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Peptidergic Modulation of Learning and Memory Processes

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I. Introduction

The ability to remember is a prerequisite for effective functioning in daily life. One of the major goals of the study of neuroscience is to understand the neuronal mechanisms of learning and memory. This will be of utmost importance for the development of drugs for learning and memory disorders, for which there is no adequate therapy.

Historically, much of the literature dealing with neuronal correlates of learning and memory has focused on a single or a small set of brain structures (for review, see Kendal et al., 1991). Now it seems clear that memory traces for many different types of learning are not restricted to any one brain structure (for review, see Thompson et al., 1984). Therefore, studies aimed at localizing certain parts of the brain important to learning and memory processes have been pursued by a variety of methods with limited success.

Results of recent studies support the hypothesis that separate regions of the brain simultaneously carry out computations on stimuli from the external and internal environment (Squire, 1986; Squire and Zola-Morgan, 1991) and that even "localized" memory traces may include multiple brain sites, and within a site the trace or traces can still be distributed among neuronal elements or ensembles (Thompson, 1986).

Lesion studies (Lashley, 1950; Olds et al., 1972) suggested that, if "engrams" resided in the cortex, they were not localized in particular parts of it; nevertheless, recent studies indicate that particular parts of the subcortical system (e.g., the posterior thalamus; Thompson, 1986) might well participate in some way in engram formation and might even contain engrams. Brain stimulation studies (for review, see Olds et al., 1972) revealed the significance of arousal and motivation for memory processes, but they did not reveal engram localization. Olds et al. (1972) studied learning centers of the rat brain mapped by measuring latencies of conditioned responses and found that "learning points" were widely distributed and present in the pons, midbrain, diencephalon, paleocortex, and cortex. However, boundaries of the distribution followed clear anatomical lines. Along the ventral part of the brain stem, they were present in the pontine reticular formation, ventral tegmentum, and the adjacent zona incerta. From the posterior thalamic nucleus there was a continuation in two directions: (*a*) in the adjacent medial geniculate body, (*b*) through the parafascicular and lateral thalamic nuclei. In the telencephalon, these neurons appeared in the CA3 field of the hippocampus, and they were present in the anterior, middle, and posterior parts of the neocortex.

The (temporary) consolidation of information is me-

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diated by limbic structures (e.g., hippocampus); the hippocampal formation plays a key role in memory processing. The view that has emerged from neuroanatomical studies of hippocampal anatomy (Lopes Da Silva et al., 1990) holds that input would arrive via the fimbria-fornix or perforant pathway and activate the pyramidal neurons directly, or indirectly, via the dentate gyrus and intrinsic pathways. Equally important extensions of the intrinsic circuitry are the CA1 projections to the adjacent subicular cortices (Andersen et al., 1973) which are responsible for a large amount of hippocampal output, at least in nonhuman primates. McGeer et al. (1978) proposed two hippocampal pathways as being responsible for the interconnections within the limbic system (fig. 1). The classical circuit of Papez (hippocampus, fornix, mamillary bodies of the hypothalamus, cingulate gyrus, parahippocampal gyrus, hippocampus) plays an important role as a neuronal substrate of emotional aspects of behavior. A second pathway leading from the cortical association areas, via the cingulate gyrus and the entorhinal cortex, to the hippocampus, and hence through the septal nucleus via the dorsomedial thalamic nucleus to the prefrontal cortex, enables the information to be stored, presumably allowing it to reverberate for some time. However, the memory trace is not established in its final form during learning but needs processing for a time after the learning trial. All available evidence indicates that long-term or "permanent" memory traces themselves are not stored in the hippocampus but in the parietal and associative cortex (McGeer et al., 1978).

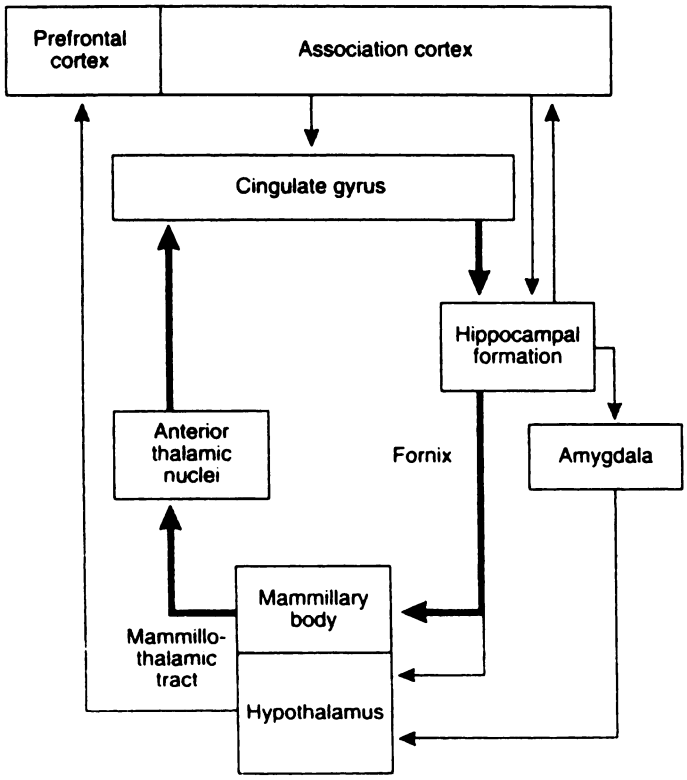

FIG. 1. Two major pathways have been proposed in the limbic system and cortical structures as being responsible for the neuronal interconnections of information processing. The classical circuit of Papez [hippocampus, fornix, mamillary bodies of the hypothalamus, cingulate gyrus, parahippocampal gyrus, hippocampus (thick line)] plays an important role as a neuronal substrate of emotional aspects of behavior. A second pathway (thin line) leading from the cortical association areas, via the cingulate gyrus to the hippocampus, through the septal nucleus via the forsomedial thalamic nucleus, to the prefrontal cortex enables the information to be stored, presumably allowing it to reverberate for some time. It is rational to regard memory encoding as a result of the formation of specific spatiotemporal patterns of activation of neuronal networks and to assume that neuropeptides (peptidergic neurons) may either be part of these networks or modulate the activity of these networks.

There are other brain structures that play an equally important role in learning and memory processes. A considerable body of experimental evidence now indicates that the amygdaloid complex also participates in the mediation of somatomotor and autonomic responses in fear-motivated learning tasks (Blanchard and Blanchard, 1972; Kapp et al., 1984). Results of neurobehavioral studies have implicated connections linking the neocortical sensory areas with the amygdala in emotional processing (LeDoux, 1986). Limbic areas are richly interconnected with sensory-processing areas of the thalamus and the cortex. The sensory-connected limbic nuclei, therefore, have a pivotal position, forming a sensory-emotional interface, allowing environmental events to gain control over the multitude of autonomic, endocrine, and behavioral response systems organized in the limbic forebrain.

Although it is widely assumed that the cerebral cortex is a principal site for long-term storage of memory, the evidence from studies with infrahuman animals is surprisingly sparse. It has been assumed that organizational strategies for information storage are under the control of the prefrontal cortex. Permanent storage, on the other hand, presumably takes place in the association regions of the parietal and temporal lobes of the neocortex (McGeer et al., 1978).

Brain areas involved in learning and memory processes can be divided into two types. In nonspecific areas a very large proportion of neurons respond to the input stimuli and show a similar nature of responses to various stimuli (generalization of neuronal response). The posterior thalamic nuclei are prototypes of such areas (Olds et al., 1972). A possible interpretation is that such brain areas contain energizing or motivating elements that become indiscriminately attached to all interesting or meaningful stimuli in a nonspecific nature. An alternative explanation might be that various stimuli "represented" in these neurons might be specific at a given time, but the neurons would change their receptive fields on short notice as the animal's attention moves from one focus to the other.

In specific brain areas a small proportion of neurons respond to familiar stimuli, and these neurons do not yield similar responses to novel stimuli (Thompson, 1986). There is also no generalization to other stimuli.

Cortical areas and the hippocampus are brain regions of this type.

Theoretically, a very important distinction has been made between intrinsic and extrinsic neuronal systems involved in learning and memory processes (Krasne, 1978; Squire and Davies, 1981). The intrinsic system refers to neuroanatomical structures in which physicochemical representations of information are built up (memory traces). The extrinsic system refers to pathways that influence the development of memory traces through the release of neurotransmitters, neuropeptides, and other neuromessengers (these extrinsic pathways modulate memory storage). The intrinsic system receives continuous input from "milieu interieur and exterieur" through the extrinsic system.

At this point, it would be important to discuss which events take place in the intrinsic system and how this multitude of structures and interconnections could constitute a single brain system critical for memory formation. A model that has been proposed (Mishkin, 1982) views the storage of the neuronal representation of sensory stimuli as a fundamental ingredient of memory. The storage of the engram is conceived of taking place within the higher-order sensory-processing areas of the cortex whenever stimulus activation of these areas triggers a cortico-limbic-thalamic-cortical circuit. Once triggered, this circuit is presumed to serve as a reverberating network. The cortical network of high-order sensory neurons may be viewed as the stored representation of the stimulus (engram), produced through plastic changes in connectivity (long-term changes in synaptic activity), which, whenever reactivated through the original sensory pathway, would result in retrieval. Through interconnections of a particular stored representation with previously or simultaneously stored representations of other stimuli and events, retrieval could be evoked through the process of associative recall. Numerous neuroanatomical and neurological facts satisfy this idea. In the monkey brain, for example, each sensory modality appears to be served by a hierarchically organized set of cortical areas that are directed from the primary projection area toward the anterior parts of the cerebral cortex (Turner et al., 1980). These areas are reciprocally interconnected directly with the amygdala and, via the entorhinal cortex, with the hippocampus. The amygdala and the hippocampus are connected in turn, also often reciprocally, with various thalamic nuclei. Via these networks, the amygdala and the hippocampus both participate in the cortical storage of the stimulus presentation. The amygdala itself contributes to this process by adding affective value to the stimulus.

Learning is defined here as the acquisition of information and skills. In rodents, aversive learning paradigms are most frequently used to study learning and memory processes. Once an animal has learned to escape from aversive events, the next beneficial strategy is to try to avoid those aversive events totally. The aversive event is made predictable (conditioned stimulus) in order that the animal can actively respond (active avoidance paradigms: e.g., jumping on a pole or platform; shuttling to the "safe" part of the apparatus) or suppress/postpone innate behavior (passive avoidance paradigms: e.g., in spite of innate dark preference, not entering the dark compartment of the apparatus). With great (over)-simplification, memory processes involve consolidation and retrieval of information. Immediately after a single, short learning trial, behavior is under the influence of the newly acquired information. A few minutes later, the behavior is less accurately controlled by the new memory, but within the next 15 to 30 minutes (depending on the species) memory consolidation takes place, which results in a higher level of control over behavior. Consolidation is the critical time period for the extrinsic system to act on the storage of information. Retrieval of memory, on the other hand, amounts to reinstatement of a prior pattern of activation, using part of the pattern as a cue. This can be measured when an endogenous (extrinsic) pathway is activated or an exogenous compound is given shortly before the retention test. However, memory retrieval is not only related to the strength of the memory trace. Memory retrieval, and the resulting behavior even more, also depends on various input conditions coming from the milieu exterieur or interieur at the time of retention (i.e., memory retrieval and the resulting behavior might be intimately related to perception, attention, motivation, stimulus selection, environmental cues, activity, or peripheral autonomic processes such as the blood pressure, etc.). Valid measurement of memory retention, therefore, requires careful control of the experimental conditions.

Although it is not exactly known which processes take place in intrinsic neuronal systems during learning and memory formation, it is generally accepted that the storage of newly acquired information causes physicochemical changes in neurons and/or neuronal circuits, mainly in the synapses which participate in the processing of information. Learning, then, amounts to making changes in the strength of synaptic interconnections. The difficulty in studying biochemical mechanisms of memory processes is that memory formation requires the coordinated activities of various innate physiological and psychological events that themselves are difficult to disentangle from memory (e.g., perception, homeostasis, activity). If the candidate chemical mechanisms of memory also participate in these "second-order" events, the conclusions might be misleading.

Early biochemical events of memory consolidation are hypothesized to occur as a result of neuronal hyperpolarization which, under normal circumstances, results from increased K^+ conductance across neuronal membranes following neuronal stimulation (Gibbs and Ng, 1977).

Glutamate is an excitatory transmitter in various ex-

trinsic and intrinsic pathways involved in learning and memory processes (Roberts et al., 1980; Di Chiara and Gessa, 1981). Glutamate is transported into nerve terminals and can be released in a Ca^{2+}-dependent manner to exert potent depolarizing effects on postsynaptic neurons (for review, see Baudry and Lynch, 1984). Various subtypes of glutamate-binding sites are associated with postsynaptic neuronal structures, e.g., in the hippocampus. It has been suggested (Baudry and Lynch, 1984) that activation of glutamate receptors (especially that of the NMDA‡ subtype) has a number of features that make it an attractive candidate for a memory-producing process. Accordingly, Ca^{2+} influx resulting from NMDA-receptor activation is thought to trigger cellular responses involved in certain types of memory. Indeed, a number of investigations have shown that the NMDA-receptor complex may play an important role in learning and memory processes (Morris et al., 1986; McCabe et al., 1988). The major inhibitory transmitters (GABA, glycine) in the brain may fine tune these processes.

Long-term potentiation (increased localized synaptic excitability that can persist for days or weeks) has become popular as a putative mechanism to explain memory formation in the brain. It was first found in the perforant path to granule cells in the dentate gyrus and for some time was thought to be unique to the hippocampus, but it has now been reported in other brain regions as well (for reviews, see Thompson et al. 1984; Rose, 1993). There is a general agreement that during long-term potentiation there is enhanced release of glutamate from presynaptic terminals and that this glutamate interacts with upregulated NMDA-receptors (Bliss, 1990). Some investigators (Bliss, 1990) suggest that the next step is the release of some retrograde messengers (e.g., components of the phosphoinositide cascade, nitric oxide, or free radicals), followed by changes in the presynaptic membrane. In particular, there is a specific presynaptic membrane phosphoprotein [a 47-kDa phosphoprotein in the literature referred to as protein B-50, GAP43, or protein F1 (Gispen and Routtenberg, 1982)] present in the brain. The phosphorylation of this protein is supposed to affect Ca^{2+} flow into the nerve cell and, hence, activates intracellular second messengers. Evidence suggests that "new: synapses may be formed in the hippocampus in as short a time as 10 minutes after induction of long-term potentiation (for review, see Thompson, 1986).

The extrinsic system uses multiple chemical entities, i.e., neuromessengers, to modulate the intrinsic system. An increasing body of experimental evidence indicates that classical neurotransmitter pathways in the brain (cholinergic, noradrenergic, dopaminergic) might be involved in learning and memory processes. The cholinergic neurons lie in the basal forebrain and project to the neocortex, amygdala, and hippocampus. Animals with lesions in the cholinergic basal forebrain structures show impaired recognition (Aigner et al., 1984). Implanting fetal basal forebrain neurons in aged rats reduced learning impairments but only when these neurons were rich in acetylcholine (Gage et al., 1984). In human patients, loss of neurons that contain acetylcholine may correlate with measures of memory and dementia (Iversen and Rosser, 1984). Noradrenergic neurons lie in the locus coeruleus and project widely to neocortical and limbic structures. Evidence has been found that noradrenergic systems are involved in human memory, because amnesics had noradrenergic dysfunctions (Victor et al., 1971). Animal studies have shown that the coeruleo-cortical noradrenergic projection and the mesotelencephalic dopamine pathway may be of importance for memory and learning and for several other behavioral functions such as attention and arousal (Kovács et al., 1979a,b,; Robbins and Everitt, 1982).

Much of the recently stored information is lost rather rapidly, but in some cases the chemical stages in memory formation lead eventually to structural changes that underlie long-term memory storage. It is widely accepted in the literature (for review, see Rosenzweig and Bennett, 1984) that de novo synthesis of macromolecules (proteins) in the brain is required for long-term memory storage.

In the last 25 years the potential contribution of neuroactive peptides in central nervous system functions (for review, see Hökfelt, 1991), and in particular in learning and memory processes (for review, see De Wied et al., 1993), has aroused a great deal of interest. Neuropeptides, with a practically limitless number of combinations of amino acid sequences (table 1), offer an extremely wide range of specific interactions with special locations on cell bodies and with fiber systems and receptor molecules in the brain. This review brings together findings concerning the role of neuropeptides in memory and learning processes, the brain structures involved in memory and learning processes, and biochemical mechanisms that mediate neuropeptide effects and their potential therapeutic effects on memory disorders.

II. Effect of Neuronal Peptides on Learning and Memory

A. Posterior Pituitary Peptides (Vasopressin, Oxytocin)

Vasopressin exerts a long-term facilitatory effect on learning and memory processes in aversion-conditioning studies (for review, De Wied et al., 1993). The influence of vasopressin is time dependent, i.e., the effectiveness

‡ Abbreviations: NMDA, N-methyl-D-aspartic acid; GABA, γ-aminobutyric acid; i.c.v., intracerebroventricular; ACTH, adrenocorticotrophic hormone; CRF, corticotropin-releasing factor; LHRH, luteinizing hormone-releasing hormone; TRH, thyrotropin-releasing hormone; VIP, vasoactive intestinal peptide; GRP, gastrin-releasing peptide; NPY, neuropeptide Y; CCK, cholecystokinin; ANP, Atrial natriuretic peptide; AVP, [arg^8]-vasopressin; MSH, melanocyte-stimulating hormone.

TABLE 1

Amino acid sequences of neuropeptides modulating learning and memory processes

Drug	Amino acid sequence
Vasopressin	Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-GlyNH_2
Oxytocin	Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-GlyNH_2
ACTH	Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Asn-Gly-Ala-Glu-Asp-Glu-Ser-Ala-Glu-ala-Phe-Pro-Leu-Glu-Phe
α-MSH	Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-ValNH_2
β-Endorphin	Tyr-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu
Prolactin	Leu-Pro-Val-Cys-Ser-Gly-Gly-Asp-Cys-Gln-Thr-Phe-Leu-Pro-Glu-Leu-Phe-Asp-Arg-Val-Val-Met-Leu-Ser-His-Tyr-Ile-His-Thr-Leu-Tyr-Thr-Asp-Met-Phe-Ile-Glu-Phe-Asp-Lys-Gln-Tyr-Val-Gln-Asp-Arg-Glu-Phe-Ile-Ala-Lys-Ala-Ile-Asn-Asp-Cys-Thr-Pro-Ser-Ser-Leu-Ala-Thr-Pro-Glu-Asp-Lys-Glu-Gln-Ala-Gln-Lys-Val-Pro-Pro-Glu-Val-Leu-Leu-Asn-Leu-Ile-Leu-Ser-Leu-Val-His-Ser-Trp-Asn-Asp-Pro-Leu-Phe-Gln-Leu-Ile-Thr-Gly-Leu-Gly-Gly-Ile-His-Glu-Ala-Pro-Asp-Ala-Ile-Ile-Ser-Arg-Ala-Lys-Glu-Ile-Glu-Glu-Gln-Asn-Lys-Arg-Leu-Leu-Glu-Gly-Ile-Glu-Lys-Ile-Ile-Ser-Gly-Ala-Tyr-Pro-Glu-Ala-Lys-Gly-Asn-Glu-Ile-Tyr-Leu-Val-Thr-Ser-Gln-Leu-Pro-Ser-Leu-Gln-Gly-Val-Asp-Glu-Glu-Ser-Lys-Asp-Leu-Ala-Phe-Tyr-Asn-Asn-Ile-Arg-Cys-Leu-Arg-Arg-Asp-Ser-His-Lys-Val-Asp-Asn-Tyr-Leu-Lys-Phe-Leu-Arg-Cys-Gln-Ile-Val-His-Lys-Asn-Asn-Cys
CRF	Ser-Glu-Glu-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Val-Glu-Met-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Ala-His-Ser-Asn-Arg-Lys-Leu-Met-Glu-Ile-IleNH_2
LHRH	Pglu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-GlyNH_2
Somatostatin	Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-CysNH_2
TRH	Pglu-His-ProNH_2
CCK-8	Asp-Tyr(SO_3H)-Met-Gly-Trp-Met-Asp-PheNH_2
Neurotensin	Pglu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu
NPY	Tyr-Pro-Ser-Lys-Pro-Asp-Asn-Pro-Gly-Glu-Asp-Ala-Pro-Ala-Glu-Asp-Leu-Ala-Arg-Tyr-Tyr-Ser-Ala-Leu-Arg-His-Tyr-Ile-Asn-Leu-Ile-Thr-Arg-Gln-Arg-TyrNH_2
Bombesin	Pglu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-MetNH_2
VIP	His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-AsnNH_2
Galanin	Gly-Trp-Thr-Leu-Asn-Ser-Ala-Gly-Tyr-Leu-Leu-Gly-Pro-His-Ala-Ile-Asp-Asn-His-Arg-Ser-Phe-Ser-Asp-Lys-His-Gly-Leu-Thr-NH_2
Substance P	Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-MetNH_2
Neuropeptide K	Asp-Ala-Asp-Ser-Ser-Ile-Glu-Lys-Gln-Val-Val-Leu-Leu-Lys-Ala-Leu-Tyr-Gly-His-Gly-Gln-Ile-Ser-His-Lys-Arg-His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-MetNH_2
α-ANP	Ser-Leu Arg-Arg-Ser-Ser-Cys-Phe-Gly-Gly-Arg-Ile-Asp-Arg-Ile-Gly-Ala-Gln-Ser-Gly-Leu-Gly-Cys-Asn-Ser-Phe-Arg-Tyr
Angiotensin II	Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

of neuropeptide treatment depends on the interval between the learning or retention trial and the treatment. Effects of drugs on consolidation and retrieval can be studied in a simple one-trial passive avoidance test. Use is made of the innate preference of rodents for a dark environment in a two-compartment apparatus. In general, after habituation to the apparatus, rats are exposed to mild electric shocks in the preferred compartment of the apparatus and tested for retention 24, 48, or more hours later. If a compound affects behavior when administered after the learning trial (electric foot shock), it is considered to influence the consolidation process; if administered prior to the retention trial, it is considered to influence the retrieval process.

Vasopressin and related peptides facilitate consolidation and retrieval processes (De Wied, 1976; Bohus et al., 1978a,b), i.e., rats treated with these peptides (immediately after the learning trial or shortly before the retention test, respectively) spend a significantly longer period than nontreated control animals in the nonpreferred light compartment. This neuropeptide has also been shown to prevent and reverse retrograde amnesia induced by various amnestic treatments, which is another measure for effects on retrieval processes (Rigter et al., 1974; Bohus et al., 1982).

The effect of vasopressin on learning and memory processes in nonaversive (food rewarded, sexually motivated, etc.) tasks is more controversial (Le Moal et al., 1984; Engelmann et al., 1992, Dantzer and Bluthé, 1993). Social recognition, a relevant memory model in rodents, is also facilitated by vasopressin (Dantzer and Bluthé, 1992; Popik et al., 1991). Learning and memory processes have been found to be disturbed in animals that are deficient in vasopressin [e.g., in the homozygous variant of the Brattleboro strain of rats (HODI); for review, see De Wied et al., 1993], and these disturbances can be normalized by vasopressin and related behaviorally active (nonendocrine) fragments. However, in several studies in HODI rats, learning and memory were not different from that of controls, although clear behavioral abnormalities were observed (for review, see De Wied et al., 1993).

In contrast to vasopressin, oxytocin facilitates extinction of a conditioned avoidance behavior (for reviews, see Kovács and Telegdy, 1987; De Wied et al., 1993). The performance in a one-trial passive avoidance paradigm is also time dependent following systemic (Kovács et al., 1978) as well as central (Bohus et al., 1978 a,b) oxytocin injections. Social recognition in rats is also affected in an opposite way by oxytocin, whereas an oxytocin antagonist facilitates social recognition (Popik and Vetulani, 1991). Extremely low doses of oxytocin, microinjected into the preoptic area, appeared to facilitate social recognition (Popik et al., 1991). In general, however, it can be stated that vasopressin and oxytocin exert opposite effects on fear-motivated avoidance behavior, and hence, the hypothesis has been proposed that oxytocin is an amnestic neuropeptide (Bohus et al., 1978b; De Wied, 1987; Kovács, 1986).

Evidence for the role of endogenous vasopressin and oxytocin stems from results of studies with central (i.c.v.) injections of specific antisera against neurohypophyseal neuropeptides. Administration i.c.v. of antivasopressin serum induced severe disturbances in the extinction of active avoidance behavior (Bohus et al., 1978a; van Wimersma Greidanus et al., 1975a) and a disruption of passive avoidance behavior (Bohus et al. 1978a,b; Van Wimersma Greidanus et al., 1975b). Administration i.c.v. of antioxytocin serum, on the other hand, resulted in an improved performance in passive avoidance behavior (Van Wimersma Greidanus and Baars, 1988). Results of time gradient studies with antivasopressin serum or antioxytocin serum also point to a modulatory role of endogenous vasopressin and oxytocin on consolidation as well as retrieval processes (Van Wimersma Greidanus et al., 1975b). Manipulations (peptide treatments, induction of amnesia, etc.) immediately after learning are supposed to measure effects on consolidation, whereas manipulations prior to a retention test are supposed to measure effects on retrieval.

If neurohypophyseal neuropeptides affect cognitive processes directly or modulate them indirectly, it is essential that these neuropeptides (or some of their active fragments) act at brain structures responsible for memory formation and/or retrieval or at brain sites responsible for information processing.

Several attempts have been made to determine the sites of action of vasopressin and oxytocin in relation to various forms, stages, or periods of learning and memory processes. Application of vasopressin in the posterior thalamic area (including parafascicular nuclei; Van Wimersma Greidanus et al., 1973, 1975a) or into the hippocampal formation (Stark et al., 1978) resulted in preservation of pole-jumping avoidance behavior. In addition, microinjections of small amounts of vasopressin in the dentate gyrus, in the dorsal septal nuclei, or in the dorsal raphe nuclei improved passive avoidance behavior (increased avoidance latencies), when administered after the learning trial (Kovács et al., 1979b). Microinjection of vasopressin into various limbic areas also improved passive avoidance behavior of rats that had been made amnestic by pentylenetetrazol (Bohus et al., 1982). Of various brain structures tested, the ventral hippocampus appeared to be the most sensitive area for vasopressin to improve passive avoidance behavior (Kovács et al., 1986). Taking the ratio of lowest effective amounts of the peptide as an index of activity, vasopressin is about 100,000 times more active after central nervous system microinjections than following peripheral treatment (Kovács et al., 1986). It is of interest to note that the ventral hippocampus contains terminals of extrahypothalamic vasopressinergic pathways (Buijs, 1983) and also putative receptors for vasopressin and oxytocin (Barberis, 1983; Biegon et al., 1984; Elands et al., 1992).

Studies of the role of vasopressin and behaviorally active metabolites of vasopressin in restricted brain regions for processes related to learning and memory functions revealed that endogenous vasopressin in the dorsal raphe nucleus (Kovács et al., 1980) and in the dorsal hippocampus (Kovács et al., 1982) plays a physiological role in the consolidation of information. Following local microinjections, the ventral hippocampus appeared to be the most sensitive brain structure for vasopressin (Kovács et al., 1986). In this limbic region, 8 pg of vasopressin facilitated passive avoidance behavior when given postlearning or preretention. [Cyt^6]AVP$_{5-9}$ and [Cyt^6]AVP$_{5-8}$ were more effective than the parent nonapeptide, in that a lower amount of these peptide fragments facilitated passive avoidance behavior in all brain regions investigated. Following microinjections into the ventral hippocampus, [Cyt^6]AVP$_{5-8}$ was more effective in a postlearning than in a preretention treatment schedule. [Cyt^6]]AVP$_{5-9}$, on the other hand, was more effective when injected shortly before the retention trial. It was suggested, therefore, that active fragments of vasopressin selectively influence different phases of information processing (De Wied et al., 1987; Kovács et al., 1986). This is in agreement with the findings with systemic administration of behaviorally active peptide fragments; [Cyt^6]AVP$_{5-8}$ was more effective on consolidation, whereas [Cyt^6]AVP$_{5-9}$ more effectively facilitated retrieval processes (De Wied et al., 1987).

As far as the role of the endogenous nonapeptide is concerned, endogenous vasopressin in the dorsal septum or in the ventral hippocampus mainly plays a role in retrieval processes. Other findings are in support of this view. In a recent experiment with mice (Metzger et al., 1993), it was determined whether the injection of vasopressin or vasopressin antisera into the ventral hippocampus has an effect on retrieval and relearning of a visual discrimination task. Pretest microinjection of vasopressin into the ventral hippocampus alleviated forgetting observed after a prolonged interval of 24 days between the acquisition of information and its retrieval.

This enhancing effect was characterized by better retrieval and relearning in vasopressin-treated mice than those in control mice. Conversely, immunoneutralization of endogenous vasopressin in the ventral hippocampus by microinjection of vasopressin antisera resulted in a drastic impairment of retrieval and relearning.

Van Wimersma Greidanus and Baars (1993) studied the role of the lateral habenular region and found that local microinjection of antivasopressin serum selectively attenuated retrieval, but not consolidation, processes.

Similarly to vasopressin, oxytocin has also been found to exert locus-specific effects on learning and memory (Kovács et al., 1979a). Oxytocin attenuates memory consolidation when microinjected into the hippocampal dentate gyrus or the midbrain dorsal raphe nucleus. The central amygdaloid nuclei did not respond to oxytocin, although this region receives a relatively dense oxytocinergic innervation. It is possible, however, that endogenous oxytocin in the amygdala is involved in retrieval rather than consolidation processes. Bilateral injections of oxytocin in the dorsal hippocampus, in rats, impaired acquisition and accelerated extinction of conditioned avoidance behavior in a shuttle box (Zhou and Zhang 1992). The data suggested that the attenuating effect of oxytocin on acquisition of shuttle box avoidance behavior was, at least partly, mediated by the hippocampus.

Results of studies with antioxytocin serum microinjected locally suggest that endogenous oxytocin in the dorsolateral septal area and in the ventral hippocampus might be important for consolidation as well as retrieval processes (Van Wimersma Greidanus and Baars, 1988). Neutralization of endogenous oxytocin in the dorsal hippocampal/dentate gyrus area, in the lateral habenular region, or in the dorsal raphe nucleus did not affect passive avoidance behavior, either following postlearning or after preretention injection (Van Wimersma Greidanus and Baars, 1993).

The memory effects of vasopressin might be explained by an influence of the neuropeptide on excitation of limbic (hippocampal and septal) neurons. A number of neurons in the lateral septum respond to microiontophoretically applied vasopressin with an increase in spontaneous single-unit activity in the same way as the excitatory neurotransmitter glutamate increases the activity of these neurons (Joels and Urban, 1984). Based on these findings, one might conclude that a neurotransmitter-like effect is associated with vasopressin in limbic brain structures. In this respect, it is of interest that vasopressin is also capable of modulating long-term potentiation, which is believed to be an electrophysiological basis of memory processes (Teyler and Discenna 1987). Long-term potentiation in slices prepared from rats with congenital diabetes insipidus could be induced but could not be maintained. Exogenous vasopressin, given in vivo or in vitro, normalized long-term potentiation (Van den Hooff et al., 1989). Studies with oxytocin comparable to those with vasopressin in the hippocampus or the septal complex have not been performed except when the two peptides were compared with each other. In these studies oxytocin generally exhibited effects in 10- to 100-fold higher concentrations.

Vasopressin is also able to enhance the response to glutamate in 60 to 70% of these cells, which might be an indication that vasopressin may also act as a neuromodulator of excitatory pathways in the limbic-midbrain (Joels and Urban, 1984). However, vasopressin also has an inhibitory effect on glutamate responses in the ventral septal area. This effect is related to the antipyretic effect of the neuropeptide (Pittman et al., 1988). Vasopressin may also modulate neurotransmitter systems in the central nervous system. This hypothesis is based on findings indicating that vasopressin and oxytocin exert regional, highly localized effects on the metabolism and turnover of noradrenaline and dopamine (and serotonin) in the brain (for reviews, see Versteeg and Van Heuven Nolsen, 1984; Kovács and Telegdy, 1987; Kovács and Versteeg, 1993) and that an intact coeruleo-telencephalic noradrenergic bundle is critical for vasopressin to facilitate the process of memory consolidation (Kovács et al., 1979a).

B. Anterior Pituitary Peptides (Adrenocorticotrophic Hormone/Melanocyte-stimulating Hormone, β-Endorphin, Prolactin)

A variety of other neuronal peptides have been found to modify behavioral processes related to learning. However, these peptides were either not investigated systematically or were found to affect "second-order" behavioral processes (attention, arousal, or motivation). Nevertheless, these second-order effects may have important consequences modifying the sensory input to the intrinsic system following learning.

ACTH/MSH neuropeptides facilitate the deficient acquisition of shuttle box avoidance behavior of hypophysectomized rats, delay extinction of shuttle box avoidance behavior and pole-jumping avoidance behavior, and facilitate passive avoidance behavior of intact rats (for reviews, see De Wied, 1993; De Wied and Croiset, 1991; Bohus and De Wied, 1981). In appetitive paradigms, α-MSH improved acquisition of a complex maze response for food reward (Stratton and Kastin, 1974), and ACTH also facilitated operant learning motivated by a water reward (Guth et al., 1971).

Classical endocrine activity of ACTH/MSH neuropeptides can be clearly dissociated from behavioral effects (for reviews, see De Wied et al., 1993). A great number of structure-activity studies were performed to investigate active and passive avoidance behavior. The main conclusion of these studies was that ACTH-(4–7) was the smallest peptide to be fully active on learned behavior. γ-2-MSH, which differs from α-MSH in various amino acid residues, attenuates acquisition and facili-

tates extinction of active avoidance behavior and attenuates passive avoidance behavior (De Wied, 1993).

Different hypotheses have been offered to explain the influence of ACTH/MSH neuropeptides. One hypothesis suggested that ACTH/MSH neuropeptides increase the motivational value of the consolidating stimulus, thereby modifying the input and the external mechanisms of learning and memory processes (Bohus and De Wied, 1981). This effect may be caused by a selective arousal in limbic midbrain structures (for review, see De Wied and Croiset, 1991). This hypothesis easily explains the effect of ACTH/MSH peptides in aversive (stressful) behavioral situations. ACTH also influences attention and concentration (for review, see Kastin et al., 1981). This hypothesis offers an explanation for the putative physiological effects of ACTH/MSH peptides in nonaversive learning. The electrophysiological finding that ACTH and related peptides increase the sensitivity (mean and peak frequency of θ-activity following stimulation of the mesencephalic reticular formation) of the hippocampus in rats (Urban, 1985) is evidence for a selective arousal effect of these neuropeptides in limbic-midbrain structures. As described above, these effects might have important consequences for learning and memory processes, especially for the retrieval of stored information. In fact, although treatments with ACTH/MSH neuropeptides were fully effective on learned behavior when administered shortly before the retention trial (Fekete and De Wied, 1982), postlearning treatments were either less effective or the effects were of a short-term nature (in contrast to the long-term effects of neurohypophyseal neuropeptides). In agreement with this is the finding that ACTH/MSH peptides readily reverse retrograde amnesia in rats (Rigter and Van Riezen, 1975). These effects are produced only when the neuropeptides are given prior to the retention test.

Relatively few studies have been performed to define the anatomical brain structures that might be important for the effects of ACTH/MSH on learning and memory processes. Implantation experiments with the decapeptide ACTH-(1–10) demonstrated that the brain region where the mesencephalon and the diencephalon merge into each other at the posterior thalamic level was an important area for the behavioral effect of this peptide. Local application of ACTH-(1–10) in the parafascicular nucleus of the thalamus, the lateral habenular nucleus, or the tectospinal tract was equally effective. No effect of the peptide was observed following implantation into the ventral and the rostral part of the thalamus, globus pallidus, and the caudate nucleus (Van Wimersma Greidanus and De Wied, 1971). The posterior thalamic region thus seems to be an essential structure for the effect of ACTH-related peptides on avoidance behavior. This is also indicated by the fact that bilateral lesioning of the parafascicular nuclei inhibits the effect of ACTH-(1–10) on extinction of pole-jumping avoidance behavior (Bohus and De Wied, 1967).

It has been suggested that ACTH/MSH peptides improve avoidance behavior because these peptides cause an acceleration of the turnover of noradrenaline in the brain. Indeed, many reports showed an increase in catecholamine and serotonin turnover or content (for reviews, see Versteeg, 1986; Kovács et al., 1987) in different brain regions after treatment with ACTH or behaviorally active ACTH fragments, but in most cases these neurochemical effects were absent (while the behavioral effects were present) after adrenalectomy or hypophysectomy (Versteeg, 1986). Geiger et al. (1987) reported that a behaviorally highly active ACTH-(4–9)-fragment and related peptide fragments affected acetylcholine turnover, e.g., in the hippocampus and the frontal cortex of the rat. Behaviorally active ACTH fragments were found to antagonize glutamate binding (Ito et al., 1988). It has been shown that ACTH/MSH peptides might affect brain receptor-mediated polyphosphoinositide hydrolysis (Jolles et al., 1980) and result in increased formation of phopsphatidylinositol-4,5-biphosphate. This mechanism may be involved in the phosphorylation of brain proteins. Although the latter effects seem to be closely related to the action of ACTH/MSH-like neuropeptides on excessive grooming, a typical behavior in novel or conflicting situations (Gispen and Isaacson, 1986), their significance cannot be ruled out in ACTH/MSH-induced effects on learning and memory processes.

Data concerning the role of β-endorphin in learning and memory processes are rather ambiguous. β-Endorphin has been found to delay the extinction of pole-jumping active avoidance behavior and to facilitate the retention of passive avoidance behavior (for review, see De Wied and Croiset, 1991). However, β-endorphin administered during the posttraining period of an inhibitory avoidance task causes retrograde amnesia (Izquierdo, 1984). According to Izquierdo (1984), the amnesic effect of β-endorphin could be attributed to peptide-induced changes in the endogenous state of the animals in the posttraining period (endogenous state dependency hypothesis). Amnesia could be counteracted by administration of β-endorphin prior to the retention test. Flood et al. (1992) found recently that in mice partially trained to avoid footshock in a T-maze both intraamygdaloid and intraventricular injections of β-endorphin resulted in amnesia. Izquierdo (1984) suggested that differences in the neurohumoral state of an animal after the learning trial and the retention trial result in poor retrieval. According to this hypothesis, β-endorphin does not affect consolidation but merely influences retrieval processes. In accordance with this hypothesis, Netto and Maltchik (1990) found that a single injection of β-endorphin prior to the retention test enhances retrieval. The experiments of Rigter et al. (1977) also confirmed this view. These authors found

that β-endorphin, injected shortly before the retention trial, attenuates retrograde amnesia in rats. However, extraordinarily low doses of met- and leu-enkephalin produced identical results when injected subcutaneously before either the acquisition or the retention test (Rigter et al., 1977). Although these results are consistent with an interpretation of an antiamnestic action of endorphins, especially on retrieval processes, other hypotheses regarding changes in arousal, fear motivation, or response to stress were not explored.

In contrast, others found postlearning-facilitating effects of enkephalins (Belluzzi and Stein, 1984) or β-endorphin (Kovács et al., 1981) on passive avoidance behavior and a dual effect of β-endorphin administered prior to the retention test (Bohus, 1980). It has been shown in these experiments that the effect of β-endorphin on performance in learning situations is largely dependent on the dose of the neuropeptide. Smaller doses of β-endorphin facilitate passive avoidance behavior, whereas higher doses have attenuating effects. This dose-dependent dual effect might be related to the fact that β-endorphin affects learning and memory processes (or second-order physiological processes closely associated to learning and memory) by more than one neuronal or neurochemical mechanism. In that respect, it is of interest that β-endorphin can be converted in the brain to γ-endorphin [β-endorphin-(1–17)], α-endorphin [β-endorphin-(1–16)], and smaller fragments. α- and γ-endorphin exert opposite effects on the performance in active and passive avoidance tasks (Kovács et al, 1981). The differential effect of α- and γ-endorphin on avoidance behavior has been replicated by other groups of investigators as well (Le Moal et al., 1979), showing, in addition, opposite effects of the two endorphins in a lever press response for food test (Koob et al., 1981).

It has been suggested (for review, see De Wied, 1987) that α-endorphin possesses amphetamine-like, whereas γ-endorphin (and various active fragments thereof) possesses neuroleptic-like activities. Effects of these peptides on the performance of animals in a learning situation might thus also be secondary to these amphetamine- and neuroleptic-like effects and do not necessarily suggest (but also do not exclude) an involvement of β-endorphin and related neuropeptides in mechanisms of learning and memory.

There is evidence that prolactin may affect learning and memory processes in experimental animals. Peripheral administration of prolactin slightly impaired the performance of female rats in a conditioning task (Banerjee, 1971). In contrast, hyperprolactinemia, induced by implantation of pituitary glands under the kidney capsule, facilitated acquisition of shuttle box and pole-jumping avoidance behavior in male rats (for review, see Drago, 1990). This is in accord with the finding that congenitally prolactin-deficient mice are unable to acquire a normal level of learning performance (Bouchon and Will, 1981). However, neither the retention of passive avoidance behavior nor the extinction of active avoidance responses in rats seem to be affected by prolactin (Van Wimersma Greidanus et al., 1979, Drago et al., 1982).

C. Hypophyseotropic Peptides (Corticotropin-releasing Factor, Luteinizing Hormone-releasing Hormone, Thyrotropin-releasing Hormone, Somatostatin)

CRF is the principal activator of the pituitary-adrenocortical system. However, CRF-containing neurons were found outside the endocrine hypothalamus in brain structures of primary importance for learning and memory processes, e.g., in the cortex, amygdala, thalamus, locus coeruleus (for review, see Dunn and Berridge, 1990). The terminal projections of CRF-containing neurons reach the brainstem (for review, see Nieuwenhuys, 1985). CRF also affects behavioral processes related to learning and memory. Low doses of CRF (following peripheral administration of the peptide) were found to facilitate passive avoidance behavior, whereas high doses had the opposite effect (Veldhuis and De Wied, 1984). The attenuating effect was predominant following central (i.c.v.) administration. The effect of CRF was present in hypophysectomized animals as well; thus, it was independent of the ACTH-releasing properties of CRF (Fekete et al., 1987b). The hypothesis has been put forward that CRF primarily exerts anxiogenic effects and has arousal properties. Anxiety has profound effects on learning and memory processes and induces bell-shaped effects on behavioral performance (moderately to high level of arousal facilitates performance; extremely intensive arousal inhibits performance). The bell-shaped relationship between anxiety and performance and the bell-shaped dose-response curve of the effect of CRF on avoidance behavior fit well together with the anxiety-promoting hypothesis of this neuropeptide. The effects of CRF on shock-prod burying are also supportive of this idea (Diamant et al., 1992).

In a recent series of studies, Diamant and De Wied (1993) found that fragment CRF-(34–41) given i.c.v. was as active as CRF-(1–41) in attenuating passive avoidance behavior. The CRF antagonist, α-helical CRF, antagonized the effect of CRF-(1–41) on passive avoidance behavior. At low doses the antagonist tended to facilitate passive avoidance behavior, but at high doses it had the same effect as the agonist. In contrast, CRF-(34–41) did not possess adrenocorticotropic activities. Also, the heart rate increase induced by CRF-(1–41) could be elicited by CRF-(34–41), but the effect was of a shorter duration. Excessive grooming, which is found after i.c.v. CRF-(1–41), was also augmented following CRF-(34–41) administration. Other fragments such as CRF-(28–41) had a minor effect on passive avoidance behavior and heart rate, whereas CRF-(1–8) was without effect on the various parameters studied. The existence of different recep-

tors for CRF-(1–41) in the central nervous system and, therefore, a dissociation among the endocrine, autonomic, and behavioral effects of this polypeptide was postulated.

Results of recent experiments by Lee et al. (1992) suggest that CRF may also directly affect neuronal mechanisms of information processing. They showed that CRF significantly improved memory in passive avoidance learning. Protein synthesis inhibitors (cycloheximide or actinomycin-D) impaired memory. At doses that did not affect performance alone, both compounds antagonized the memory-enhancing effect of CRF. Specific increases in the optical density of three protein bands in the cytosolic fraction of hippocampal cells were found in rats showing good memory. There were also marked increases in the optical density of two protein bands in the nuclear fraction. Similar results were observed in animals treated with CRF.

Lee and Lin (1991) found that the Ca^{2+} channel blockers, nifedipine and verapamil, impaired the effect on avoidance behavior of CRF following intrahippocampal microinjections in rats. The same group of investigators (Chen et al., 1992) studied the role of CRF in the locus coeruleus, a brainstem nucleus that gives rise to ascending noradrenergic neurons of the coeruleo-telencephalic tract and that has been implicated in attention and behavioral arousal. Microinjections of CRF into the locus coeruleus significantly improved retention performance. A decrease in norepinephrine levels was found in the hippocampus and the amygdala of these animals. Intrahippocampal destruction of catecholaminergic neurons by 6-hydroxydopamine antagonized the memory-enhancing effect of CRF in the locus coeruleus. This finding suggests that the dorsal noradrenergic pathway is involved in the effects of CRF on memory processes. This is of interest, because vasopressin also needs this pathway for its effect on memory consolidation. Because the locus coeruleus is regarded as an anatomical substrate for anxiety, CRF may enhance memory processes through its anxiogenic actions. It may well be that the effects of vasopressin and related peptides on arousal are mediated through this pathway.

There is some evidence that the hypothalamic releasing hormone LHRH might affect learning and memory processes. De Wied et al. (1975) found that LHRH (and TRH) delayed extinction of pole-jumping avoidance following subcutaneous administration. This behavioral effect was explained by the presence of the pGlu-His moiety of LHRH and TRH, which resembles the Met-Glu-His sequence of ACTH-(4–10). Mora and Diaz-Veliz (1985) found that posttraining subcutaneous administration of LHRH modified the retention of either active or passive avoidance conditioning in male rats. Injection of LHRH immediately after the acquisition of an active avoidance response (two-way shuttle box avoidance) enhanced retention of the response, assessed 7 days later.

In a more recent study (Nauton et al., 1992), it was reported that LHRH induced changes in defensive learning. In middle age, females exhibit a decline in the activity of their reproductive axis. Results of several studies with rodents suggest that this is due to a decline in LHRH functions. No differences were found between young and middle-aged females in acquisition, retention, and reversal of a simple discrimination test in a T-maze. However, after removal of motor and spatial cues, discrimination based on visual cues was impaired in middle-aged females as compared to young mature animals. Administration of [D-Trp^6]LHRH enhanced performance during the visual discrimination in young females but not in middle-aged animals. These results suggest a direct effect of LHRH (and LHRH analogs) on spatial orientation processes associated with learning, which apparently disappears in aging rats. Therefore, these processes may play a role in reproductive behavior.

TRH is the stimulatory hormone of pituitary thyroid-stimulating hormone secretion. The central actions of this tripeptide are also not confined to its role as a releasing hormone in the hypothalamo-pituitary-thyroid axis. TRH, which has analeptic properties, produces behavioral excitation and hyperlocomotion, probably by interacting with central nervous noradrenergic and dopaminergic mechanisms (Bennett et al., 1989). As mentioned above, TRH delays extinction of a pole-jumping avoidance response (De Wied et al., 1975). TRH and behaviorally active TRH analogs were able to reverse amnesia produced by anoxia in mice (Yamazaki et al., 1986; Yamamura et al., 1991). Thus, TRH probably has an ameliorating effect on retrieval processes. However, retrograde amnesia induced by scopolamine treatment could not be antagonized by TRH (Yamazaki et al., 1986). It has been suggested that TRH interacts with septohippocampal cholinergic neurotransmission and that this mediates its influence on learning and memory processes (Horita et al., 1989). However, the evidence is not particularly overwhelming.

Somatostatin (somatotropin release-inhibiting factor), a cyclic tetradecapeptide, is a release-inhibiting hormone originally described as growth hormone release-inhibiting hormone (Brazeau et al., 1973). Somatostatin is highly concentrated in the extrahypothalamic areas of the brain, including the frontal and parietal cortex and the hippocampus. At these locations somatostatin may play a fundamental role in the modulation of cognitive functions. Indeed, somatostatin was found to affect behavioral processes related to learning and memory (Vécsei, 1989; Cacabelos et al., 1988). Following i.c.v. administration, the neuropeptide inhibits extinction of an active avoidance response and attenuates retrograde amnesia induced by electroconvulsive shock in rats.

Cysteamine, a drug that produces a rapid, albeit moderately selective, reversible depletion of somatostatin in the brain (for review, Vécsei, 1989), was found to exert

opposite effects and to inhibit active avoidance behavior. Intrahippocampal administration of cysteamine disturbed passive avoidance behavior.

It is of interest that i.c.v. administration of somatostatin increased the turnover of acetylcholine in the hippocampus (as was found for peptides related to ACTH; Geiger et al., 1987) brainstem and the diencephalon of rats (Malthe-Sörenssen et al., 1978). A facilitated release of cortical and hippocampal serotonin and noradrenaline was also observed in in vivo and in vitro experiments following somatostatin administration (Tanaka and Tsujimoto, 1981; Tsujimoto and Tanaka, 1981). In a recent study by Schettini (1991), activation of somatostatin receptors in the brain inhibited adenylate cyclase and reduced intracellular Ca^{2+} levels. The peptide caused hypopolarization of hippocampal and cortical cells by inducing outward K^+ currents. Florio et al. (1991) found a significant reduction of preprosomatostatin mRNA levels in aged animals in the frontal and the parietal cortex but not in the hypothalamus. These results demonstrate that age-related alterations in somatostatin gene expression occur in the rat. This suggests that such alterations may participate in the behavioral and cognitive impairments that occur during aging. A systematic analysis of brain sites sensitive to the effects of somatostatin on learning and memory processes has not been performed.

D. Brain-Gut Peptides (Cholecystokinin, Neurotensin, Neuropeptide Y, Gastrin-releasing Peptide, Bombesin, Vasoactive Intestinal Peptide, Galanin)

Peptides related to CCK have been detected in the brain. The predominant form is the COOH-terminal octapeptide (CCK-8). Pathways of CCK-8 have been demonstrated in the cerebral cortex (Goltermann et al., 1981; Hökfelt, 1991) as well as in subcortical structures. In the cerebral cortex CCK is present in very high concentrations (Crawley, 1985). The connections made by CCK neurons can be divided into three major systems: (*a*) local circuit neurons, which are primarily located in the cerebral cortex, amygdala, raphe nuclei, etc.; (*b*) ascending projections, which include the mesotelencephalic fibers arising from the dopaminergic and serotonergic cell body areas of the brainstem to innervate, among others, limbic and cortical areas; (*c*) descending CCK pathways, which include cortical projections to the thalamus, limbic structures, etc. (Crawley, 1985; Hökfelt, 1991). CCK has been shown to coexist with dopamine in several dopamine-containing neurons (Hökfelt, 1991). Behavioral, endocrine, and metabolic effects of CCK are extremely widespread. Recent findings suggest the existence of different types of CCK receptors. CCK-A receptor is present in the pancreas and the gallbladder, and a second type, the CCK-B receptor, is found in the central nervous system (Moran et al., 1986; Dourish and Hill, 1987).

In relation to learning and memory processes, early findings have shown that peripheral injections of CCK-8 impaired acquisition and facilitated extinction of active avoidance behavior (for review, see Fekete et al., 1987a). CCK-8 was found to impair acquisition in a shuttle box (two way) avoidance paradigm. In contrast, in a passive avoidance learning paradigm CCK-8 improved retention (lengthened avoidance latency) when the neuropeptide was injected either after the single learning trial (Fekete et al., 1987a) or prior to the retention test (Van Ree et al., 1983). Two forms of CCK-8 are known to exist in the central nervous system. The unsulfated form is 1000-fold less potent than the sulfated octapeptide in binding to CCK-A receptors. Because CCK-8 sulfate ester has a sedative effect (for review, see Fekete et al., 1987a), the results in the passive avoidance test may be explained by an effect on locomotor activity. This was corroborated by experiments in which CCK-8 was microinjected into the nucleus accumbens (Van Ree et al., 1983) and found to attenuate passive avoidance behavior. The authors suggested that these local effects were more related to an antipsychotic-like profile of this neuropeptide than to its action on information processing itself.

More recent findings argue for a significant role of CCK in information processing (Itoh and Lal, 1990), because CCK receptor agonists and antagonists have repeatedly been demonstrated to improve and impair, respectively, learning and memory functions (Flood et al., 1992; Meziane et al., 1993). The effect of subcutaneously injected caerulein (a nonselective CCK receptor agonist) on memory impairment induced by protein kinase C inhibitors was examined in rats (Takashima et al., 1991). Injection of protein kinase C inhibitors i.c.v. caused marked memory impairment in a one-trial passive avoidance test and in a Morris water maze. When rats were pretreated with caerulein before the training trials, the CCK receptor agonist offered protection.

Itoh et al. (1992) studied the effect of subcutaneously administered caerulein on amnesia induced by protein synthesis inhibitors in passive and active avoidance behavior and in the Morris water maze test. The amnestic effect of the protein synthesis inhibitors was abolished by combined administration with caerulein.

In a more recent study (Harro and Oreland, 1993), the effect of CCK receptor agonists and antagonists on the ability to acquire a task motivated by appetite and to influence spatial memory was investigated. Drugs were given before each test session to well-trained animals. Proglumide, an unselective CCK receptor antagonist, and devazepide, a rather selective CCK-A receptor antagonist, as well as caerulein and CCK-4, had no reliable effect. Fekete et al. (1987a) measured the acquisition of shuttle box avoidance behavior, extinction of bench-jumping active avoidance behavior, food-motivated conditioned approach behavior, and one-trial learning passive avoidance behavior and found that, following

peripheral administration, both the sulfated and non-sulfated octapeptides and the COOH-terminal tetra-, penta-, hexa-, and heptapeptides were almost equally active on extinction of active avoidance behavior and on passive avoidance behavior.

Studies have been carried out in which endogenous CCK was blocked in the posterior cingulate cortex of mice using a local injection of CCK-8 antiserum (Meziane et al., 1993), and memory effects were tested using visual discrimination conditioning. Injection of CCK-8 antiserum 10 to 15 minutes before each session produced substantial learning impairment in the discrimination task. But when injections were stopped, animals began to learn the task normally, showing that the CCK antiserum effect was reversible. When the antiserum was administered at the same dose before a single test session 14 days after the end of the initial training, the retention was also affected. These results show that cingulate CCK can affect retrieval processes. In addition to the cerebral cortex, the amygdala is likely to play an essential role in mediating the effect of CCK (also peripherally injected) on retrieval processes (Flood et al., 1992).

As far as the mechanism of action is concerned, CCK has been shown to coexist and interact with various neurotransmitters, especially with dopamine in the brain (for review, see Itoh and Lal, 1990). Electrophysiological findings support the notion that CCK has excitatory effects on neurons (Brooks and Kelly, 1985), an effect that is similar to that of glutamate. Takashima et al. (1990) found that caerulein prevented the memory deficit induced by an NMDA receptor antagonist, suggesting an interaction of endogenous CCK with the NMDA subtype of glutamate receptors. A similar interaction has been hypothesized for the effects of some ACTH fragments (e.g., ACTH-4–9) on locomotor (open field) behavior. The peptide counteracted the negative effect of the NMDA antagonist, AP5, on acquisition of spatial learning and the NMDA-induced explosive running behavior (Spruijt, 1992).

Neurotensin is a natural brain-gut tridecapeptide localized in a complex network of pathways in the brain. Although the number of studies of the effect of neurotensin on learning and memory processes are scarce, neurotensin has also been implicated as a mediator of events that are of importance in learning and memory processes. Van Wimersma Greidanus et al. (1982) found that systemic administration of neurotensin induced a dose-dependent inhibition of extinction of pole-jumping avoidance behavior. Treatment of rats with neurotensin immediately after the learning trial, as well as before the first retention trial, facilitates passive avoidance behavior in rats (Van Wimersma Greidanus et al., 1982). Glimcher et al. (1982) investigated the role of neurotensin in the regulation of reinforcement, using conditioned place preference, a paradigm that forms an association between an experimental manipulation and a fixed location. They found that rats treated with neurotensin showed a significant increase in place preference.

NPY is an amidated 36-amino acid peptide with a wide distribution in the central and peripheral nervous systems. NPY forms a family of peptides together with pancreatic polypeptide and the intestinal peptide YY (Wahlestedt et al., 1990). NPY is highly concentrated in the hippocampus and the amygdala (for review, see Morley and Flood, 1990). Cholinergic interactions of NPY in the neocortex have been reported (Poulakos et al., 1990). Of particular interest are the findings of the potential influence of NPY transmission in memory and cognition. Posttraining i.c.v. administration of NPY to mice that were undertrained resulted in improved retention when mice were retested 7 days later (for summary, see Morley and Flood, 1990). When the performance of mice in a T-maze active avoidance task was tested, i.c.v. administered NPY had no effect on acquisition but improved retention. Peripheral administration had no effect. The effect of NPY on memory retention was time dependent. When NPY was administered immediately prior to the retention test, enhanced recall was observed. However, because NPY did not alter acquisition, this enhanced recall most probably reflects enhanced retrieval of previously stored memories. NPY was found to reverse retrograde amnesia induced by scopolamine treatment and by protein synthesis inhibitors (Morley and Flood, 1990). When NPY was injected into the rostral hippocampus and the septum, it had an opposite effect (promoted amnesia) compared to injections into the amygdala or the caudal hippocampus. Injections of NPY into the caudate nucleus, thalamus, or cortical sites above the rostral hippocampus were without effect (Flood et al., 1989; Morley and Flood, 1990). The optimum dose of NPY after intracerebral microinjections was 0.5 μg. This is about 100,000-fold higher than the amounts of vasopressin or oxytocin needed to affect behavior following i.c.v. treatment. It would be of interest, therefore, to measure the effect of neurohypophyseal neuropeptides in this paradigm.

The physiological role of NPY on T-maze avoidance was studied following local microinjections of NPY antibodies into various brain structures. NPY antibodies caused amnesia when injected into the rostral hippocampus and septum and were found to facilitate the behavior when administered into the caudal hippocampus or the amygdala (Flood et al., 1989).

A part of the activity of NPY to modify learning and memory processes is likely to reside in the COOH-terminal part of the molecule, because the COOH-terminal peptide fragment, NPY-(20–36), was as active as the whole molecule. A shorter COOH-terminal fragment, NPY-(26–36), was ineffective (Flood and Morley, 1989). Two distinct subtypes of NPY receptors have been found, a postsynaptic (Y_1) receptor, for which effects could only be obtained with the complete NPY molecule, and a

presynaptic (Y_2) receptor, for which effects could be elicited by long COOH-terminal fragments as well as the whole molecule. Taken together, it is likely that Y_1 receptors mediate the effects of NPY on food intake, and Y_2 receptors are responsible for the effects of NPY and NPY fragments on learning and memory processes (Flood and Morley, 1989). The latter effect, which is localized in the hippocampus, most probably is the result of an inhibition of the release of GABA from the basket cells (Morley and Flood, 1990); thus, in this way NPY facilitates the firing of glutamate-containing pyramidal cells.

Bombesin is a peptide originally identified in frog skin (Anastasi et al., 1971). There are two peptides known in mammalian species that are structurally related to bombesin, gastrin-releasing hormone, and neuromedin B. The relationship concerns the COOH-terminal decapeptide which is essential for biological activity (Spindel, 1986). Biological activities of these peptides include smooth muscle contraction and release of gastrointestinal and pituitary hormones. In the brain, the effects involve the cardiovascular system, thermoregulation, metabolism, and behavior (Tache and Brown, 1982). It has been reported (Flood and Morley, 1988; Morley et al., 1992) that GRP and bombesin enhance the retention of T-maze training after peripheral administration. The dose-response curves showed a characteristic inverted U-shape, with high doses of both GRP and bombesin causing amnesia. The effect of the two peptides was time dependent and both reversed amnesia induced by scopolamine. GRP-(14–22) had the same effect as GRP-(1–27), whereas GRP-(1–16) was without effect. Of special importance is the observation that i.c.v. administration of the peptides required higher doses than did systemic injections to produce an effect on T-maze behavior, suggesting that the effect of GRP and bombesin is mediated predominantly through peripheral mechanisms, which most probably involve activation of ascending vagal fibers (Flood and Morley, 1988).

VIP is a neuropeptide that is widely distributed throughout the central and peripheral nervous systems. It meets the commonly agreed criteria for a neurotransmitter. It affects a variety of physiological functions including behavior. The peptide possesses powerful excitatory effects on neurons in the hippocampus, and it increases choline acetyltransferase activity in these neurons (for review, see Flood et al., 1990a). VIP, administered into the third ventricle of the mouse, has been found to cause amnesia as measured in a left-right foot shock avoidance task in a T-maze (Flood et al., 1990a). VIP also resulted in amnesia when administered directly into the rostral portion of the hippocampus. The effect of VIP is time dependent. The VIP receptor antagonist [(4-Cl-D-Phe^6, Leu^{17})VIP] enhanced retention when administered into the hippocampus, suggesting that VIP plays a physiological role in memory modulation (Flood et al., 1990a). It has been concluded that VIP, like oxytocin, might be a potent amnestic neuropeptide. However, Glowa et al. (1992) presented evidence that the acquisition of spatial discrimination and performance in the Morris swim maze were retarded by an antagonist of VIP that competitively inhibits VIP binding and blocks VIP-mediated functions in cell cultures from the central nervous system.

Galanin, a 29-amino acid neuroactive peptide, affects diverse processes throughout the nervous system and coexists with several "classical" neurotransmitters, including norepinephrine, serotonin, and acetylcholine (Robinson and Crawley, 1993). Galanin coexists with acetylcholine in neurons of the medial septum, diagonal band, and nucleus basalis of Meynert. The cholinergic forebrain neurons appear to play a significant role in learning and memory, as suggested by a severe loss of these neurons in Alzheimer's disease. In the ventral hippocampus, galanin inhibits the release of acetylcholine and inhibits carbachol-stimulated phosphatidylinositol hydrolysis. Galanin impairs choice accuracy in learning and memory paradigms in rats (Robinson and Crawley, 1993). Malin et al. (1990) investigated whether galanin, administered i.c.v. immediately after the learning trial, might interfere with a one-trial discriminative reward learning task. Rats treated with galanin showed significantly less retention. Administered before the retention trial, galanin had no effect, suggesting that galanin may interfere with memory formation rather than memory retrieval or task performance.

To test the possibility that galanin acts on the cell bodies of medial septal neurons (Givens et al., 1992), two measures of septohippocampal function were assessed following intraseptal microinfusion of galanin or two of its synthetic fragments, galanin-(1–16) and galanin-(21–29). The behavioral measure was choice accuracy in a memory task in a T-maze. The electrophysiological measure was hippocampal θ activity recorded from the dentate hilus. Both the galanin fragment, galanin-(1–16), and the complete peptide, galanin-(1–29), decreased choice accuracy and decreased hippocampal θ activity in a dose-dependent fashion. Sensorimotor performance was unaffected by the neuropeptide. These findings demonstrate that galanin impairs memory when administered directly into the medial septal area and suggest that galanin inhibits medial septal neural activity.

The involvement of endogenous galanin in learning has been demonstrated by the use of a recently synthesized high-affinity galanin antagonist, M35 [galanin-(1–13)-bradykinin-(2–9)amide]. Administration of M35 i.c.v. facilitated acquisition of spatial learning in the Morris swim maze without an increase in swim speed. Thus, M35 shortened escape latency, reduced the number of failures to reach the platform, and shortened the path length to reach the hidden platform. M35 also tended to enhance retention performance 7 days after the last

training session (Ogren et al., 1992). Receptor autoradiographic studies of the distribution of ^{125}I-M35 following i.c.v. administration showed that binding sites were present in particular periventricular regions, including the hippocampus.

Age-related alterations in cue-training and place-training tasks were evaluated (De Bilbao et al., 1991) and compared to alterations in galanin-like immunoreactive neurons in the medial septal area of the rat. The majority of aged male rats, compared to young rats, exhibited impaired performance in a Morris water maze. In addition, there was a significant loss of galanin-like immunoreactive cells in the medial septal-diagonal band complex and a marginal loss of septohippocampal galanin positive neurons in aged rats.

E. Tachykinins (Substance P, Neuropeptide K, Neurokinin A)

The tachykinins, substance P, neurokinin A, neurokinin B, and neuropeptide K, are present in various brain (including limbic) nuclei, where the neurons that express these peptides are intimately associated or colocalized with neurons containing classical neurotransmitters, e.g., acetylcholine in the basal forebrain nucleus or dopamine in the striatum (Bannon et al., 1991). Substance P is considered to be a putative transmitter substance in sensory nerves exerting a slow excitatory influence.

Only a few studies have investigated the role of tachykinins in learning and memory processes. Substance P given intraperitoneally (Hecht et al., 1979) disrupted learning to turn off an aversive stimulus that was conditioned to an acoustic stimulus (Huston and Staubli, 1981). In a more recent study (Nagel et al., 1993), the effect of peripheral injections of substance P on performance in two different configurations of an automated tunnel maze was examined. In a hexagonal maze, which measures activity, exploratory efficiency, habituation, and perimeter walking, injection of substance P facilitated perimeter walking only. In a radial maze, substance P produced a facilitation of long-term and short-term memory without affecting activity. When the effect of pre- and postlearning injections of substance P was tested on performance in the radial maze configuration, only pretrial injections facilitated performance with respect to measures of efficiency and short- and long-term memory. Virtually no effect was seen with postlearning injections.

Postlearning injections of substance P into the substantia nigra and in the amygdala disrupted passive avoidance learning and, thus, resulted in amnesia (Huston and Staubli, 1981). In contrast, microinjections of substance P into the lateral hypothalamus or the medial septal nucleus improved avoidance learning (Staubli and Huston, 1980). When injected 3 hours after the learning trial, substance P no longer affected passive avoidance behavior, suggesting that the neuropeptide primarily affected consolidation processes. Postlearning injections were not effective when the peptide was administered into the prefrontal cortex.

Differential functions and individual sensitivity of various anatomical brain sites may not be the only reason for the opposite effects of substance P on learning and memory processes. Following unilateral injection into the nucleus accumbens, the intact peptide [substance P-(1–11)] and the COOH-terminal fragment substance P-(7–11) disrupted, whereas the NH_2-terminal fragment substance P-(1–7) facilitated, passive avoidance behavior (Gaffori et al., 1984). It has been concluded that, similarly to various other neuropeptides, substance P may require processing by enzymatic cleavage to activate moieties that modulate avoidance behavior (Gaffori et al., 1984). Thus, it seems that substance P can modulate avoidance learning and facilitate or inhibit performance depending on the site of injection and the formation of biologically active fragments.

Neuropeptide K is a 36-amino acid peptide that contains the sequence of the substance P precursor, neurokinin A. Neuropeptide K is present in high concentrations in the hippocampus, where receptors for this neuropeptide have been found (Arai and Emson, 1986; Saffroy et al., 1988). Both NPK and neurokinin A have been shown to enhance memory in a T-maze paradigm when administered centrally (i.c.v.) immediately after the learning trial (Flood et al., 1990b). Local microinjections of NPK into the caudal hippocampus or the amygdala of mice resulted in facilitation of retention ((Morley and Flood, 1990), suggesting that this tachykinin peptide may influence learning and memory processes via limbic structures. It is of interest that NPK and NPY (see above) modulate memory processes via the same brain structures; however, whereas NPY enhances retrieval, NPK affects consolidation processes.

F. α-Atrial Natriuretic Peptide and Angiotensin II

ANP is present in the heart as well as in the brain. It affects spontaneous and angiotensin II-induced drinking in rats (Masotto et al., 1985). It also inhibits vasopressin release induced by dehydration and hemorrhage in rats (Samson, 1985). Preliminary data suggest that α-ANP might influence learning and memory processes. Bidzseranova et al. (1991) investigated the effects of rat ANP [ANP-(1–28)] on passive avoidance behavior in rats following administration into a lateral ventricle immediately after the learning trial. α-ANP-(1–28) dose-dependently facilitated passive avoidance behavior. When injected before the learning trial, α-ANP had the same effect. When, however, the peptide was given shortly before the retention trial, there was no effect on passive avoidance behavior. The data suggest that ANP-(1–28) facilitates acquisition and the consolidation of passive avoidance behavior. Electroconvulsive shock-induced partial retrograde amnesia could also be prevented

by i.c.v. administered α-ANP (Bidzseranova et al., 1991). Structure activity studies revealed that the active moiety of ANP resides in the sequence ANP-(15–23) (Bidzseranova et al., 1992). The same authors, in addition, showed that i.c.v. injection of an α-ANP antiserum attenuated passive avoidance behavior when administered immediately after the learning trial; it also facilitated extinction of an active avoidance response. The results suggest that endogenous ANP is involved in the modulation of learning and memory processes. Brain natriuretic peptide has the same effect on avoidance behavior.

Abundant evidence indicates that angiotensin II influences central nervous system activity (Mendelsohn, 1985). Effects on blood pressure, thirst, salt appetite, and release of such pituitary hormones as vasopressin, oxytocin, ACTH, and LHRH have been reported (Wright and Harding, 1992). Behavioral effects include effects on exploratory and stereotype behavior as well as on learning and memory processes. A single subcutaneous injection of angiotensin II failed to modify extinction of active avoidance behavior in rats (De Wied, 1971). However, angiotensin II administered i.c.v. facilitated retention of a food-motivated T-maze task, shuttle box avoidance training, and passive avoidance behavior (Braszko et al., 1988). Similar effects were found by others after i.c.v. administration of angiotensin II (for review, see Wright and Harding, 1992). Injection of an extremely high dose of angiotensin II into the dorsal neostriatum disrupted passive avoidance behavior (Morgan and Routtenberg, 1977). Baranowska et al. (1983) found that i.c.v. angiotensin II facilitated acquisition of a conditioned avoidance response but not extinction.

Angiotensin-converting enzyme inhibitors impaired the behavior of rats in a water maze (Costall et al., 1989). Because these compounds inhibit the conversion of angiotensin I to angiotensin II, it might be that both peptides have a similar effect on learning and memory processes. This might be the case because structure-activity studies showed that angiotensin-(3–7) was as active as angiotensin II on acquisition of active avoidance behavior and retention of passive avoidance behavior. The enzyme inhibitor captopril counteracted the deficiency in passive avoidance behavior caused by i.c.v. administration of renin (De Noble et al., 1991). Saralasin, another angiotensin-converting enzyme inhibitor, abolished the effect of angiotensin II on passive avoidance behavior (Georgiev, 1990). Bilateral lesions of the hippocampus do not interfere with the effect of angiotensin II on passive avoidance behavior (Winnicka et al., 1989).

The above-cited studies seem to indicate that the influence of the angiotensin system on learning and memory processes as such are of little importance. The influence of angiotensin II on learning and memory may well be explained by its effect on the release of other neuropeptides. Accordingly, the essential role of angiotensin II in water metabolism points to the possibility that its memory effects are related to water intake. In this respect it is of interest to note that angiotensin II injections into the lateral preoptic area or septum elicited a previously learned bar-pressing response for water in satiated rats (Rolls et al., 1972; Graef et al., 1973).

III. Discussion

Animals, as well as human beings, acquire new information about their environment by learning and subsequent retention of that information. The brain interacts with the internal and external environment through axon discharges and synaptic transmission, and it follows that the substrates of memory are triggered by and act on these physiological events. The integrated activity of primary physiological and behavioral processes is a necessary condition for the occurrence of memory.

The strategy for studying the biology of learning and memory is based on the belief that information is stored as changes in neuronal interactions in the brain. If learning and memory processes involve the formation of new synaptic contacts or modification of existing ones, then these modifications are likely to require changes in the quantity, turnover, metabolism, release, or receptor-mediated events of specific biochemical mechanisms. Although the precise nature of these changes is not yet understood, a good deal is known about the morphology, physiology, and biochemistry of neurons and about the ways in which neurons can change the way they communicate with other neurons. The complexity of the problem is well characterized by the fact that the mammalian brain consists of at least 10^{10} neurons and 10^{14} synaptic contacts. A major discovery of the past two decades has been that, within the cascade of processes involved in learning and memory, neuropeptides play a significant part. As described earlier in this review, neuropeptides, which are widely distributed in the brain, affect neuronal excitability and modify behavior.

Synaptic connections between one neuron and another are generally complex and redundant. Considering the great diversity in the distribution and actions of neuropeptides in the brain and on the behavior, one might ask the intriguing question, do identical or similar neuropeptide effects merely represent "redundancy" of the system? However, the psychological, biological, and biochemical complexity of the problem (the facts that memory processes have different stages with different biochemical mechanisms and neuroanatomical pathways involved and that memory-related changes are often localized in different places throughout the nervous system) suggest that neuropeptides participate in learning and memory processes.

The early days of research on the biology of learning were confounded by the postulate that argued that, from the biochemical change subserving structural encoding of information, there might be a memory "code" residing in a unique "memory molecule," which then could be the

biochemical basis of engram formation (Ungar, 1967). This approach, which led to some sensational and irreproducible findings, has resulted in an everlasting suspicion and resignation toward more rational and methodologically sound approaches to the role of neuropeptides in learning and memory processes. There is no evidence whatsoever that any of the neuropeptides would be the ultimate memory molecule, and thus, it is also not probable that neuropeptides are themselves encoding the experimental information.

Another possibility is that their function is related to those processes that affect the response of neurons to impulses from neighboring neurons by changing the connectivity between neurons so that new pathways become functional. It is, therefore, more rational to regard memory encoding as a result of the formation of specific spatiotemporal patterns of activation of neuronal networks and to assume that neuropeptides (peptidergic neurons) may either be part of these networks or may modulate the activity of these networks (extrinsic peptidergic neuronal networks and neuropeptides in the general and cerebrospinal circulation). Many of the neuropeptides known to facilitate learning and memory processes are also present in limbic or cortical structures. The areas involved, i.e., limbic-midbrain areas, in particular, are innervated by neuropeptide systems or are characterized by the presence of neuropeptides. This is an argument for the significance of these compounds in the activity of this system. In limbic-midbrain regions, neuropeptides also affect biochemical and electrophysiological processes intimately involved in the formation of memory (long-term potentiation, neuronal excitability of the hippocampus, modification of the responses of the neurons to glutamate, functions of NMDA receptors, phosphoinositide metabolism, c-*fos* expression, etc.). Inasmuch as a phenomenon such as long-term potentiation (and related biochemical events) might be considered as a model of the form on which synaptic connections are able to store new information, and if many neuropeptides exert effects in this respect, one would almost have explained why many of these peptides modulate learning and memory processes. To our present knowledge vasopressin, oxytocin, pro-opiomelanocortin-derived peptides, CCK, and NPY have been shown to affect these processes (table 2).

Another important question relates to the specificity of the effect and of the involvement of neuropeptides. Specificity can be viewed from quite different angles. None of the neuropeptides is specific in the sense that the only effect would be on information processing. Almost all of them have well-characterized, widespread endocrine activities either on the pituitary gland or in the periphery. Release of "endocrine" neuropeptides may occur in response to specific stimuli (e.g., vasopressin release to thirst, oxytocin release to suckling, CCK release to hunger and satiety), but very often nonspecific stimuli (stress, anxiety, fear, etc.) provoke the release of these neuropeptides (e.g., CRF, ACTH, β-endorphin, α-MSH, prolactin, vasopressin, oxytocin) in the blood and the brain, and thus, it looks as if central and peripheral effects might act in concert on a given response. For example, various peripheral mechanisms (e.g., vagal stimulation: CCK, GRP, bombesin; blood pressure changes: angiotensin II, vasopressin) might be integral parts of the internal environment representing a particular "state" in different phases of learning or memory processes (e.g., state dependency hypothesis for the effects of endorphins). Especially in aversively motivated learning situations, which are of vital importance for survival (as are behavioral reactions to other motivations, such as hunger, thirst, reproduction), such signals from the periphery may have enormous significance for learning.

One of the important discoveries in the field of neuropeptides and learning and memory processes is the principle that classical endocrine activities and central nervous activities of the same neuropeptides can be dissociated; thus, potent behavioral activities may reside in smaller, more selective peptides that are devoid of endocrine activity. These findings, based originally on experiments with vasopressin, oxytocin, ACTH/α-MSH, and the endorphins, prompted the hypothesis that neuropeptides are endogenous substances in the central nervous system, formed following gene expression in nerve cells, and produced in large precursor molecules

TABLE 2
Neuropeptide effects on putative mechanisms of neural plasticity related to learning and memory

Neuropeptide	LTP*	Glutamate† (NMDA)	Neuronal excitability‡	Locus specificity§
Vasopressin	+‖	+	+	+
Oxytocin	±	0	±	+
ACTH/α-MSH	+	+	+	+
β-Endorphin	0	0	+	+
Prolactin	0	0	0	0
CRF	0	0	0	+
LHRH	0	0	0	0
Somatostatin	0	0	+	0
TRH	0	0	0	0
CCK-8	0	+	+	+
Neurotensin	0	0	0	0
NPY	0	+	+	+
Bombesin	0	0	0	0
VIP	0	0	+	0
Galanin	0	0	+	+
Substance P	0	0	0	+
Neuropeptide K	0	0	0	+
α-ANP	0	0	0	0
Angiotensin II	0	0	0	+

* Effects on long-term potentiation.
† Effects on glutamate/NMDA metabolism or receptors in the hippocampus or cortex.
‡ Effects on the neuronal excitability of the hippocampus.
§ Locus-specific effects in limbic-midbrain or cortical structures.
‖ Symbols: +, facilitatory effects; ±, moderate effects; 0, not investigated.

that undergo a cascade of processes to express the genetic information into biologically active peptides (De Wied, 1987). These processes determine the quantity of peptides synthesized and their biological activity through size, form, and derivatization of the end product. In this way, neuropeptides with different, sometimes opposite, effects with more selective properties are formed from the same precursor. This concept gave an explanation for the multitude of behavioral effects of neuropeptides involved in various brain structures and in different learning situations. It is probably best demonstrated with neurohypophyseal peptides (Burbach et al., 1983; Burbach, 1986). Peptide fragments such as [Pglu^4 Cyt^6 AVP]-(4–9), which are devoid of classical endocrine effects, are rapidly formed in the brain from Arg^8-vasopressin. Such neuropeptides may be responsible for the influence of neurohypophyseal peptides on learning and memory (De Wied et al., 1993). It is now clear that this is a rather general phenomenon.

CCK-8 octapeptide has been shown by various groups of investigators to modulate learning and memory processes. However, it has also been demonstrated that a behaviorally active fragment (CCK-4) is formed in the brain by aminopeptidases, and behavioral effects of the tetrapeptide might be basically different from (in certain respects, opposite to) that of the parent molecule (for review, see Itoh and Lal, 1990). NPY is also rapidly converted in the brain. Morley and Flood (1990) observed that shorter NPY fragments were capable of producing memory enhancement, whereas only the intact peptide was capable of producing an increase in food ingestion. These authors also showed that the parent peptide and the behaviorally active fragment interact with different receptors in the brain (the parent peptide stimulates postsynaptic Y_1 receptors, whereas the fragments interact with presynaptic Y_2 receptors in the hippocampus). Similar results were found with substance P (Huston and Staubli, 1981; Gaffori et al., 1984), galanin (Givens et al., 1992), and somatostatin (Vécsei, 1989). Thus, the in vivo (intracerebral) formation of behaviorally active, smaller peptide molecules might be functional in synaptic plasticity during memory formation in the 10^{14} synapses of the mammalian brain.

Another aspect of specificity is whether (any of the) neuropeptides are selectively involved in cognitive processes of memory consolidation and retrieval or whether they also have secondary effects through second-order events that modulate the input to information processing, i.e. processes such as perception, motivation, emotionality, attention, or arousal. Most behavioral acts involve three major functional systems in the brain, i.e., sensory, motor, and motivational systems. Sensory stimuli provide input to cortical areas through cortical connections and also through multisynaptic pathways involving the basal ganglia, the cerebellum, and the thalamus. The motivational system, which includes a portion of the limbic system of the brain, also sends information to the cortex. Activation of the brain for behavioral arousal and for different levels of awareness is one of the physiological roles of the brainstem reticular formation. Neuropeptides located in the spinal cord, ascending sensory pathways, the reticular formation, the thalamus, or the cerebellum (Nieuwenhuys, 1985) might have an integrative function in these processes.

The output of performance (motor skill) of adequate behavior in a learning situation could also be affected by neuropeptides in a selective (goal-directed motor patterns) or nonselective (locomotor activity in general) manner. Widespread effects of various neuropeptides on dopamine and acetylcholine turnover in the basal ganglia or the red nucleus have been found (for reviews, see Versteeg 1986; Kovács and Versteeg, 1993). Memory processes, the retrieval of memory in particular, must be intimately related to perception, attention, and stimulus selection. It is disappointing that a fairly large part of the literature offers merely a superficial reasoning concerning the effect of neuropeptides on behavioral processes related to learning and memory (effects have been found on some performance parameters with a single dose of a particular peptide in one specific learning paradigm that is generalized to "memory" without careful analysis). This reasoning has led to a certain amount of justified skepticism as to the possible merits of the entire research line. Time- and dose-dependent postlearning effects, modification of neuronal excitability, the presence of these neuropeptides and their receptors in brain structures critically involved in information processing (cortex, hippocampus, amygdala, thalamus), greater effectiveness following intracerebral administration into these brain structures than following systemic treatment, and disturbances of cognitive processes following immunoneutralization or receptor blockade of the neuropeptides are the most important criteria for a putative physiological involvement of a neuropeptide in cognitive processes per se. Studies of vasopressin, oxytocin, CCK, and NPY seem to best fulfill these criteria (table 3).

There is also evidence that these memory neuropeptides might have additional, more situation- or context-specific effects on some aspects of learning and memory or on some second-order processes. Vasopressin, for example, has the most robust behavioral effects in fear-motivated behavioral test situations (for review, see De Wied et al., 1993), when the neuropeptide is also normally released into the brain and the periphery. The effects of CCK, NPY, and galanin, on the other hand, are most prominent in food-motivated behavioral tasks. It has been suggested, therefore, that CCK is a physiological mediator of food-induced enhancement of memory processing. Other types of learning (sexual, social, etc.) may also have their specific signaling in which neuropeptides might play a significant role. Examples are oxytocin, LHRH, and ACTH for sexual components

TABLE 3
Neuropeptide effects on learning and memory processes

Neuropeptide	Avoidance postlearning*	Behavior preretention†	Non-aversive‡	Amnesia§
Vasopressin	+ (AP)‖	+ (AP)	±	+
Oxytocin	− (P)	− (AP)	0	−
ACTH/α-MSH	± (AP)	+ (AP)	+	+
β-Endorphin	? (P)	+ (AP)	0	+
Prolactin	× (AP)	× (AP)	0	0
CRF	? (AP)	? (AP)	0	0
LHRH	+ (AP)	+ (A)	0	0
Somatostatin	0	0	0	+
TRH	0	+ (A)	0	+
CCK-8	+ (AP)	+ (AP)	+	+
Neurotensin	+ (P)	+ (AP)	+	0
NPY	+ (P)	+ (AP)	+	+
Bombesin	+ (A)	+ (A)	0	+
VIP	− (A)	− (A)	?	−
Galanin	− (P)	× (P)	−	0
Substance P	? (P)	± (AP)	0	0
Neuropeptide K	+ (A)	0	0	0
α-ANP	+ (P)	+ (P)	0	+
Angiotensin II	± (P)	± (AP)	0	0

* Time-dependent postlearning effects following a single peptide injection.

† Preretention effects.

‡ Effects on non-aversively motivated learning.

§ Effects on retrograde amnesia.

‖ Symbols and abbreviations: +, facilitatory effects; −, inhibitory effects; ±, moderate effects; ?, contradictory findings in the literature; 0, not investigated; x, no effect; A, active avoidance behavior; P, passive avoidance behavior.

of learning and oxytocin, ACTH, and β-endorphin for social components of learning. Therefore, it should not be surprising that there are many biological correlates of learning and memory and that these biological events are also correlated with other psychological constructs (e.g., search for food and water, recognition of offspring, search for mates).

Memory representations are largely determined by the organization of critical attributes, and the neuronal network representing memory is normally in an inactive state until it is activated by the triggering of appropriate attributes. During the state of activation, a number of important features (e.g., duration, extent, and rate of activation) are determined by arousal, motivational, or attentional processes. Prolonged and extensive activation can also trigger consolidation processes which, in turn, can alter the neuronal network representation of memory. The hypothesis has been proposed that some neuropeptides do not directly affect information processing per se but modify it through motivation (motivational states are inferred mechanisms postulated to explain the intensity and direction of a variety of complex behaviors), attention, or arousal. For example, ACTH/MSH peptides are thought to affect motivation and attention through an increase in arousal and CRF is thought to act via sympathetic activation. Vasopressin (Sahgal and Wright, 1984) and behaviorally active vasopressin fragments (Skopkova et al., 1991) may also have an immediate effect on arousal, which, under certain circumstances, may have a functional significance (this effect can be clearly distinguished from direct effects of vasopressin on learning and memory processes). These peptides may act either directly on the reticular formation (Urban and De Wied, 1987) or indirectly via the nuclei of the autonomic nervous system (De Wied et al., 1993). The recent hypothesis that neuronal peptides are often not released under basal conditions but become released as auxiliary messengers in synaptic signaling when activated (Hökfelt, 1991) is in complete agreement with their putative role in biochemical events of information processing, arousal, attention, or motivation.

A third aspect of specificity is related to the selective involvement of brain structures, in which neuropeptides exert their effects on learning and memory processes. This aspect, however, cannot be viewed independently of the other (behavioral and neurochemical) aspects of selectivity, because cortical and limbic structures are primarily involved in mechanisms of information processing and in aspects of emotional behavior, whereas arousal and activity are mainly determined by the ascending reticular activating system. The available evidence confirms that some neuropeptides exert highly specific local effects in the brain with respect to their action on learning and memory processes. Locus specificity appears on three levels:

1. Some brain nuclei show high sensitivity for a particular neuropeptide. For example, vasopressin and behaviorally active fragments of this neuropeptide very sensitively modulate memory processes when microinjected into the ventral or dorsal hippocampus, whereas other (sometimes adjacent) brain nuclei are insensitive to the same peptide. Local sensitivity could be found with other peptides as well. Examples are oxytocin (septum, hippocampus), ACTH (thalamus), CRF (locus coeruleus), CCK (cingulate cortex), NPY (hippocampus, septum), VIP (hippocampus), substance P (amygdala, substantia nigra), and galanin (septum). In most of these cases receptors have been found for the effective neuropeptide, and one must also assume that the interaction of the neuropeptide with its own receptors took place in a brain region that is intimately involved in learning and memory processes. Peptide-receptor interactions do not necessarily induce changes in information processing. There are brain areas that are "silent" in this respect, but here neuropeptides may induce a variety of other central nervous system effects, e.g., on cardiovascular regulation or on thermoregulation. For example, vasopressin in the lateral septal area modulates memory processes, whereas the same neuropeptide microinjected in the adjacent ventral septal area has powerful effects on thermoregulation (Pittman et al., 1988).

2. A neuropeptide or, conversely, the local absence (neutralization) of a neuropeptide in a brain region may selectively affect a particular aspect of memory processes

(e.g., antivasopressin serum in the lateral habenular region attenuates retrieval, but not consolidation; Van Wimersma Greidanus and Baars, 1993). Whether this means that the retrievability and the consolidation of a given piece of information is under the control of different neuropeptides or whether retrieval and consolidation depend on additional attributes (arousal, attention, motivation) affected by these neuropeptides at a different intensity remains an open question at this moment. Another example is the differential sensitivity of a brain region to the same neuropeptide (e.g., following local microinjection of a behaviorally active vasopressin fragment into the ventral hippocampus, 8-fold higher amounts of peptides were required to modulate consolidation than retrieval; Kovács et al., 1986). However, the possibility that consolidation and retrieval use different brain pathways cannot be ruled out.

3. Following local microinjection into different brain structures, the very same neuropeptides may induce principally different (occasionally opposite) effects on learning and memory processes, using the same behavioral paradigm. Examples are available for oxytocin which attenuates passive avoidance behavior following microinjection into the dorsal hippocampus but facilitates this behavior when applied into the dorsal septum. NPY enhances memory following rostral hippocampal and septal microinjections but promotes amnesia when given into the amygdala or caudal hippocampus. These types of effects confirm the view that it is not the chemical structure of the neuropeptide alone, but its local interactions with various anatomical regions, neurotransmitter pathways, etc., as well as the functional significance of these structures in learning and memory, that determines the final appearance of the effect of the peptide.

A certain degree of specificity may also appear at the level of the interaction of neuropeptides with classical transmitters or other peptidergic pathways in the brain. It is widely accepted that most neuropeptides modulate the ongoing neuronal activity of other transmitters. The physiological importance of these interactions is related to the fact that neuronal peptides have been found to be colocalized with one or more transmitters (for review, see Hökfelt, 1991). It has been suggested that a neuron releases the same combination of transmitters at all terminals (Hökfelt, 1991). It might be that coexisting transmitters and peptides interact in both a synergistic and antagonistic manner, whereby neuropeptides are functioning as auxiliary messengers. A variety of findings support this idea. Of interest are the interactions with classical transmitter pathways known to be closely associated with information processing in limbic and cortical structures (noradrenergic, acetylcholinergic, GABAergic, etc., neuronal pathways). Accordingly, vasopressin has been found to modulate noradrenaline turnover in the terminal projection areas of the dorsal noradrenergic bundle (Kovács et al., 1979b), and the effects of this neuropeptide were no longer present after destruction of the dorsal noradrenergic bundle (Kovács et al., 1979a). The same pathway has also been implicated in the effect of CRF on arousal and anxiety (Chen et al., 1992). Behaviorally relevant interactions were also demonstrated with other neuronal peptides [e.g., CCK with dopamine, galanin and NPY with acetylcholine in the neocortex (Hökfelt, 1991), NPY with GABA in the hippocampus]. The role of neuropeptides as neuromodulators might be to coordinate activity of neuronal processes involved in learning and memory. This is in accordance with the finding that neuropeptides (or the absence or neutralization of endogenous neuropeptides) never induce "all or none" type effects in information processing. Accordingly, the result of different peptidergic inputs that modulate neurotransmission might be part of synaptic plasticity.

Despite intensive experimentation and theorizing, the discussion of the role of neuropeptides in learning and memory processes makes no claim to completeness. One of the conclusions is that the mammalian brain does not possess a single neuropeptidergic mechanism that could account for the modulation of learning or memory processes. On the contrary, a symphony of neuropeptides of different chemical nature, localization, and origin seem to act in concert with each other and with classical transmitters, and in some instances one of them may become more effective or even specific in a particular behavioral situation. What makes the role of some of these neuropeptides very attractive is that they may contribute to plastic changes in the connectivity of neurons whose relationships are being reconstructed during learning and memory formation. In addition, neuropeptides are also likely to participate in physiological processes and biochemical and anatomical events, central and peripheral signaling, which are, under many conditions, closely related to and essential for learning and memory. This, in a broad sense, might not only include adequate behavioral reactions to conditioned stimuli but processes involved in drug and alcohol tolerance, muscle hypertrophy as a result of exercise, or antigen-antibody reactions. Although it is far too early to determine their exact roles, there exists abundant evidence that neuropeptides modulate learning and memory processes at the behavioral, the cellular, and the synaptic level. The belief that biology, in general, and neuropeptide mechanisms, in particular, are important for an understanding of some of the most fascinating and important of all human psychological functions provides a strong motivation for all of those who devote their research to learning and memory.

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