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Review

Neuropeptides in learning and memory processes with focus on galanin

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ABSTRACT

Neuropeptides represent by far the most common signalling molecules in the central nervous system. They are involved in a wide range of physiological functions and can act as neurotransmitters, neuromodulators or hormones in the central nervous system and in the periphery. Accumulating evidence during the past 40 years has implicated a number of neuropeptides in various cognitive functions including learning and memory. A major focus has been on the possibility that neuropeptides, by coexisting with classical neurotransmitters, can modulate classical transmitter function of importance for cognition. It has become increasingly clear that most transmitter systems in the brain can release a cocktail of signalling molecules including classical transmitters and several neuropeptides. However, the neuropeptides seem to come into action mainly under conditions of severe stress or aversive events, which have linked their action also to regulation of affective components of behaviour. This paper summarises some of the results of three neuropeptides, which can impact on hippocampal cognition by intrinsic (dynorphins, nociceptin) or extrinsic (galanin) modulation. The results obtained with these neuropeptides in rodent studies indicate that they are important for various aspects of hippocampal learning and memory as well as hippocampal plasticity. Recent studies in humans have also shown that dysregulation of these neuropeptides may be of importance for both neurodegenerative and neuropsychiatric disorders associated with cognitive impairments. It is concluded that compounds acting on neuropeptide receptor subtypes will represent novel targets for a number of disorders, which involve cognitive deficiencies.

Contents

1. Introduction

David de Wied's research on neuropeptides during the 1960's was the starting point for the investigations of the role of these molecules in cognitive functions. He was one of the first to establish the concept of "neuropeptides". He also recognized that brain peptides can modify and orchestrate complex behaviours (see the accompanying paper by Gispen et al. in this issue) and play an important role in the pathophysiology of mental disorders (De Wied and Sigling, 2002).

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His pioneering studies suggested that hypothalamic peptides such as adrenocorticotropin hormone (ACTH), besides being involved in neuroendocrine regulation, also could play a role in learning and memory. Moreover, he proposed that central nervous system fragments of peptide hormones, which have lost their hormonal actions can modulate brain function (de Wied et al., 1993). The work of David de Wied and his associates pioneered and foreboded the current intensive research on the role of transmitters and molecular systems in cognitive processing and in human pathologies characterized by cognitive disturbances.

Cognitive disturbances are a hallmark of a number of psychiatric and neurological disorders including depression, anxiety, schizophrenia, bipolar disorders but also stroke, parkinsonism and of course various dementias such as Alzheimer's disease. Accumulating evidence mainly from animal work, but now also supported by some human data, suggests that dysregulation of endogenous neuropeptide systems, particularly in the hippocampus, may play a role in the development of cognitive impairments.

Our paper will first give a brief and general characterization of neuropeptides to present the problems associated with analyzing these molecules in cognition. We will then summarise the role of some selected neuropeptides expressed in brain circuits or neurochemical systems of the hippocampal formation known to play an important role in various mental disorders, psychopathologies and in cognitive functions.

2. General characteristics of neuropeptides of relevance for cognitive functions

Neuropeptides, which represent by far the largest group of messenger molecules in the brain (De Wied and Burbach, 1999; Hökfelt and Mutt, 1999), share several important characteristics, which must be taken into account when analyzing their physiological roles. Neuropeptides, which usually are highly conserved between species, show a large variety in size ranging from 3 to 80, or so, amino acids in length. However, marked species differences exist, not only in peptide expression in various brain systems but also in receptor distribution and localization. Neuropeptides differ from classical transmitters with regard to synthesis, storage and release-mechanisms. They are synthesized in the cell body of a neuron as prepropeptides and, following processing in the Golgi apparatus and package into large dense core vesicles, reach the neuron terminal by fast axonal transport (Gainer, 1981). Classic neurotransmitters are stored in small clear synaptic vesicles located in nerve endings close to the release sites. The large dense core vesicles are formed away from the active zone and fuse with the presynaptic membrane, mostly outside the synapse, in response to high Ca^{2+} influx. As a consequence, the neuropeptides are mainly released at extrasynaptic sites during 'burst activity' or high frequency firing unlike classic neurotransmitters, which are also released at low frequency firing into the synaptic cleft (Tallent, 2008). Recent data indicate that some neuropeptides, such as dynorphins as well as the hypothalamic peptides vasopressin and oxytocin, also have a prominent dendritic release in the brain (Ludwig and Leng, 2006; Schwarzer, 2009). Following extensive neuronal activation the stores of neuropeptides can be depleted, since replacement after release is dependent on ribosomal synthesis and axonal transport, contrasting reuptake and reuse of most small transmitters.

The physiological signalling of neuropeptides is mediated mainly by G-protein coupled receptors located both pre- and post-synaptically (e.g. Branchek et al., 2000). The neuropeptide receptors are mostly not localized in the post-synaptic density but located at extrasynaptic sites, involving so called volume transmission (Agnati et al., 1995). This implies that neuropeptides can act at a distance by diffusing from the release site in the extracellular space to interact with extrasynaptic receptors (Ludwig and Leng, 2006; Tallent, 2008). There exists at least one receptor for each neuropeptide (usually several receptor subtypes), which means that there are presumably several hundred neuropeptide receptors, which can affect multiple intracellular transduction pathways. However, considerable species differences exist with regard to neuropeptidergic immunoreactivity and receptor binding sites in various brain regions, which complicates the interpretation of their receptor functions.

Coexistence of neuropeptides or co-distribution with other transmitters is a rule rather than the exception in the central nervous system. In fact, most neuropeptides are expressed in neurons that co-express at least one classic transmitter and often more than one neuropeptide (Table 1) (Hökfelt et al., 2000). Many neurons in the central nervous system can in principle release a 'cocktail' of chemical messengers, including a fast-acting, excitatory transmitter amino acid such as glutamate together with a monoamine as well as one or more neuropeptides. Physiologically, neuropeptides mainly behave as neuromodulators with a prolonged action on multiple physiological and behavioural actions. Their physiological effects involve changes in membrane excitability, neuromodulatory and trophic actions, gene transcription, changes in affinity of receptors and modulation of neurotransmitter release. The versatility in their actions explains the multiple physiological effects executed by neuropeptides. Consistent with their location in the hippocampus, amygdala, hypothalamus, striatum and spinal cord, the physiological functions of neuropeptides involve learning and memory, emotional control, locomotion, neuroendocrine and stress regulation and pain perception (Heilig et al., 1994; Ögren et al., 2006; Schwarzer, 2009).

3. Neuropeptides and cognitive functions

Based on their distribution in the brain, neuropeptides have increasingly been recognised as regulators of 'cognitive' pathways in the brain, but they are also involved in anxiety and depression circuitries (Heilig et al., 1994; Holmes et al., 2002). Based on various physiological, biochemical and behavioural criteria, a number of neuropeptides have also been implicated in cognitive functions such as learning and memory. These peptides include corticotropin-releasing factor, urocortin, neuropeptide Y, vasoactive intestinal polypeptide, neurotensin, galanin, opioid peptides, nociceptin, oxytocin and angiotensin, to name a few (Fig. 1).

A recent search in PubMed using the search phrase (memory OR learning) AND (neuropeptide) generated 4996 articles. Thus, there has been considerable interest in the topic. However, the issues are complex in studying the functional role of neuropeptides. Additionally, there are problems of translating the results from animal models to humans and there is a lack of knowledge of neuropathologies associated with neuropeptides derangement.

Table 1
Coexistence of some neuropeptides and neurotransmitters in brain areas associated with cognitive functions.

Peptide	Transmitter	Location
Dynorphin	Glutamate	Dentate gyrus
		Paraventricular nucleus
	GABA	Striatum
NPY	Noradrenaline	Locus coeruleus
		Medulla oblongata
	Adrenaline	Medulla oblongata
	GABA	Cortex, hippocampal formation
Somatostatin	GABA	Cortex, hippocampal formation
Cholecystokinin	Dopamin	Cortex, hippocampus, ventral mesencephalon
Galanin	5-HT	Dorsal raphe nuclei
	Noradrenaline	Locus coeruleus
	Histamine	Tuberal and caudal magnocellular nuclei
	Acetylcholine	Basal forebrain
	GABA	Tuberal and caudal magnocellular nuclei

GABA, γ-aminobutyric acid; NPY, neuropeptide Y. Modified from Hökfelt and Mutt (1999).

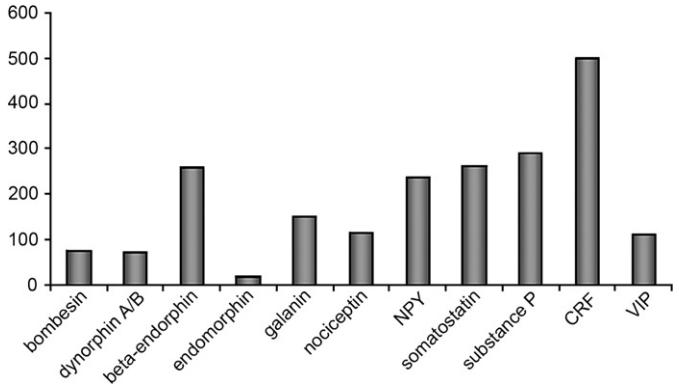

Fig. 1. A summary of the number of hits related to different neuropeptides and learning or memory. A search was performed on PubMed using the search phrase (memory OR learning) AND (name of neuropeptide). The search on dynorphin included dynorphin A, B and big dynorphin. NPY, neuropeptide Y; CRF, corticotropin-releasing factor; VIP, vasoactive intestinal polypeptide.

There are a number of factors that have hampered our understanding of the functional roles of neuropeptides. Since most neuropeptides do not penetrate the blood-brain barrier, their effects on brain functions are mostly investigated after central administration (mainly intracerebroventricular; i.c.v.) into the brain of rodents. Such studies have raised concerns about relevant physiological concentrations of the neuropeptides and their half-life in different brain tissues, which depend on chemical structure, peptidase activities and possibly also various uptake mechanisms. In fact, the biological half-life of most neuropeptides after injection into brain tissue is poorly known but is generally short (Schött et al., 1998b). Another major problem in the analysis is the lack of specific pharmacological tools, including blood-brain-barrier-penetrating, small-molecule agonists and antagonist to dissect peptidergic mechanisms and functions (Lu et al., 2005b). In recent years several compounds with selective actions on neuropeptide receptors have been developed. For example, compounds with selective antagonistic properties for the galanin receptor type 3 (GAL3) that pass the blood-brain-barrier have been shown to possess both antidepressant and anxiolytic properties (Swanson et al., 2005).

Studies using intracerebral (mainly i.c.v.) injections of several neuropeptides or receptor ligands have reported changes in performance of hippocampal-dependent memory tasks, involving both emotional memory, e.g. passive avoidance or spatial learning in the water maze. In contrast, studies on peptidergic antagonists have mostly failed to reveal any significant effect on learning. This lack of effect is probably due to the fact that neuropeptides are mainly released when neurons are strongly activated (see above), while endogenous peptidergic transmission during basal physiological states is low. Therefore, it is likely that the action of neuropeptides can mainly be revealed under pathological or aversive situations e.g. severe stress. In fact, neuropeptides such as e.g. galanin (see below) are upregulated in brain areas such as the hippocampus following stress or traumas (Diez et al., 2003) and they can also modify behavioural and neurochemical consequences of stress (Holmes et al., 2002; Kuteeva et al., 2005, 2008).

4. Neuropeptides and hippocampal memory circuits

Both animal and human studies indicate that the hippocampal formation play a crucial role in encoding and consolidation of new information into declarative memory (Eichenbaum, 1997). The present article focuses on investigations, which were designed to elucidate neuropeptides that may function either as 'intrinsic' (dynorphin, nociceptin) or 'extrinsic' (galanin) modulators of hippocampal information processing. The analysis of hippocampally mediated learning has mostly been investigated using the Morris swim maze (Morris, 1984). Performance in this visual–spatial task depends on the integrity of the hippocampal formation (Morris et al., 1986b). Rats or mice are required to localize an invisible platform that is submerged below the water surface in a circular pool. Spatial cues surrounding the water tank (extra-maze cues) are used to locate the platform. This reference memory task differs from spatial working memory tasks, in which the rodent has to remember the spatial information from trial to trial. In addition, the effects of neuropeptides on emotional memory were often assessed by the use of the passive avoidance procedure, which is based on Pavlovian aversive conditioning, involving both the hippocampal formation and the amygdala (Ögren et al., 2008).

Hippocampal synaptic plasticity is believed to be a mechanism for spatial memory (Morris et al., 1986a). The importance of glutamate and the *N*-methyl-D-aspartate (NMDA)-receptor for the induction of long-term potentiation (LTP) and spatial memory in rodents is well documented (Collingridge et al., 1983; Dudek and Bear, 1992). Glutamatergic and γ-aminobutyric acid (GABA)-ergic neurons, which play a critical role in hippocampal information processing, are modulated by intrinsic and extrinsic modulatory inputs. Brain neuropeptides may contribute to learning and memory processing via a direct or indirect modulation of excitatory/inhibitory systems in the hippocampal formation. Several neuropeptides are expressed in the glutamatergic neurons of the trisynaptic pathway of the hippocampus (Fig. 2, Table 2). Opioid peptides such as enkephalin and dynorphin, which coexists with glutamate in the perforant path projection from the entorhinal cortex and are, thus, in a position to modulate neurons in the dentate gyrus (Schwarzer, 2009). In principle, all neurons in the mossy fibre projection to the CA3-subregion of the hippocampus also express dynorphin A and B, as well as κ-opioid receptors (McGinty et al., 1983) (Table 2). The opioid-like peptide nociceptin is expressed in both CA1 and CA3 pyramidal cell layers and dentate gyrus, presumably by GABAergic neurons (Neal et al., 1999), but evidence for coexistence is still lacking. Galanin, on the other hand, is an extrinsic modulator of hippocampal function. In the rat this peptide coexists with noradrenaline in the locus coeruleus, with serotonin (5-hydroxytryptamine; 5-HT) in the dorsal raphe nucleus, and, after experimental manipulations, with acetylcholine in the medial septal area (Melander et al., 1986a) (Table 2). Thus, galanin is in the position to influence hippocampal function by modifying the inputs of noradrenaline, 5-HT and acetylcholine.

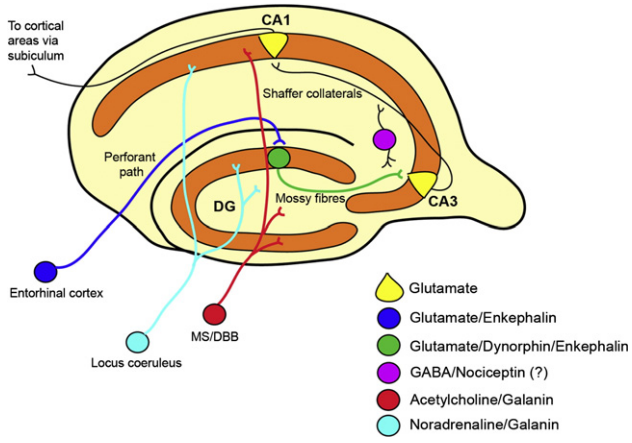

Fig. 2. Neuropeptide expression in the hippocampal network of the rat. This simplified, schematic figure summarises the coexistence of some neuropeptides with classical neurotransmitters within the hippocampus and its input neurons. GABA, γ-aminobutyric acid; DG, dentate gyrus; MS/DBB, medial septum/diagonal band of Broca.

Table 2
Neuropeptides localized in hippocampal circuitry important for cognition.

Mossy fiber pathway (glutamatergic neurons)
Dynorphin A and B, big dynorphin; enkephalin
Pyramidal neurons and GABA interneurons
Nociceptin
Afferent neurons (Raphe 5-HT neurons, locus coeruleus noradrenaline neurons and medial septal acetylcholine neurons)
Galanin

GABA, γ-aminobutyric acid; 5-HT, 5-hydroxytryptamine.

5. Neuropeptides as intrinsic and extrinsic modulators of hippocampal cognition

5.1. Dynorphins

The dynorphins belong to the opioid peptide family and mediate their functions mainly via the κ-opioid receptors. Both the synthesis and release of dynorphin is complex (Schwarzer, 2009). Processing of the prodynorphin gene gives rise to several biologically active peptides, such as dynorphin A, dynorphin B, α-neoendorphin as well as the intermediate big dynorphin, which consists of dynorphin A and B sequences (Day and Akil, 1989). The release of dynorphin is also complex, since released peptide may mediate its action at both axonal, auto- or heteroreceptors, or dendritic heteroreceptors. This complexity of release has been shown to occur also in hippocampal granule cells. There exist both post-synaptic κ-opioid receptors on dendrites of the granule cells as well as presynaptic κ-opioid receptors located on perforant path neurons. The axons from the granule cells, which co-express dynorphin, send their terminals (mossy fibres) and form synapses with dendrites of CA3 pyramidal neurons, which express κ-opioid receptors (Schwarzer, 2009). Activation of κ-opioid receptors exerts an inhibitory effect on glutamatergic pyramidal neurons, and thereby reduces hippocampal excitability (Simmons and Chavkin, 1996). Thus, stimulation of κ-opioid receptors in the hippocampus potently inhibits hippocampal transmission and the induction of LTP (Huge et al., 2009).

Since the κ-opioid receptor system has been associated with aversive behaviour (Kreek et al., 2002), the results obtained in the passive avoidance test based on aversive conditioning are of special interest. Both dynorphin A (0.0005–5 nmol/mice, i.c.v.), dynorphin B (0.007–7 nmol/mice, i.c.v.) and big dynorphin (0.0025–2.5 nmol/mice, i.c.v.), injected in mice prior to the training session, enhanced memory retention in the passive avoidance, as evidenced by a significant increase in step-through latency examined 24 h post training (Kuzmin et al., 2006). These data agree with previous observations on the facilitatory effects of dynorphin A in rodents on memory retention in the passive avoidance task (Hiramatsu and Inoue, 2000). The impairing effect of dynorphin A but not that of big dynorphin, was blocked by the κ-opioid receptor antagonist nor-binaltorphimine (Nor-BNI), indicating that both dynorphin A and dynorphin B mainly act via κ-opioid receptors (Kuzmin et al., 2006). In contrast, (5R, 10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine hydrogen maleate (MK-801), a NMDA receptor antagonist, blocked the action of big dynorphin on passive avoidance (Kuzmin et al., 2006), suggesting that big dynorphin mediates its effects on cognition via NMDA receptors.

The enhancement of aversive memory by dynorphins may indicate that these peptides enhance the negative motivational properties of exposure to stressful events, e.g. foot shock in case of passive avoidance. This means that activation of the dynorphin system may be involved in the physiological coping with stressful events, since the aversive effects of stress appear to be mediated by dynorphin release and κ-opioid receptor activation (Land et al., 2008). Since the studies with passive avoidance are based on i.c.v. administration, the relative role of hippocampus or amygdala in the action of dynorphins is not possible to determine. Importantly, microinjection of the κ-opioid receptor-selective agonist 3,4-dichloro-*N*-methyl-*N*-(2-(1-pyrrolidinyl)-cyclohexyl)-benzeneacetamide hydrochloride (U50,488H) into the CA3 region of the dorsal hippocampus decreased context-induced fear conditioning, as well as water maze performance in mice (Daumas et al., 2007). These impairments were blocked by co-infusion of Nor-BNI, suggesting that κ-receptors in the CA3 subregion are involved in the hippocampus-dependent tasks. Further studies on local administration into the amygdala and hippocampus are critical, since these structures interact, but also probably serve different aspects of aversive learning (Ögren et al., 2008).

Induction of LTP potentiation in the mossy fibre pathway to the CA3 region has been shown to be impaired by dynorphin peptides (Simmons and Chavkin, 1996). Infusion of dynorphin B into the CA3 region of the dorsal hippocampus also impaired spatial acquisition (Sandin et al., 1998). Nor-BNI (2 nmol/rat) infused into the hippocampus fully blocked the acquisition impairment caused by dynorphin B (10 nmol/rat), while Nor-BNI alone did not affect spatial learning. In another study, dynorphin A administration in the dorsal hippocampus (CA3 region) impaired acquisition of a reference memory task, and this impairment was reversed by naloxone, an unselective opioid receptor antagonist (McDaniel et al., 1990). Consistent with this finding, prodynorphin knockout mice showed attenuation of age-related impairment in spatial learning in comparison to wild-type mice (Nguyen et al., 2005). These findings suggest that dynorphin peptides may play a role in hippocampal plasticity by acting on hippocampal κ-opioid receptors. Also clinical data support a role for dynorphins in mechanisms underlying Alzheimer's disease (Yakovleva et al., 2007), alcohol dementia (Bakalkin et al., 2008) as well as addiction (Koob and Le Moal, 2008). In chronic alcoholism, there is recent evidence that dysregulation of the dynorphin system may be important for the development of alcoholism and associated cognitive impairments (Bakalkin et al., 2008). In post mortem brains of alcoholics prodynorphin expression was upregulated in the hippocampus and prefrontal cortex. In view of the importance of the dynorphins in emotional and stress circuits, it is not surprising that they have also been implicated in various neuropsychiatric disorders associated with cognitive deficits, such as anxiety, depression and schizophrenia (see Schwarzer, 2009). Although the evidence based on animal studies suggests that increase in endogenous dynorphin expression may be detrimental for cognitive functions, the underlying mechanisms are still not known. In view of the complexity of the processing of the prodynorphin gene encoding dynorphins, as well as the different functional effects of the dynorphin fragments, it will be important to analyse the expression and distribution of dynorphins and κ- opioid receptors in various psychopathologies. This is illustrated by the recent finding that polymorphisms in the prodynorphin gene are critical for the performance in episodic memory tasks in elderly (Kölsch et al., 2009). It is, therefore, crucial to evaluate the role of dynorphins and κ-opioid receptors in cognitive functions in relevant animal models of psychopathology.

5.2. Nociceptin

Nociceptin/orphanin FQ (N/OFQ) was identified as an agonist for the G-protein coupled opiate-like 1 receptor, currently termed the NOP receptor (previously ORL-1 receptor) (Meunier et al., 1995; Reinscheid et al., 1995). Although nociceptin shows structural homologies with the opioids (dynorphin A), it has negligible affinity for classical opioid receptors, and its biological effect is not blocked by naloxone (Meunier, 1997). The wide expression of nociceptin and the NOP receptor in the temporal lobe areas, such as CA1, molecular layer of the dental gyrus, subiculum and the entorhinal cortex (Meunier, 1997; Micheau and Marrewijk, 1999; Higgins et al., 2002) have suggested that this peptide is important for cognitive, attention and emotional processes, including fear and anxiety (Jenck et al., 1997; Civelli, 2008).

Studies in rodents have shown that nociceptin plays an important role in hippocampal-dependent learning (Sandin et al., 1997; Noda et al., 2000). The potential role of this peptide for hippocampal function was first examined after infusion of nociceptin into the hippocampus of the rat. Intrahippocampal administration of nociceptin was shown to produce a profound impairment of spatial learning, first in rats (Sandin et al., 1997; Redrobe et al., 2000) and later in mice (Kuzmin et al., 2009). However, the effects of intrahippocampal nociceptin were shown to be biphasic, since high doses impaired, while lower doses improved spatial learning in the rat. Both the impairments (Redrobe et al., 2000) and the facilitating effects of nociceptin were blocked by the putative NOP receptor antagonists [Nphel]Nociceptin (1–13)–NH2 (Sandin et al., 2004), suggesting that both effects are NOP-mediated. Systemic injections of [(1S,3aS)-8-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one] (Ro 64–6198), a brain-penetrating agonist at the NOP receptor, produced a dose-dependent impairment of spatial memory in the mouse (Kuzmin et al., 2009). Assessment of the role of endogenous nociceptin supports mainly a negative role of this peptide in learning and memory (Noda et al., 2000). Knockout mice lacking the NOP receptor displayed facilitated learning and memory in the water maze task and enhanced LTP induction in the hippocampal CA1 region (Manabe et al., 1998). Also mice deficient of the nociceptin peptide showed some evidence of improved spatial learning, which became evident during retention trials and in the test of reversal training in the water maze task (Higgins et al., 2002; Kuzmin et al., 2009). However, in the study by Higgins and co-workers, synaptic plasticity was not changed in the mutant mice, evidenced by unchanged LTP induction in the CA1 region. In another study, targeted disruption of the nociceptin gene failed to result in facilitation of spatial learning and enhanced hippocampal LTP (Köster et al., 1999). These mice were characterised by heightened emotional reactivity and fear, which further support the role of nociceptin in the neurobiological regulation of stress coping and fear expression (Köster et al., 1999). However, the different behavioural phenotypes after targeted disruption of the NOP receptor and variable results after disruption of nociceptin gene could indicate involvement of a related neuropeptide or additional receptor subtypes (see Köster et al., 1999).

Nociceptin also plays an important role in emotional memory, as assessed in the passive avoidance task, since nociceptin knockout mice displayed enhanced retention latencies, probably indicative of aversive memory facilitation (Noda et al., 2000; Higgins et al., 2002; Kuzmin et al., 2009). In addition, NOP receptor knockout mice showed better memory in the passive avoidance task (Manabe et al., 1998). Moreover, nociceptin injected i.c.v. or intrahippocampally before training, mainly impaired passive avoidance retention in a wide dose range (Nabeshima et al., 1999; Noda et al., 2000; Kuzmin et al., 2009), but at a very low dose retention performance was improved (Kuzmin et al., 2009). Also systemic Ro 64–6198 produced a biphasic effect with memory facilitation at lower doses and memory impairment at higher doses (Kuzmin et al., 2009). Both the putative nociceptin antagonist [Nphel]Nociceptin (1–13)–NH2 and naloxone benzoyl hydrazone failed to influence retention in the passive avoidance task but attenuated or blocked the impairing effects of nociceptin on passive avoidance (Noda et al., 2000; Kuzmin et al., 2009).

Both animal and human studies have demonstrated a potential role for the nociceptin system in both ethanol reward (Kuzmin et al., 2007) and in alcoholism. For instance, in human alcoholics, pronociceptin mRNA expression is down-regulated in the hippocampus (Kuzmin et al., 2009). Moreover, in view of its importance for stress regulation, nociceptin appears to also be important in both depression and anxiety, as shown in a number of preclinical studies (Gavioli and Calo, 2006). It is concluded that the NOP system might represent a potential target for pharmacological interventions in cognitive functions. NOP antagonists may be beneficial in disorders characterized by memory impairments such as dementias and affective disorders, including depression and anxiety.

5.3. Galanin

Much attention has focused on galanin, a 29 amino acid, C-amidated peptide originally isolated from the porcine gut (Tatemoto et al., 1983). In humans it consists of 30 amino acids with a non-amidated C-terminal. Early work on galanin and cognition was initiated by the discovery that galanin coexists with acetylcholine in the septohippocampal projection in the rat (Melander et al., 1985), in addition to linking galanin to Alzheimer's disease, that is human pathology (see below).

Galanin coexists with choline acetyltransferase in basal forebrain cell bodies in several species. In the rat, galanin is expressed after colchicine treatment in 50–70% of cholinergic choline acetyltransferase-positive neurons in the medial septal nucleus and diagonal band of Broca area, which project to the hippocampus, i.e. the septohippocampal projection (Melander et al., 1985). However, there exist important species differences. In human, galanin is not co-localized in acetylcholine neurons of the nucleus basalis of Meynert (Kordower and Mufson, 1990), the main source of cortical acetylcholine innervation in humans. In the rat, the majority of hippocampal galanin-containing cholinergic neurons project to the ventral hippocampal region. It is important to note that a substantial number of galanin nerve terminals within the hippocampal formation are noradrenergic, derived from locus coeruleus somata (Melander et al., 1986b; Xu et al., 1998a). Galanin is also expressed after colchicine treatment in a population of 5-HT neurons in the dorsal raphe (Melander et al., 1986a; Xu et al., 1998b). Galanin binding sites have been detected in the ventral hippocampal formation, septum, ventral aspect of the amygdala complex and entorhinal and perirhinal areas with relatively low binding in the dorsal cortex and in the striatum (Skofitsch and Jacobowitz, 1985; Melander et al., 1988). In the hippocampal formation the binding sites are concentrated to the most ventral part with medium dense labelling in CA3, CA1 and CA2 regions, with a high density labelling in the subiculum.

Galanin mediates its physiological action via three G-protein coupled receptors (Branchek et al., 2000) with widespread but partially overlapping distribution in the brain (O'Donnell et al., 2003), and by partially different transduction mechanisms (Iismaa and Shine, 1999; Branchek et al., 2000). The galanin receptor 1 (GAL1) is coupled to G_i/G_o types of G-proteins and mediates inhibitory actions of galanin. Also the galanin receptor 3 (GAL3) is coupled to G_i/G_o-proteins and mediates a hyperpolarization response. The galanin receptor 2 (GAL2), on the other hand, mainly mediates stimulatory effects of galanin on neurotransmitter release, since it is coupled to the phospholipase C pathway, intracellular Ca^{2+} mobilization and Ca^{2+}-dependent Cl^- channel activation. Since galanin mediates its physiological function via three receptor subtypes, GAL1–GAL3, it will be critical to further analyze the contribution of receptor subtypes in animal learning and in memory impairments such as dementias (see below).

Studies in rodents suggest that central administration of galanin (mainly i.c.v.) plays an inhibitory role in hippocampal-dependent learning (Crawley, 2008). Thus, i.c.v. administration of galanin to rodents prior to training impaired performance in a wide range of tasks, including spatial learning and passive avoidance (Crawley, 1996, 2008). These studies indicate that galanin has a role in both short-term working memory (Robinson and Crawley, 1993) as well as long-term associative memory processes (Crawley, 1996). The effects of i.c.v. galanin on cognition have been related mainly to inhibitory effects of galanin on acetylcholine transmission at the terminal level within the ventral hippocampus (Crawley, 1996). Animal studies indicate that cholinergic cells of the septohippocampal projection, which terminate on all types of hippocampal cells, play a role in cognition, particularly spatial learning (Fibiger, 1991). However,

results with i.c.v. galanin must be interpreted with caution since i.c.v. administration of peptide decreased hippocampal noradrenaline and 5-HT release but not basal acetylcholine release in the ventral hippocampus (Ögren et al., 1996; Kehr et al., 2002; Yoshitake et al., 2003). The contribution of galanin has also been analysed by the use of putative galanin receptor antagonists. Thus, i.c.v. administration of the peptidergic galanin receptor antagonist galanin-(1–12)-Pro3-(Ala-Leu)2-Ala amide] (M40) failed to change performance in a working memory task, but blocked the impairing effect of i.c.v. galanin (McDonald and Crawley, 1996). In contrast, i.c.v. administration of [galanin(1–13)–bradykinin(2–9)amide] (M35), a non-selective peptidergic antagonist, enhanced spatial performance in the water maze task by a mechanism, which still is not clarified (Ögren et al., 1992).

Intrahippocampal administration of galanin has given evidence for the role of this peptide in hippocampal processing of cognition. Galanin, infused into the ventral hippocampus, impaired spatial learning and memory in the water maze task without influencing swimming ability (Ögren et al., 1996; Schött et al., 1998a,b) (Fig. 3A). The impairing effect on spatial learning correlated with the temporally kinetics of the infused peptide in the hippocampus (Schött et al., 1998a). Moreover, infusion of galanin via a chronic microdialysis cannula reduced in a dose-dependent manner basal acetylcholine in the ventral hippocampus at the doses, which impaired spatial learning (Ögren et al., 1996) (Fig. 3B). However, the mechanism behind the impairing effect of galanin on spatial learning has remained unclear. Infusion of galanin via microdialysis cannula failed to influence noradrenaline and 5-HT release in the ventral hippocampus (Kehr et al., 2002; Yoshitake et al., 2003). It is, therefore, possible that galanin by affecting cholinergic mechanisms both at the pre- and post-synaptic level, e.g. by blocking slow cholinergic excitatory post-synaptic potentials in CA1 pyramidal neurons, contributes to the learning deficits (Dutar et al., 1989). However, other mechanisms are also likely. Since galanin inhibits glutamate release in the hippocampus (Zini et al., 1993), it is possible that galanin also reduces excitatory hippocampal tone important for cognition. A recent study has shown that the impairment of memory caused by galanin is correlated with in vivo inhibition of both LTP and cAMP response element binding (CREB) phosphorylation (Kinney et al., 2009). Interestingly, this inhibitory effect on CREB phosphorylation is related to the expression of the galanin GAL1 receptor subtype, and related to the protection of neuron from excitotoxicity by endogenous galanin (Mazarati et al., 2000).

Since the galanin GAL1 and GAL2 receptors have a differential expression within the hippocampus, it is notable that microinjection of galanin in the subregion of the hippocampus results in the differential effects on spatial learning. Infusion of galanin into both the dorsal and ventral dentate gyrus, which mainly contains galanin GAL2 receptors and high degree of galanin–noradrenaline coexistence, significantly impaired spatial learning (Schött et al., 2000). This spatial learning deficit was blocked by pre-treatment with the nonselective galanin antagonist M35. In contrast, when galanin was infused into the dorsal CA1 region (Schött et al., 2000), which does not express galanin receptors, it did not influence spatial learning performance, unlike infusion into ventral CA3 region mainly containing galanin GAL1 receptors (Ögren et al., 1996). Interestingly, the effects of galanin on acetylcholine release differed also between the dorsal and ventral hippocampus, since perfusion through the dorsal hippocampus increased acetylcholine release in microdialysis studies, in contrast to a decrease in the ventral hippocampus (Ögren et al., 1998). The possible importance of the galanin receptor subtypes is also illustrated by studies on the medial septal cholinergic neurons, which provide cholinergic input to the hippocampus, i.e. the septo-hippocampal projection. Infusion of galanin into the medial septal area of the rat was associated with a slight improvement of spatial acquisition, accompanied by increase of acetylcholine release in the ventral hippocampus, as measured by microdialysis (Elvander et al., 2004) (Fig. 4). This finding suggests that galanin can activate the cholinergic neurons projecting to the hippocampus. In contrast, galanin reduces acetylcholine release at the nerve terminal level in the ventral hippocampus (Ögren et al., 1996) (Fig. 3B). This indicates that galanin may have both inhibitory and facilitatory effect on cognition mediated possibly by different receptor subtypes at the level of cholinergic cell bodies and the hippocampal cholinergic nerve terminals, respectively. This differential regulation of the cholinergic systems may be critical for development of compounds useful for treatment of e.g. Alzheimer's disease (see below).

The role of endogenous galanin and galanin receptor subtypes in learning and memory processes has been evaluated using mice with targeted mutations of galanin or galanin receptor genes. Mice overexpressing galanin under the dopamine beta-hydroxylase promoter, aged 8, 16 and 24 months, showed normal spatial acquisition but impaired spatial memory in the probe trial in the water maze task. Moreover, these mice were also impaired in the social transmission of

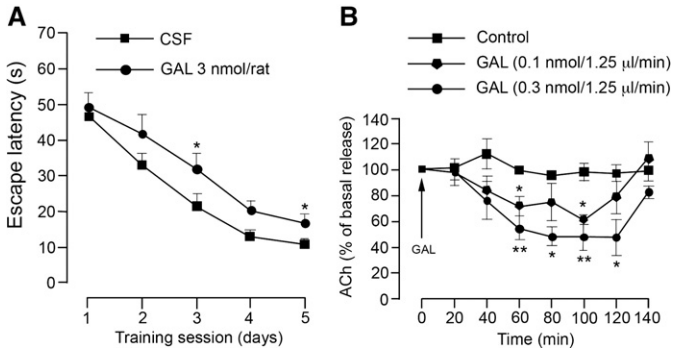

Fig. 3. The effects of intracerebral galanin on water maze learning (A) and on basal acetylcholine release in the ventral hippocampus of freely moving rats (B). A. Galanin was infused locally into the ventral hippocampus of the rat via cronical cannulae, 20 min before training on each training day. Training consisted of four trials per day for five consequtive days. Values represent the mean ± S.E.M. CSF, artificial cerebrospinal fluid; GAL, galanin. $^{*}P<0.05$ vs. CSF. B. Galanin was perfused via the microdialysis probe placed in the ventral hippocampus. Arrow indicates start of galanin infusion. Values represent the average acetylcholine concentration (mean ± S.E.M.) in 20-min samples. GAL, galanin. $^{*}P<0.05$ and $^{**}P<0.01$ vs. control. For further details, see Ögren et al. (1996). Published with permission from Elsevier Science Ltd.

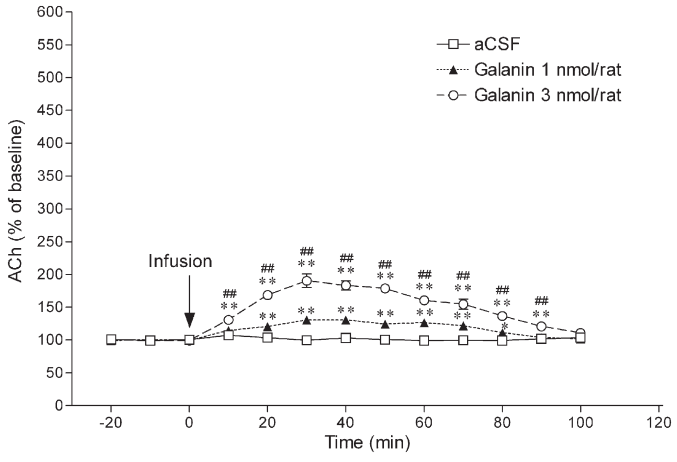

Fig. 4. Effects of intraseptal injections of galanin or artificial cerebrospinal fluid (aCSF) on acetylcholine release in the ventral hippocampus of freely moving rats. Galanin was injected via a cronic cannual placed in the medial septal area, and extracellular acetylcholine concentrations were measured via a microdialysis probe located at the terminal level of the cholinergic neurons in the ventral hippocampus. Values represent the average acetylcholine concentration (mean ± S.E.M.) in 10-min samples. $^{*}P<0.05$ and $^{**}P<0.01$ vs. control. For further details, see Elvander et al. (2004). Published with permission from Elsevier Science Ltd.

food preference in an olfactory memory test (Steiner et al., 2001; Wrenn et al., 2004). The mechanisms behind this selective memory deficit have, however, remained unclear. Interestingly, these transgenic mice displayed considerably higher levels of ectopic galanin overexpression in the hippocampal formation and cerebral cortex, but no significant correlation could be established between the overexpression of galanin levels and the performance in the cognitive tasks (Wrenn et al., 2002). However, overexpression of galanin was associated with a reduction in the number of neurons producing acetylcholine in the horizontal limb of the diagonal band of Broca (Steiner et al., 2001). The consequences of this reduction for hippocampal cognition were not established, since no measures of hippocampal acetylcholine transmission were reported. This line of mice were also impaired in trace-cued fear conditioning (Kinney et al., 2002), suggesting that galanin also has a role in emotional memory processes, consistent with a number of studies showing a role of galanin in anxiety and the affective domains of behaviour (Holmes et al., 2002; Morilak et al., 2003).

Another line of mice, overexpressing galanin under the platelet-deriver growth factor B promoter (Kuteeva et al., 2004) has more widespread overexpression of brain galanin than mice under the dopamine beta-hydroxylase promoter. They did not differ from the wild-type controls in spatial learning in the water maze at the age of 5 months (Kuteeva et al., 2005). However, there is evidence that the behavioural effects of galanin overexpression may be age-dependent. When tested at 19 months of age, this strain displayed spatial learning and memory impairments in the water maze without any deficiency in swimming behaviour (Pirondi et al., 2007). However, the results of genetic manipulations of galanin are not consistent. Intriguingly, also galanin knockout mice were reported to be deficient in the Morris water maze task (O'Meara et al., 2000).

Analysis of the contribution of galanin receptor subtypes (GAL1–GAL3) indicates differences in the functional role of the particular subtypes. Several lines of galanin receptor knockout mice have been generated. Galanin GAL1 receptor knockout mice were unimpaired in performance of either Morris water mice task or social transmission of food preference (Wrenn et al., 2004). Also, these mutant mice did not differ from wild-type controls in various emotional memory tasks, including cued or contextual fear conditioning. However, galanin GAL1 receptor knockout mice were impaired in a trace-cued fear conditioning (Wrenn et al., 2004; Rustay et al., 2005), suggesting a role for the galanin GAL1 receptor in some aspects of aversive memory. In contrast, galanin GAL2 receptor knockout mice did not differ from wild-type controls in trace-cued and contextual fear conditioning tasks (Gottsch et al., 2005; Bailey et al., 2007) or Morris water maze performance (Bailey et al., 2007).

Clinical findings in post mortem brains suggest that galanin may be involved in Alzheimer's disease (Counts et al., 2008). Accumulating data indicate that impairment of cholinergic transmission within the hippocampus and cortex are major features of senile dementia of Alzheimer's type. Based on such data, it has been proposed that galanin may inhibit acetylcholine transmission within the nucleus basalis and in the septal nuclei and thereby further accentuate acetylcholine transmission in Alzheimer's disease (Chan-Palay, 1988; Mufson et al., 1993). The number of galanin binding sites has shown to be increased in the hippocampus and subiculum in patients with Alzheimer's disease (Rodriguez-Puertas et al., 1997; McMillan et al., 2004). In post mortem human brains, galanin hyperinnervates the surviving neurons of the basal forebrain, e.g. nucleus basalis, and of the cholinergic ventral lines of the diagonal band (C2) in Alzheimer's disease (Chan-Palay, 1988; Mufson et al., 1993). Studies on brains from Alzheimer's disease patients indicate that increased levels of galanin in nerve terminals may preserve the function of nucleus basalis neurons (Counts et al., 2008). This observation has lead to a re-interpretation of the action of galanin at the level of the cholinergic cell bodies. Instead of exerting an inhibitory action on cholinergic neurons, galanin may instead stimulate these neurons, which may in turn attenuate the development of Alzheimer's disease symptoms (Counts et al., 2008). This suggests that, at the cell body level of the human brain, galanin probably mediates its action via the galanin GAL2 receptor, which has been recently shown to have neurotrophic effects on brain neurons (Elliott-Hunt et al., 2004; Elliott-Hunt et al., 2007). This interpretation is consistent with studies in rats, showing that galanin, when infused into the medial septal area, stimulates cholinergic transmission (Elvander et al., 2004).

Since galanin plays a major role in fear and anxiety-related behaviour, as well as in the neurobiology of stress regulation in rodents, it is possible that galanin affects cognitive functions by modulating these processes. Importantly, overexpression of galanin in mice under the platelet-deriver growth factor B promoter enhances both unconditioned and conditioned stress responses (Yoshitake et al., 2004). There is also evidence that galanin is involved in the regulation of coping with stressful events (see Ögren et al., 2006; Kuteeva et al., 2008 and references therein), since mice overexpressing galanin under the platelet-deriver growth factor B promoter display increased immobility in the forced swim test (Kuteeva et al., 2005), a rodent test for depression-like behaviour. Also in the rat, intracerebral administration of galanin into the ventral tegmental area (Weiss et al., 1998, 2005) or in the lateral ventricle (Kuteeva et al., 2007, 2008) resulted in a pro-depressive effect in the forced swim test. Furthermore, galanin antagonists administered alone decreased immobility time, suggesting antidepressant-like effect (Weiss et al., 1998, 2005; Kuteeva et al., 2007, 2008). Thus, activation of endogenous galanin is an adaptive response, which results into a failure of coping with stressful event. Importantly, there is a differential involvement of galanin receptor subtypes in regulation of depression-like behaviour. Thus, stimulation of the galanin GAL1 and/or GAL3 receptors results in pro-depressive effect (Swanson et al., 2005; Barr et al., 2006; Kuteeva et al., 2008), while activation of the galanin GAL2 receptor subtype results in antidepressant-like effect (Lu et al., 2005a, 2008; Kuteeva et al., 2008). These data suggest that galanin receptor subtypes may represent a novel target for development of antidepressant drugs.

6. Conclusion

The role of neuropeptides and their multiple receptors systems is still a more or less unexplored area in cognition and in cognitive disturbances related to different pathologies (Hökfelt et al., 2003; Ögren et al., 2006). Detailing the role of the neuropeptides in brain plasticity during normal and pathological conditions is a prerequisite for further progress. A major problem is the limited knowledge of the molecular and neurochemical changes underlying the particular human disorder. It will be critical to develop better animal models, which takes into account the species differences in neuropeptide expression and receptors and integrates information on peptide-biology in pathological states. Such knowledge may enable the development of cognitive-improving drugs with a fundamentally novel mechanism of action.

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