with CRF to exert synergistic actions on ACTH release from pituitary corticotrope cells (Gibbs, 1984; Gillies et al., 1982). Maybe, a similar interaction occurs in other areas in the brain as well. For instance, both CRF and vasopressin terminals have been found in the amygdala, periaqueductal gray, dorsal motor nucleus of the vagus and nucleus tractus solitarius (Buijs, 1978; Gray, 1992; Gray and Bingaman, 1996; Gray and Magnuson, 1987; Nilaver et al., 1980), areas which are known to be involved in autonomic function.

3.3. Vasopressin and behavior

Vasopressin (arginine–vasopressin) and its fragments, as small as vasopressin-(4–8), are involved in learning and memory processes (De Wied, 1969, 1971, 1977, 1980, 1984; De Wied et al., 1986). A single injection of vasopressin given either before the training, immediately after the acquisition period, or before extinction, increases resistance to extinction of pole-jumping avoidance behavior (conditioned avoidance behavior). This effect is of long duration and may last for days, depending on the dose. Vasopressin also facilitates avoidance acquisition of hypophysectomized rats, which are impaired in their learning ability.

There is a critical time period for the behavioral effect of vasopressin. Administration immediately after the last acquisition session of the pole-jump avoidance behavior produces the maximal behavioral effect. If injection is given at 3 h before or after the session, the effectiveness of the treatment is markedly decreased while administration at a time interval of 6 h before or after the session is ineffective (Gaffori and De Wied, 1986). This suggests that vasopressin exerts its effect on the consolidation phase. Passive avoidance behavior is also affected by vasopressin and related fragments. The period immediately after the learning trial is critical for information storage. Memory can be prevented by prior treatment with enzyme inhibitors, electroconvulsive shock treatment, etc. It is in this period that vasopressin is active. Besides effects on consolidation, vasopressin also exerts effects on retrieval of information. Administration of vasopressin 1 h prior to the retention test facilitates passive avoidance behavior.

Part of the learning and memory effects of vasopressin can be explained by an increase in arousal. Skopkova et al. (1991) demonstrated an immediate and a long-term effect of des-Gly^{9}[Arg^{8}]vasopressin on acquisition and extinction of avoidance behavior. Rats that were pre-estimated in an open field test to be low active, showed a lower number of conditioned avoidance responses during acquisition and extinction of a conditioned avoidance task than high active rats. When a low dose of des-Gly^{9}[Arg^{8}]vasopressin was administered prior to the first acquisition session in low active rats, an increase in acquisition was observed, while a decrease was found with a high dose in high active rats. The immediate effect of des-Gly^{9}[Arg^{8}]vasopressin on acquisition is explained as a shift to the right in the bell-shaped curve of the relation between arousal and performance (according to the theory of Hebb (1966)). Independent of the acquisition performance, the extinction was inhibited in a dose-dependent manner in both low and high active rats. From these effects, it was suggested that des-Gly^{9}[Arg^{8}]vasopressin has an immediate effect on

arousal, which is reflected in acquisition performance and a long-term effect indicating the formation of memory traces (Skopkova et al., 1991). The arousal hypothesis is also supported by the modulation in mean and peak frequency of theta-activity which has been found during paradoxical sleep or stimulation of the mesencephalic reticular formation (Urban and de Wied, 1978) following vasopressin treatment. However, the long-term effect, the time dependency and the antiamnesic influence of vasopressin and related peptides point to an effect on memory processes.

Learning and memory effects of vasopressin may be explained by effects on excitation of septal and hippocampal neurons (Joels and Urban, 1984a). Furthermore, vasopressin is also able to enhance the response to glutamate in 60–70% of these cells (neuromodulation) (Joels and Urban, 1984b). Memory formation may be related to processes associated with the development of long-term potentiation (Bliss and Lomo, 1973). It was demonstrated that acquisition of active avoidance behavior evokes a long-term increase in glutamatergic transmission between the fimbria fibres and the lateral septum. This phenomenon does not occur in Brattleboro diabetes insipidus (Di/Di) rats, which lack vasopressin. In addition, vasopressin is also implicated in the in vitro maintenance of long-term potentiation.

Besides electrophysiological findings, studies including lesions and local application also show that the hippocampus and the septum are sites of action of vasopressin. The sites of action of vasopressin in affecting retrieval processes are located in the amygdala and the dentate gyrus of the hippocampal complex, whereas in consolidation processes, the sites of action are located in the dorsal septum, dorsal raphe and dentate gyrus of the hippocampus and the subiculum (Kovács et al., 1986; Van Wimersma Greidanus et al., 1986).

The modulatory effect of vasopressin and related peptides on memory processes is exerted in the brain rather than via peripheral pathways. Whereas nanogram amounts suffice when administered directly into the brain, microgram quantities are required after s.c. administration. It has been suggested that peripheral effects of vasopressin leading to increased arousal of animals are responsible for some of the behavioral effects of the peptide (Ettenberg et al., 1983; Le Moal et al., 1981; Sahgal et al., 1982). These peripheral effects are particularly apparent within the first hour after systemic injection. Ettenberg et al. (1983) found that rats avoid situations which were previously paired with the administration of vasopressin. Both the toxic agent lithium chloride and vasopressin induced conditioned taste aversion. The authors concluded that properties of vasopressin depend on its aversive and consequently arousing actions. In these studies, classical endocrine effects such as increases in blood pressure, diuresis and oxygen consumption may be important confounders. However, vasopressin is a precursor molecule for highly active fragments. These behaviorally active fragments are generated in the brain and are devoid of the classical endocrine effects. In brain extracts, metabolites as small as [pGlu^4]vasopressin-(5–9) were found (Burbach, 1989).

The presence of peripheral catecholamines appears to be essential for central effects of vasopressin on passive avoidance behavior. Rats that were adrenalectomized 2 days before a learning trial of a passive avoidance task, displayed a marked deficit in retention, which was not normalized by post-learning or pre-retention administration of vasopressin (s.c. or i.c.v.) (Borrell et al., 1983a). Conversely, vasopressin is needed for the effect of catecholamines on passive avoidance behavior, since the facilitating effects of catecholamines is not found in the Brattleboro diabetes insipidus rats, which lack the ability to synthesize vasopressin (Borrell et al., 1984).

The involvement of basal forebrain-septal cholinergic neurons in learning and memory has been well established (Araujo et al., 1990). The fields of termination of the septohippocampal cholinergic projections are maintained by a continuous tropic supply of nerve growth factor and brain-derived neurotrophic factor. Vasopressin-(4–8) administered in rat hippocampus enhances expression of these factors (Du et al., 1999). In a recent study from Tanabe et al. (1999), it was demonstrated that vasopressin-(4–9) enhances acetylcholine release from hippocampal slices. Whether this effect contributes to learning and memory processes has not been elucidated yet. Vasopressin-(4–9) counteracted the passive avoidance response of scopolamine (a cholinergic blocker)-induced memory-deficient mice.

4. Concluding remarks

This chapter focuses on the role of the ANS and neuropeptides in learning and memory processes. Learning and memory processes are essential requirements for adaptation to occur. Adaptation may thus be regarded as a concerted action of stress hormones and neuropeptides. Neuropeptides are abundantly present in the limbic midbrain system together with fibres containing monoamines, acetylcholine, excitatory and inhibitory transmitters. The level of activity (arousal) in the limbic midbrain is determined by the ascending reticular activating system which integrates sensory information from the external milieu with the internal state of the organism. Neuropeptides as CRF affect arousal and in this way affect learning and memory processes. The endogenous CRF system seems to counteract emotional stress-induced vagal stimulation. This effect is in part responsible for stress-induced tachycardia. So far, it has not been demonstrated that during aversive stimuli CRF is responsible for activating the sympathetic nervous system. Nevertheless, the release of peripheral catecholamines is a prerequisite for central effects of vaso-

pressin. Vasopressin enhances memory consolidation and retrieval processes. The mechanism beyond this effect has in part been elucidated. Vasopressin, like other treatments known to affect memory consolidation, modulates the maintenance of hippocampal long-term potentiation. During aversive stimuli, endogenous vasopressin counteracts the stress-induced sympathetic and vagal activity and thus seems to act as a dearousal hormone. This may also be the final part of the learning and memory process by terminating/reducing the peripheral stress response and in this way, terminating the loop between peripheral sympathetic responses and subsequently activation of limbic midbrain structures.

Acknowledgements

The authors thank Dr David de Wied for critically reading the manuscript.

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