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Review article

Neuropeptidases, Stress, and Memory—A Promising Perspective

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Abstract: Stress has been demonstrated to be a key modulator in learning and memory processes, in which the hippocampus plays a central role. A great number of neuropeptides have been reported to modulate learning and memory under stressful conditions. Neuropeptidases are proteolytic enzymes capable of regulating the function of neuropeptides in the central and peripheral nervous system. In this regard, a number of neuropeptidases, i.e. angiotensinases, oxytocinase, or enkephalinases, have received attention. Their involvement in stress and memory processes is a promising perspective, as it is possible to influence their activities through various activators or inhibitors and, consequently, to pharmacologically modulate the functions of the endogenous substrates that are involved. The present review describes the key findings showing the involvement of neuropeptides and neuropeptidases in stress and memory and highlights the role of the hippocampus in these processes.

Keywords: stress; memory; hippocampus; aminopeptidases; angiotensins; oxytocin; vasopressin; enkephalins

1. Stress and Memory

In order to increase the chances of survival under stressful conditions, the body coordinately responds to maintain homeostasis (i.e. the internal environment stability) despite changes in the external surrounding [1]. Allostasis is the process of achieving stability or homeostasis through

anticipatory adjustments connecting, among others, various brain corticolimbic regions, the hypothalamic-pituitary-adrenal (HPA) axis, and the autonomic nervous system (ANS) [2]. Allostasis is essential to maintain viability in a changing environment.

Although an unspecific basal response exists under the multiplicity of various stressor stimuli, important nuances diversify the response. Thus, different stressors may be perceived by diverse sensory pathways and act upon the disparate brain regions responsible for the resultant response. Thus, the stressors can be divided into two classes: stimuli that require a rapid response to avoid an immediate danger and directly involving the hypothalamus and other areas of the brain stem and stressors that require emotional and cognitive processing before sending a response. The latter class of stressors involve higher regions such as the prefrontal cortex, amygdala, or hippocampus [3,4]. These brain regions constitute the corticolimbic circuitry, which is particularly susceptible to the influence of stress through modification of their interactions which consequently may alter not only the central, but also the peripheral functions in which they are involved [3–8].

It has been demonstrated that stress exerts a marked influence (facilitating or impairing) on learning and memory, which is dependent on factors such as source, stressor duration, intensity, and timing of exposure, and learning type [9,10]. For example, the amygdala and hippocampus act in concert to form memories of emotional experiences which activate the interaction between these brain regions and promote the consolidation of memories. Moreover, acute stress, such as brief periods of restraint, may intensify memory formation while chronic stress may impair it [11].

Among the brain regions involved in the stress response, the hippocampus is especially sensitive and is critically involved in memory formation [12]. Stress affects the hippocampus and the effect is dependent on the type of stressor and on its acute or chronic timing. Stress influence may lead to changes in hippocampal morphology [13], alteration in the connectivity with other brain regions [14], or even variations in hippocampus-peripheral neuroendocrine connections [8].

Multiple animal models have been developed to study different types of stress, of which the most common is restraint stress. In this model, animals are introduced into cylindrical, ventilated tubes and kept immobilized for different time periods in order to induce acute or chronic stress. This model produces stress with a low rate of adaptation and high levels of anxiety following the stress period [15,16].

A broad variety of factors, including a great number of neuropeptides, have been reported to be modulators of memory in stressful conditions [17,18]. Among the factors involved in the stress response, the neuropeptides angiotensin, enkephalin, and oxytocin play key roles through their action as either anxiogenic or anxiolytic agents [19–24]. These peptides are partially regulated by the proteolytic enzymes angiotensinase, enkephalinase, and oxytocinase [25–28]. However, the influence of stress on the neuropeptidases which regulate the neuropeptides in brain regions directly involved in the stress response and memory processing is poorly known. Only few indirect studies concerning the involvement of these enzymes and the influence of stress on memory processes have been reported [7,8]. In the next sections, we share a brief review of the peptides involved in stress and

memory, with particular attention to the contribution of the aminopeptidases involved in these processes at both central and peripheral levels.

2. Neuropeptides, Stress, and Memory

2.1. Angiotensins, stress, and memory

The components of the Renin-Angiotensin System (RAS) have been found in the brain where it is firmly established that they are synthesized independently of peripheral sources [23,24,28]. As summarized Figure 1, angiotensin I (Ang I), produced by the action of renin on its substrate angiotensinogen, is metabolized to Ang II by the activity of angiotensin converting enzyme (ACE). Ang II is hydrolyzed by aminopeptidase-A (AP-A) to produce Ang III which is converted to Ang IV by aminopeptidase-M (AP-M). AP-M also acts on Ang IV to generate new Ang fragments that are currently without known function. Ang I may also be converted to other active angiotensin peptides, such as Ang 1–7, by neutral endopeptidase (NEP). Ang 1–7 may also be derived from Ang II by the action of the ACE homolog ACE_2. Focusing only on the Ang metabolites cited above, the angiotensin 1 receptor (AT_1) binds mainly with Ang II, but can also bind Ang III and Ang IV. The AT_2 receptor binds primarily Ang III and Ang II, but is also able to bind Ang IV. Finally, the AT_4 receptor, identified as insulin-regulated aminopeptidase (IRAP), binds exclusively to Ang IV, whereas the Mas-receptor binds specifically to Ang 1–7 [28,29]. Ang IV and the hemoglobin β-chain fragment Leu–Val–Val-hemorphin 7 (LVV-H7) are both endogenous competitive inhibitors of AT_4 receptor, but are not substrates of the enzyme IRAP [30].

Studies on angiotensin and stress have primarily been centered on the behavior of central and peripheral Ang II. The AT_1 receptor has been detected in brain regions directly involved in the stress response and in the sympathetic nervous system. Blockade of AT_1 receptors inhibit the stress response and has peripheral consequences, as well as being anti-anxiogenic in animal models. Therefore, the use of AT_1 receptors antagonists has been suggested as a possible therapy for stress-induced disorders [24].

Regarding the influence of the RAS cascade on memory, Ang II, acting through its binding to AT_1, impaired memory, whereas when Ang IV bound to AT_4, memory was improved. Compared to Ang II, Ang III is less efficient at the impairment of the memory processes. In contrast, the binding of Ang 1–7 to the Mas receptor improved memory processes. All of angiotensin's effects are exerted at the hippocampal level [23,31]. More recently, and in contrast to previous observations, De Bundel et al. [32] proposed that Ang IV and LVV-H7 improve memory processes through their binding to the AT_1 receptor or IRAP/AT_4 receptor, respectively.

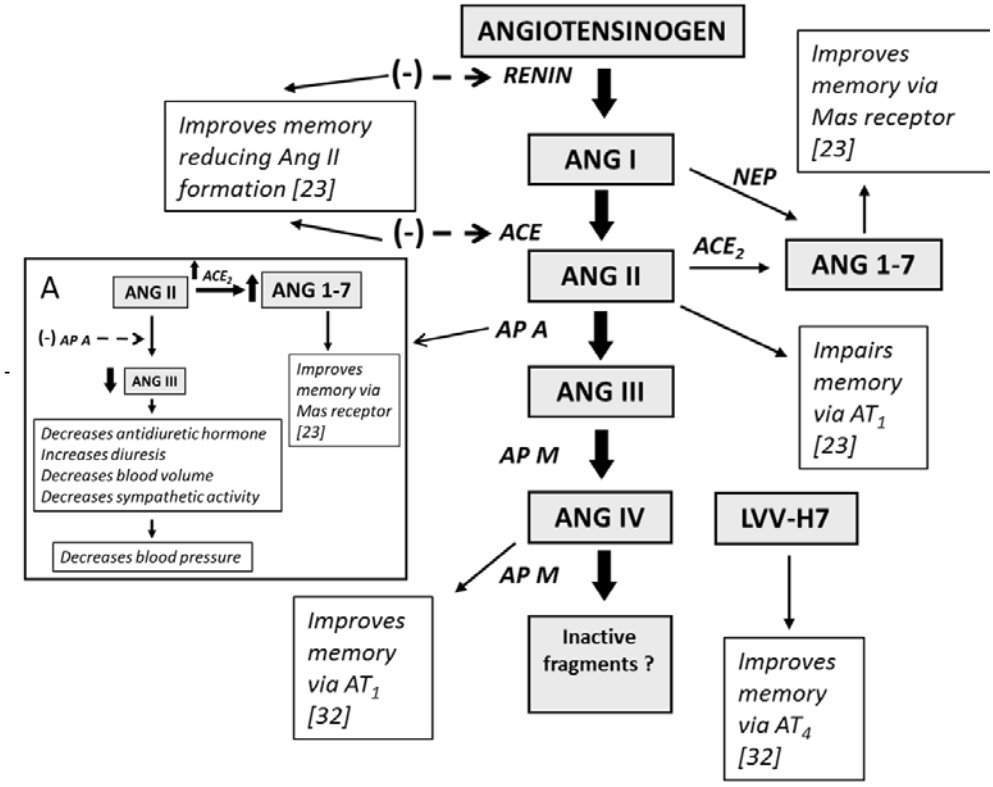

Figure 1. The RAS and memory. Simplified scheme of the renin-angiotensin system (RAS), highlighting the peptides, enzymes, and receptors hypothesized to be involved in stress and memory processes. The possible influence of RAS components, as well as that of inhibitors ("-"; denoted by discontinuous arrows) of certain neuropeptidases on memory is also indicated. The possible consequences of AP-A inhibition on memory are indicated in box A [65,66] (See text for abbreviations).

2.2. Enkephalins, stress, and memory

There is consensus on the role of opioid peptides in the regulation of the stress response at behavioral, autonomic, and endocrine levels. Opioids seem to decrease the autonomic and neuroendocrine responses induced by stress by inhibiting or stimulating the sympathetic or parasympathetic activity, respectively. Opiates dampen the feeling of anxiety and the component of pain without removal of the painful sensation. In fact, the high content of enkephalins in the limbic system suggests a direct role for them in the stress response. Enkephalins may participate in the allostatic response to stress, anticipating stressors and therefore reducing their negative impact. The functions of the whole enkephalinergic system, including enkephalins, their regulating neuropeptidases, and their receptors, are necessary for the adaptation of an organism to stress. Different types of stressors modify enkephalins, their receptors [33,34], and as discussed later, the proteolytic enzymes that regulate their functions. More than three decades of investigation on opioid

peptides have demonstrated their involvement as modulatory substances in learning and memory processes, either enhancing or impairing learning and memory depending on the experimental conditions [35–37]. Stressful conditions are variable depending on the type of stress and it is thought that under acute stress conditions, opiates improve memory consolidation, whereas under chronic stress situations, opiates impair memory processes [37].

2.3. Oxytocin, stress, and memory

Considering the positive role assigned to oxytocin for its role as an anxiolytic agent in social behavior and stress regulation, this peptide has received increased attention due to its possible therapeutic use in several psychiatric disorders [38]. Numerous data link oxytocin with stress control. In response to several stressors, such as restraint stress, oxytocin increases at both central and peripheral levels [39,40]. In humans, increased oxytocin reduces the consequences of the stress response, including elevation of blood pressure [41], decreases cortisol release [42], and increases parasympathetic nervous system activity [43]. In animal models, oxytocin diminishes the neuroendocrine stress response of the HPA axis [21], an effect which may involve several corticolimbic areas, such as the prefrontal cortex, amygdala, and hippocampus [44]. Based on studies which demonstrated that intranasal administration of oxytocin reduces the activity in the amygdala [45] and diminishes the connectivity between the amygdala and brain stem [46], it is speculated that oxytocin may inhibit the amygdala and, consequently, attenuate the hypothalamic response to stress [47]. Other investigations also suggest that oxytocin increases the connectivity between amygdala and prefrontal cortex [48]. Studies on oxytocin and memory in mice lacking oxytocin demonstrated remarked social memory impairment without deficits in non-social memory [49]. Oxytocin's influences on memory involve brain regions including the hippocampus, amygdala, and prefrontal cortex. However, the mechanisms by which oxytocin exerts its effects are still speculative. Some authors suggest such effects may simply be linked to the reduction of anxiety, whereas other investigators propose that oxytocin produces its effects through a temporal inhibition of working memory [50]. If working memory, which is dependent on prefrontal cortex function, inhibits the automatic impulses to trust, then oxytocin may facilitate positive social behaviors [50]. Stress activates the HPA axis response of increased cortisol and epinephrine levels which, in turn, may enhance or impair memory depending once more on the type of acute or chronic stress [50]. The levels of oxytocin increase during stress [40] and oxytocin downregulates the HPA axis response to stress [21]. Therefore, if oxytocin inhibits the HPA axis response to stress and if cortisol influences memory, the effects of oxytocin on memory may be modulated by hormones of the HPA axis depending on the type of stress [50].

3. Neuropeptidases, Stress and Memory

3.1. Neuropeptidases

Proteolytic enzymes are enzymes that catalyze the splitting of proteins through hydrolysis of the peptide bonds between amino acids. In agreement with the International Union of Biochemistry and Molecular Biology (IUBMB), these enzymes are included in class 3 due to their hydrolase activity and the subclass 3.4, which includes all peptide hydrolases. These enzymes fall into two main groups: exopeptidases and endopeptidases. Exopeptidases catalyze the cleavage of the peptide bonds of one to two amino acids from a terminal peptide, whereas endopeptidases hydrolyze the peptide bonds of non-terminal amino acids [51]. The substrate specificity of most of the aforementioned enzymes is broad. Therefore, enzymatic activities will be referred to because the same enzyme can act on different substrates. The exopeptidases that require a free α-amino group and release individual amino acids are called aminopeptidases and are the most abundant proteolytic enzymes in the nervous system [52]. Aminopeptidases are located in both the soluble and membrane-bound fractions of tissues and both forms are capable of hydrolyzing the same substrates. Membrane-bound enzymes show more brain heterogeneous distribution than soluble enzymes. The processes regulating each of these forms are different and, thus, may exert different functions. The regulation of membrane-bound enzymes is primarily under nuclear control. Enzymes are directly connected with the functions performed by their substrates and are not inclined to be influenced by variations in the biochemical environment. In contrast, enzymes localized in the soluble fraction have a more homogeneous distribution throughout the brain. Therefore, the aminopeptidase activities in plasma, those localized in the soluble fraction of the cell, in the interstitial fluid, or bound to cell membranes are under the influence of different regulatory mechanisms depending upon their location in brain [29].

Neuropeptides are largely regulated by the action of soluble and membrane-bound aminopeptidases, generically termed neuropeptidases. These neuropeptidases are the most abundant proteolytic enzymes in the nervous system [52]. Despite the fact that low substrate specificity is a limitation in studies involving enzymatic activities, enzymatic analysis is an important tool that reflects the functional status of their endogenous substrates. Knowledge of the functional role of these enzymes is essential to know the function of the neuropeptides they catalyze and offers the possibility of pharmacologically controlling the processes where these peptides are involved by specific enzyme activators or inhibitors [53]. In addition to stress, which is the central objective of the present review, multiple other endogenous and external factors can regulate the expression and activity of neuropeptidases in physiologic and pathologic conditions. These additional factors may impair or improve learning and memory processes.

The knowledge of how these factors modulate both the expression and/or activity of neuropeptidases is imperative for pharmacologically action on such enzymes. For example, alcohol administration modified enkephalinase expression and activity in regions of the mesocorticolimbic system [54]. Also, development and aging produce important modifications in enkephalinase,

oxytocinase, and angiotensinase activity at the synaptic level in rats. Furthermore, there is a marked increase in enkephalinase, oxytocinase, and angiotensinase in early development but a severe decrease in aged animals [55]. Circadian disorders are also associated with impairments of cognitive processes [56] such as learning and memory [57]. Additionally, neuropeptidases exhibited circadian variations dependent on the type of enzyme and the brain region involved [58]. Interestingly, neprilysin (neutral endopeptidase; EC 3.4.24.11) hydrolyzes enkephalins and amyloid-beta peptide, both of which are directly associated with the pathogeny of Alzheimer's disease [59]. Since a decrease in neprilysin led to deposition of beta-amyloid [60], neprilysin activators may be beneficial for the treatment of Alzheimer's disease [61]. In this regard, it has been observed that neprilysin activity is significantly elevated in the brains of mice exposed to an enriched environment in comparison to controls [62] and has also been found to increase with exercise [63].

3.2. Angiotensinases

Angiotensinases are the enzymes involved in the metabolism of angiotensin peptides (Figure 1). In this review, the primary is renin (EC 3.4.23.15), ACE (EC 3.4.15.1), AP-A (EC 3.4.11.7), and AP-M (EC 3.4.11.2) [28]. As previously indicated, Ang IV and LVV-H7 increase learning and memory [30]. Although it was initially proposed that this effect was due to their binding of the AT_4 receptor [64], more recent experimental data suggests that the influence of Ang IV on learning and memory is due to its binding of the AT_1 receptor, whereas the effect of LVV-H7 was undoubtedly due to its binding of the AT_4 receptor [32], which has been suggested to be IRAP (insulin-regulated aminopeptidase), an enzyme with broad distribution in the brain, particularly in the hippocampus [64]. However, other authors have suggested that AT_4 is the growth-factor receptor c-Met, which is also involved in learning and memory consolidation [23].

Considering the influence of Ang II as anxiogenic factor [24] and its negative effect on learning and memory [23], the use of ACE inhibitors, such as captopril or enalapril, in hypertensive subjects not only can reduce blood pressure, but can also improve cognitive functions by reducing the formation of Ang II [23]. Following this reasoning, the beneficial effects of the renin inhibitors, such as aliskiren, on learning and memory could be speculated. Finally, the involvement of AP-A in the formation of Ang III in memory processes may also be hypothesized. Blockade of AP-A with inhibitors of this enzyme, such as EC33 ((S)-3-amino-4-mercaptobutyl sulfonic acid), decrease blood pressure in DOCA salt rats and prevent Ang III formation in the brain with activation of the ACE_2 pathway, but without increased Ang II. In the brain, this gives rise to the formation of Ang 1–7, which bind to the Mas receptor and, thus, can also improve memory [65,66].

3.3. Enkephalinases and oxytocinase

Enkephalinase activity may be analyzed by determining alanine-aminopeptidase to be present in membrane-bound (AP M) [26] or soluble (puromycin-sensitive aminopeptidase EC 3.4.11.14) form.

This enzyme is abundant in brain and is considered to be the major degrading enzyme of enkephalins [27]. In addition, soluble and membrane-bound leucine aminopeptidase activity (EC 3.4.11.1) has also been described to degrade enkephalins [67].

There are several names used to identify oxytocinase. Initially, because the use of cystinyl-beta-naphthylamide as substrate, it was named cystinyl-aminopeptidase (CysAP) [68]. Later, it was demonstrated that leucine-aminopeptidase, purified from the placenta (P-LeuAP) [69], hydrolyzed both oxytocin and vasopressin and was identical to CysAP. On the other hand, IRAP was also identified to be the same enzyme as oxytocinase [70]. Therefore, CysAP, P-LeuAP, and IRAP are all the same enzyme (EC 3.4.11.3) [29] and, as previously indicated, the AT_4 receptor was identified to be IRAP [64]. However, other authors have proposed that the AT_4 receptor was the tyrosine kinase receptor c-Met, which is also involved in learning and memory consolidation [23]. If c-Met is the AT_4 receptor, binding of Ang IV to its receptor AT_4 (IRAP/oxytocinase) results in the inhibition of its enzymatic activity, increases levels of its substrates (oxytocin and vasopressin) and therefore prolongs its action on the memory processes [71]. IRAP and the glucose transporter GLUT4 are colocalized and are both expressed in the plasma membrane, where GLUT4 promotes insulin-induced glucose uptake. It has been proposed that the inhibition of IRAP following its binding to Ang IV increases glucose uptake in neurons and therefore improves cognitive processes. The increased local blood flow, also induced by Ang IV, collaborates with the other beneficial effects of IRAP inhibition on cognitive processes [71–74].

Recently, Hernández et al. [7] reported the possible interaction of enkephalinase and oxytocinase activity in the medial prefrontal cortex, amygdala, and hippocampus of rodents in basal conditions and under conditions of acute restraint stress. These brain areas constitute a corticolimbic circuit involved in the stress response and the memory process. Results (Figure 2) demonstrated that in control animals, there was a marked interaction between the amygdala and prefrontal cortex, without connection of the prefrontal cortex or amygdala with the hippocampus. However, following acute restraint stress, while the amygdala and prefrontal cortex reduced their connectivity, both regions established a marked interaction with the hippocampus. The authors suggested that these interactions between neuropeptidase activities could be established through feedback between these brain regions involving paracrine mechanisms and/or by bidirectional axonal transport of these enzymes [75]. These results may be related to the functional role of the hippocampus in facilitating the formation of new circuits within cortical columns [14]. Modification of the interactions between corticolimbic areas under stress conditions may be important for the connection between emotion and memory formation [76], while the hippocampus may play a prominent role in enhancing memory consolidation [77,78].

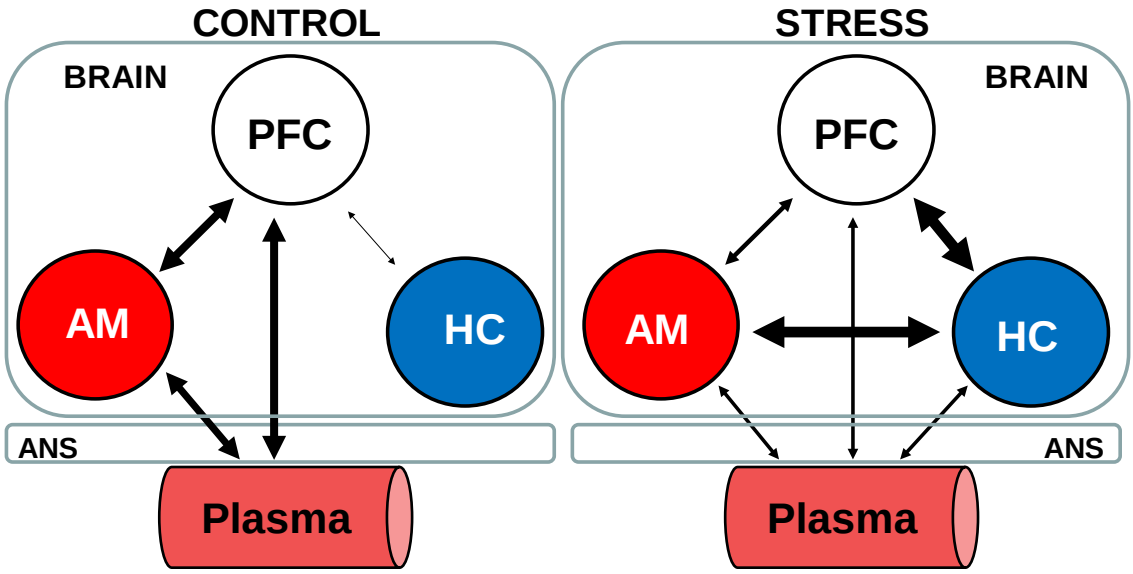

Figure 2. Stress consequences on neuropeptidase interactions. Main interactions of the corticolimbic regions of the amygdala (AM), medial prefrontal cortex (PFC), and hippocampus (HC) between themselves and between the plasma in basal conditions (control) and following acute restraint stress. Line thickness is proportional to the number of correlations. Whereas a marked interaction between the AM and PFC (without interaction of either region with the HC) was observed in brain of controls, under stress, the AM and PFC reduced their connectivity and both regions established a striking interaction with HC. Additionally, in controls, the plasma associated with the AM and PFC (without interaction with HC), but following acute restraint stress, a correlation with the HC also appeared (modified from [7,8]). Since angiotensins, enkephalins, and oxytocin have been involved in emotional and memory processes, changes in the interactions between corticolimbic areas and their regulatory neuropeptidases support an important role for these enzymes in these cognitive processes.

However, since stress causes a coordinated response of the body structured within a proposed neurovisceral integrative model, in which the brain connects with virtually the entire organism by means of reciprocal regulatory mechanisms [75,79], an interaction between brain and plasmatic peptidase activities was assumed [8]. The results confirmed this hypothesis as they demonstrate that there were significant correlations between plasma and the amygdala and plasma and prefrontal cortex without interaction with the hippocampus in control animals. In contrast, after acute restraint stress, a clear interaction between the plasma and hippocampus was observed [8]. These results suggest a parallelism with the interaction observed between the corticolimbic regions themselves, leading to the hypothesis that an integrative response mediated by the ANS occurs between the brain and the periphery [8]. Following acute restraint stress, a marked hippocampal interaction (which did

not exist at rest) was observed between the amygdala, prefrontal cortex, and plasma. Other possible interactions between brain and plasmatic peptidase activities had previously been reported in sham animals with simulated lesions and in rats with the nigrostriatal system lesions, suggesting that peptidases may be secreted into the bloodstream through modulation by the ANS [80].

4. Concluding Remarks

If acute immobilization stress influences memory consolidation, the results demonstrating the potentiation of the hippocampal neural connectivity with corticolimbic regions, as well as the establishment of neuroendocrine interactions between hippocampus and plasma, suggest an important role for neuropeptidase activity in this cognitive process. We can therefore speculate that if there is an interaction between the peripheral and corticolimbic structures involved in the stress response and the modulation of memory processes, the peripheral changes of plasmatic neuropeptidase activities might also be related to those processes. It is also speculated that these effects are exerted through feed-back mechanisms, presumably via ANS.

Angiotensins, enkephalins, oxytocin, and their regulatory enzymes angiotensinases, enkephalinases, and oxytocinase have been demonstrated to be related to the stress response (being either anxiogenic or anxiolytic agents) and to possibly be modulators of memory processes. Therefore, both neuropeptides and their neuropeptidases may constitute targets for the development of new therapeutic strategies for the treatment of stress consequences and memory disturbances using activators or inhibitors of such enzymes. Potentiating or diminishing the action of the neuropeptidase substrates may have beneficial or detrimental effects depending on the neuropeptidase involved. However, stress has been reported to induce the elevation of numerous neuropeptides in brain and plasma, as well as result in elevation of some of their regulatory enzymes, some of which may have opposing effects on memory depending on the stress characteristics Thus, further investigation should be performed to improve our understanding of this complex puzzle.

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Conflict of Interest

The authors declare no conflicts of interest.

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