Neuropeptides in Depression and Anxiety

Subjects: Neurosciences

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Behavioral disorders, such as anxiety and depression, are prevalent globally and touch children and adults on a regular basis. Therefore, it is critical to comprehend how these disorders are affected. It has been demonstrated that neuropeptides can influence behavior, emotional reactions, and behavioral disorders.

neuropeptides depression anxiety gut–brain peptide

1. Gut–Brain Peptides

1.1. Neuropeptide Y (NPY)

NPY is a neuropeptide of the gut–brain axis constituting 36 amino acids, rich in tyrosine residues, with a molecular weight of 4272 Da. It is abundant in both the central and the peripheral nervous systems [1]. NPY plays a role in regulating various systems throughout the body such as memory, anxiety, fear, and stress [2]. The cerebral cortex, locus coeruleus, hippocampus, brainstem, and hypothalamus are the major sites of NPY production in the brain. The hypothalamus has the highest concentration of NPY.

- NPY in Depression

It has been shown that depressed patients' plasma [3] and cerebrospinal fluid [4] levels of NPY are reduced. Additionally, depressed suicide patients had lower levels of NPY mRNA and higher levels of neuropeptide Y1 receptor (NPY1R) and NPY2R mRNA in the prefrontal cortex (PFC) and hippocampus areas [5]. Moreover, a study conducted on 34 adult patients with epilepsy undergoing a temporal lobe surgery for seizure control showed a significant positive correlation of the density of NPY-positive neurons in the basolateral amygdala with depression scores [6]. Furthermore, treatment with antidepressants, specifically venlafaxine and escitalopram, showed increased normalized serum levels of NPY after 8 weeks in depressed patients in comparison to healthy controls, in a study that included 40 patients with depressive and anxiety symptoms and 32 healthy controls. However, following therapy with sertraline and fluoxetine, there were no noticeable changes in NPY levels [7]. Therefore, current research has shown that NPY has an antidepressant impact. Depressive-like behavior in a rat SPS (Single Prolonged Stress) model of post-traumatic stress disorder (PTSD) diminished following NPY intranasal treatment [8]. In the same animal model, another study showed that administration pre-SPS of NPY with HS014, an MC4R (melanocortin four receptor) antagonist, at low doses, averted the development of depressive-like behavior. Furthermore, the administration of NPY and HS014 post SPS reduced the FST (Forced Swim Test) behavior of

"giving up", a sign of depressive-like behavior [9]. Another research study using the SPS rat model of PTSD revealed that intranasal injection of the NPY Y1R agonist [D-His26] NPY stopped depressive-like behavior from emerging. However, intranasal administration of the Y2R agonist (NPY 3-36) was unable to prevent this behavior. Therefore, it is possible that [D-His26]NPY activation of Y1R is sufficient to control or stop depressed behavior [10].

- NPY in Anxiety

The involvement of NPY in anxiety disorders has been proven in multiple recent studies. Serum NPY levels were found to be lower in patients with anxiety and depression compared to healthy controls. Additionally, a study conducted on 616 adults that faced the 2004 Hurricane in Florida revealed that the rs16147 NPY gene, a functional single-nucleotide polymorphism in the promoter region of NPY, was linked to an elevated risk of a diagnosis with generalized anxiety disorder (GAD) with the condition of having been highly exposed to the hurricane [5]. Additionally, a study on two strains of zebrafish (NPY-KO7 and NPY-KO11) with deletions of seven and 11 nucleotides in NPY, respectively, revealed that, under extreme stress, the NPY gene-deficient strains (NPY-KO) displayed anxious behavior such as reduced movement, freezing, and swimming on the tank's edge in comparison to wildtype fish. Moreover, levels of genes associated with anxiety were notably higher in the NPY-KO strain than in the wildtype fish. These findings indicate that a deficiency in the NPY gene induces anxiety-like behavior in zebrafish [11]. This severe anxious behavior after acute stress exposure in NPY-deficient zebrafish was reduced by treatment with Ninjinyoeito, a Japanese Kampo medicine that activates NPY neurons. However, its anxiolytic effects were probably brought about by the deactivation of noradrenaline neurons [12].

1.2. Substance P (SP)

SP is an 11-amino-acid undecapeptide neuropeptide belonging to the neuropeptide family of tachykinin and largely distributed in both the central and the peripheral nervous system [13]. There are three NK receptors, the neurokinin 1 receptor (NK1), NK2, and NK3 [14]. SP acts through its preferred receptor, neurokinin type 1 (NK-1R), which is a transmembrane receptor bound on various body cell types including white blood cells, endothelia of the blood vessels, fibroblasts, and neurons. Through altering cellular signaling pathways, SP functions in the brain as a neurotransmitter and/or neuromodulator. SP plays an important role in many functions such as memory processes, vasodilation, cell growth and proliferation, and behavior modulation. Furthermore, SP acts via G-protein-coupled receptors, which are abundantly expressed in brain regions responsible for behavior regulation, and it acts via inositol trisphosphate/diacylglycerol (IP3/DAG) and cyclic adenosine monophosphate (cAMP) depending on the cell type [13].

- SP in Depression

Recent research has demonstrated SP's role in the pathogenesis of depression. A total of 91 stroke patients were included in a study, and they were split into PS and PSD (post stroke with depression and post stroke without depression). SP plasma and cerebrospinal fluid levels were much higher in PSD patients than in PS patients. The results also showed a positive correlation between the levels of SP and the degree of depression [15]. Furthermore,

a study conducted on two rat models of depression, one exposed to chronic mild stress (CMS) and the other chronically administered the antidepressant clomipramine (CLI), showed that the microinjection of SP receptor antagonist (SPA) into the lateral habenula (LHb) lessened the time of immobility and elevated the time of climbing. These findings suggest that the SPA has an antidepressant effect mediated by the LHb [16]. Moreover, a study on olfactory bulbectomized mice showed that the deletion of NK1 receptor lessened the OB-triggered elevation in exploratory behavior and locomotor activity. Furthermore, the NK1 deletion reduced the OB-induced changes in serotonin within the amygdala. These findings indicate the antidepressant role of NK1 following bulbectomy [17].

- SP in Anxiety

A large number of studies have demonstrated the role of SP in the pathogenesis of anxiety and anxious disorders. According to a study on rats using the elevated plus maze (EPM) model, animals given intra-cerebrospinal injections of the selective NK-1 receptor antagonist L822429 displayed noticeably higher rates of entry into open arms and were more likely to remain in them for longer periods of time than unaffected controls. These findings suggest the anxiolytic effect of the antagonist of the NK-1 receptor [18]. This is in accordance with a study conducted on EPM model of rats that showed the anxiogenic effect of SP via its NK-1 receptor. Their study demonstrated that the injection of SP into the central nucleus (CeA) and the medial nucleus of the amygdala (MeA), but not into the basolateral nucleus of the amygdala, caused anxiogenic-like effects. These findings were confirmed by injecting Sar-MetSP, a neurokinin agonist with high affinity for the NK1 receptor in brain tissue. This indicates that the SP neuropeptide may cause the effects of reducing anxiety via the activation of the NK-1 receptor in the MeA and the CeA [19]. Furthermore, when injected to the dorsal hippocampus (DH), SP presents anxiolytic-like effects, whereas the injection of SP into the ventral part of the hippocampus showed no modification of behavior [20].

1.3. Neurotensin (NT)

NT is a neuropeptide made up of 13 amino acids and was first isolated from the hypothalamus of a bovine. NT is largely distributed through the central nervous system. This neuropeptide has been implicated in various physiological functions such as pain, reward, appetite, memory, and behavioral processes. Neurotensin acts by interacting with specific receptors NTS1, NTS2, and NTS3. NTS1 and NTS2 are G-protein-coupled receptors, whereas the NTS3 is a single transmembrane receptor. NT is highly selective for the NTS1 [21]. This receptor has been at the center of interest of several studies targeting the treatment of mental disorders as it has an influence on the monoamine neurotransmitter system and produces antipsychotic and anxiolytic effects [22].

- NT in Depression

The effect of NT was shown in a study conducted on 160 men and women suffering from obesity with symptoms of depression and anxiety by studying the correlation between these symptoms and levels of NT and xenin, which is an anorexigenic neuropeptide. Their study indicated that both neuropeptides were positively correlated with stress, anxiety, and depression in women but not in males. This suggests a sex-specific association of NT with the

pathophysiology of depression and anxiety [23]. Furthermore, the effect of the NST1 receptor agonist (PD149163) was shown on a FST model of mice. The intraventral tegmental administration of PD149163 caused an antidepressant-like effect in the forced swim test. An animal model with the antidepressant imipramine was used to further demonstrate the NST1 receptor agonist's function. In this model, the agonist also displayed an anti-depressive-like effect [22].

- NT in Anxiety

The effect of NT on anxiety has been shown in recent research. A study conducted on the EPM rat model of anxiety showed that the bilateral microinjection of NT into the ventral pallidum had an anxiolytic-like effect at the dose of 100 ng but no effect was noted at the dose of 250 ng. Furthermore, in an OPF (Open Field Test) rat model of anxiety, they injected 35 ng of an NT1R SR 48,692 alone or 15 min prior to NT treatment. The results showed that the antagonist alone had no effect; however, when injected before the treatment with NT, the antagonist inhibited the effect of neurotensin. These findings suggest that NT has an anxiolytic effect acting through its NT1 receptor [24]. Similar results were observed in another study conducted on an EPM model of rats [25]. Moreover, the effect of the neurotensin receptor 1 was further studied in research on an EPM, LBD (Light–Dark Box), and OF anxiety model of rats. Teir study showed that the injection of a NTS1 agonist or NT into the prelimbic region of medial prefrontal cortex (PrL) induced anxiogenic-like effects. In contrast, the injection of an NTS1 antagonist into the PrL had no anxiety-like effect on normal rats but reduced the anxiogenic stress-related effects. Their study also showed that the downregulation of NTS1 in the PrL caused anti-anxiety-like effects in stressed rats. These findings imply that NTS1 in the PrL plays a role in anxiety regulation [21].

1.4. Galanin (GAL)

GAL is a 29–30-amino-acid neuropeptide distributed in the central nervous system of humans and other mammals [26]. GAL appears to play a significant role in the neurobiology of mood disorders, as shown by its colocalization with serotonin in the DRN and with noradrenaline in the locus coeruleus [27]. GAL acts through the activation of GAL1, GAL2, and GAL3 metabotropic receptors that are largely found in the brain of rats. GAL1 and GAL3 have inhibitory effects by acting on a Gi protein inducing a K^+ efflux, thus reducing neurotransmitter release, whereas GAL2 acts by activating a Gq protein, causing an increase in intracellular Ca^{2+} concentration and, therefore, increasing neurotransmitter release mediated by GAL [28]. Hence, the effect of GAL in brain regions depends on the distribution of these receptors. GALR1 is majorly expressed in the locus coeruleus, hypothalamus, ventral hippocampus, and nucleus accumbens. GALR2 is expressed in the hypothalamus and in the limbic system [29]. Contrarily, the hypothalamic–pituitary (HP) axis expresses GALR3 abundantly while the brain expresses it in low levels [30].

- GAL in Depression

The effect of GAL on depressive-like symptoms highly depends on the receptor it is acting on. A study conducted on an FST rat model of depression showed that exposure to stressors induce the release of GAL but the effect on

its receptors varies. In their study, the i.c.v administration of GAL, GALR1 agonist M617, or GALR2 antagonist M871 increased immobility time, whereas the i.c.v. administration of GalR2(R3) agonist AR-M1896 decreased it. These findings suggest that GALR1 mediates the pro-depressive effect of GAL, while GALR2 mediates its anti-depressive effect. [27]. On the basis of the findings of their study, a subsequent study using the FST rat model of depression revealed that the intra-DRN injection of galanin and a GAL2 agonist (AR-M1896) resulted in an antidepressant effect during the forced swim test, whereas the intra-DRN administration of a GAL1 agonist (M617) had no effect. Additionally, the OFT (Open Field Test) rats' locomotor activity was unaffected by the intra-DRN delivery of AR-M1896 and M617.Furthermore, an intra-DRN pretreatment with the selective GALR2 antagonist M871 reduced the antidepressant effect of GAL. These findings suggest that galanin exerts an antidepressant-like effect in the dorsal raphe nucleus via its GAL2 receptors [31].

- GAL in Anxiety

Similar to how it affects depression, GAL's impact on anxiety is dependent on the receptor it is acting on. In contrast to the deletion of GAL2R, the loss of GAL3R led to anxiety-like symptoms in mice [32]. The intra-DRN administration of GAL1R agonist M617 improved inhibitory avoidance in ETM and OF anxiety model of rats, indicating an anxiogenic effect. However, anxiolytic-like effects were produced by the intra-DRN infusion of the GAL2R agonist AR-M1896. Neither of these agonists had a significant influence on OF's locomotor activity or altered ETM's escape behavior. Moreover, the prior treatment with WAY100635, a 5-HT1A antagonist, via intra-DRN infusion decreased the anxiolytic effect induced by AR-M1896 in rats tested in the ETM. This suggests that the anxiolytic effect mediated by GAL2 receptors depends on the serotonergic systems [33]. Furthermore, on an EPM anxiety model of rats the intra-dorsal hippocampal administration of GAL caused anxiogenic effects, while the administration of GAL2R antagonist M871 had anxiolytic-like effects. M871 therapy, on the other hand, prevented the GAL-induced anxiogenic effect in the dorsal hippocampus [34]. Furthermore, a study conducted on 597 subjects who handed in their DNA samples showed a significant association between anxiety and the GAL rs948854_C–rs4432027_C haplotype and the rs1042577_T single-locus allele, respectively [35].

2. Hypothalamic Releasing Hormones (HRH)

2.1. Corticotrophin-Releasing Factor (CRF)

CRH is a 41-amino-acid hormone regulated by the HPA axis [36]. CRF functions as a hormone when secreted in the parvocellular neurons of the hypothalamic paraventricular nucleus. However, when it is secreted in other brain regions, it acts as a neurotransmitter. CRF mainly acts through two different receptors CRF1 and CRF2 [37]. CRF's involvement in depression and anxiety have been demonstrated in recent studies.

- CRF in Depression

The involvement of CRF in depression and depressive-like symptoms has been well demonstrated in the majority of studies. A corticotropin-releasing factor 1 receptor blocker, CP154526, and an antidepressant, fluoxetine, were

each given to different groups of rats in the chronic unpredictable mild stress (CUMS) model. In a third group, both medications were given. The findings demonstrated that CP154526 improved locomotor function, decreased immobility time, and boosted sucrose preference. This suggests that CP154526 has an antidepressant-like effect. Moreover, their study found that CP154526 inhibits CRH expression in the serum of CUMS rats and downregulates the expression of BDNF and GAP43 in the hypothalamus of CUMS rats. This suggests that the antidepressant effect of CP154526 may be associated with HPA axis modulation effects such as lower serum CRH concentrations, as well as lower BDNF and GAP43 expression in the hypothalamus [36]. Moreover, the i.c.v administration of CRF in mice noted reduced immobility in TST (Tail Suspension Test) and FST which is an anti-depressive-like behavior. However, in chronically foot-shocked mice, i.c.v administration of CRF had no similar effects. Additionally, floating was reduced in mice but increased in rats when the i.c.v. CRF was used. The responses in rats to the highly stressful environment were reversed by CRF [38].

- CRF in Anxiety

CRF was shown to also be involved in anxiety and anxiety-like symptoms. Stress-induced anxiety-like symptoms were reduced by lowering CRF in the amygdala's central nucleus. Moreover, the reduction of CRF in the bed nucleus of the stria terminalis (BNST) also decreased stress-induced modifications in the CRF receptor expression [39]. In accordance with these findings, another study conducted on juvenile rainbow trout i.c.v injection of CRF showed mouth opening in the subjects, constant opercula flaring, and aggressive head shaking from side to side, all of which are indications of anxiety [40]. Furthermore, in a study conducted on male EPM rats, bilateral injection of CRF into the Fr2 region of the frontal cortex displayed anxiolytic-like effects. Stressin 1, a CF1R agonist, was administered, and the same outcome was seen. Administration of NBI 27914, a CF1R antagonist, however, blocked this effect [41].

2.2. Hypocretin/Orexin

Hypothalamic neuropeptides called orexins, also referred to as hypocretin, are highly expressed in the central and peripheral nervous systems. There are two types of orexin, orexin-A (or OrxA hypocretin-1) made up of 33 amino acids, and orexin-B (OrxB or hypocretin-2) made up of 28 amino acids. Both derive from the same precursor peptide prepro-orexin [42] and are similar in structure. Orexin-A has a higher affinity to the orexin-1 receptor (OX1R), whereas orexin-2 has an equal affinity for both receptors 1 and 2 (OX2R). These receptors are coupled to G-proteins and are found on presynaptic neurons, as well as on postsynaptic neurons. Orexinergic neurons are found primarily in the lateral hypothalamus area (LHA) and posterior hypothalamus, and they project to the entire neuroaxis [43].

- Orexin in Depression

Orexin has been shown to be involved in the pathophysiology of depression. Orexin levels were found to be higher in a rat FSL (Flinder's Sensitive Line) depression model compared to FRL healthy controls [44]. Orexin has also been shown to induce antidepressant behavior through GABAergic ventral pallidum (VP) neurons. Furthermore,

the inhibition of orexin receptors, by microinjecting TCS1102, an ORX1 and ORX2 receptor antagonist, in the central pallidum elicited depressive-like behavior [45]. Additionally, a different study using an FST rat model of depression revealed a connection linking orexin distribution, its mRNA receptors, and depressive state. Results showed that, in the hippocampus, animals that showed more depressive-like behavior had a lower expression of OrxA. In the amygdala, there was a curvilinear association between OrxA and FST. However, a positive correlation was noted between Orx1 receptors and depressive behavior [43].

- Orexin in Anxiety

Several studies have found orexin to be involved in anxiety. Orexin-deficient mice displayed increased anxiety in LBD, OF, and carnivore-induced avoidance tests. They were observed to be normal in terms of fear and safety learning. This shows that orexin plays a role in the manifestation of anxiety [46]. Moreover, a study conducted on 56 adolescents diagnosed with any anxiety disorder and not taking medication and 32 healthy controls showed that orexin-A levels were notably higher in the anxiety group than in healthy controls. A positive correlation was noted between anxiety traits and orexin-A [47]. Furthermore, in a study carried out on an EPM model of anxiety, microinjections of OxA and OxB in the paraventricular nucleus of the thalamus (PVT) reduced open arm time and entries, which is indicative of anxious behavior. This behavior was counteracted by the microinjection in the PVT of CRF antagonists or opioid kappa receptors. Additionally, following a foot-shock stress, microinjection of the Ox2R antagonist TCSOX229 in the PVT showed anxiogenic effects [48].

2.3. Melanin-Concentrating Hormone (MCH)

MCH is a cyclic neuropeptide made up of 19 amino acids [49]. MCH-synthesizing neurons are primarily localized in the lateral hypothalamus and incerto-hypothalamic region. MCH acts through the activation of two receptors MCH receptor 1 (MCHR1) and MCH-R2 that are coupled to a G-protein. The first type of receptor is the only one found in rodents and is highly expressed in limbic brain regions such as the prefrontal cortex, nucleus accumbens, amygdala, and hippocampus [50]. MCH is thought to play a role in the pathophysiology of depression and anxiety.

- MCH in Depression

The involvement of MCH in depression is evident, as injection of a low dose of MCH in the dorsal raphe nucleus (DRN) increased immobility time and increased climbing in a forced swim test model of rats, indicating pro-depressive behavior. As a result, this depressive behavior was reduced after treatment with fluoxetine, a selective serotonin reuptake inhibitor antidepressant. Similarly, MCH immunoneutralization resulted in an antidepressant effect [51]. In a forced swim test model of rats, the depressive behavior elicited by MCH was reversed after intra-DRN administration of ATC0175, an MCH-1 receptor antagonist, or intraperitoneal pretreatment with nortriptyline, a noradrenergic antidepressant [52]. This indicates that the melanin-concentrating hormone induces a depressive behavior in the dorsal raphe nucleus.

- MCH in Anxiety

The MCH neurons of the LHA project to the basolateral amygdala (BLA). Mice developed an anxiety disorder as a result of the chemogenetic stimulation of MCH neurons and the microinjection of MCH intra-BLA. This anxious behavior was, however, decreased by the administration of SNAP-94847, an MCHR1 antagonist. Furthermore, intra-BLA administration of MCH in a chronic acute combining stress model of mice had an anxiolytic effect by boosting anxiety-like behaviors [53]. However, the intra-DRN administration of MCH to an elevated plus-maze model of rats caused no changes in anxiety behaviors [52]. Nevertheless, the central injection of TPI 1361-17, an MCH1R antagonist with high affinity, revealed strong anxiolytic effects in mice using elevated maze and light–dark tests as models of anxiety [54]. Consequently, the MCHR system may contribute to the emergence of anxious behavior.

2.4. Oxytocin (OT)

OT is a neuropeptide, made up of nine amino acids, synthesized mainly in the supraoptic nucleus (SON), paraventricular nucleus (PVN), and accessory nuclei of the mammalian hypothalamus. Numerous brain areas, including the medial amygdala, suprachiasmatic nucleus, BNST, locus coeruleus, and dorsomedial hypothalamus, contain oxytocinergic neurons. Magnocellular neurons and smaller parvocellular neurons make up the two subpopulations of neurons found in the PVN of the hypothalamus. While parvocellular OT neurons project toward brain areas such as the brainstem, spinal cord, or supraoptic nucleus to release OT in a somato-dendritic manner, magnocellular OT neurons primarily project to the neurohypophysis, where OT is secreted into the peripheral bloodstream via neurohemal contacts [55]. OT receptors are found in a variety of peripheral sites, including the adrenal and pituitary glands, as well as central receptors in the limbic area [56]. OT functions as a neurotransmitter or neuromodulator in the central nervous system [57]. The expression of OT and OT receptors has been found to be involved in the manifestation of behavioral disorders such as depression and anxiety.

- OT in Depression

In order to understand the correlation between depression and oxytocin, a study was conducted on 108 Hispanic women who were in their third trimester of pregnancy. Their study showed that 28% of women had potential depression during their pregnancy, and that 23% had potential depression 6 weeks postpartum. OT levels were significantly reduced from prenatal to postpartum in all participants, with the exception of those with potential prenatal depression, who showed no significant variations in OT levels. Moreover, OT levels were significantly higher in women who were anxious or depressed 6 weeks postpartum [58]. Another study, however, discovered that mothers with persistent perinatal depression had markedly increased overall OT receptor methylation than other groups [59]. Another study assessed OT levels in a group of 40 patients (30 women and 10 men) who had been diagnosed with major depressive disorder or a bipolar affective disorder depressive episode, and then compared them to a group of 32 healthy controls (20 women and 12 men). The results showed that serum levels of OT were lower in all diagnosed patients when compared to healthy controls. Moreover, serum OT levels were not modified by the treatment with antidepressant drugs or electroconvulsive therapy. A gender difference was also observed, with female patients having significantly lower OT levels than healthy females, whereas no significant difference was observed between diagnosed males and male controls [56].

- OT in Anxiety

The involvement of OT in anxiety disorders and anxious behavior has been demonstrated in multiple studies. A study was conducted on 56 male soccer players to understand the relationship between anxiety and OT level in human models, and levels of salivary OT and cortisol were measured before and after a soccer match. The results revealed that those who won had significantly less cognitive anxiety, higher self-confidence, and higher OT levels. However, those who lost had lower OT levels but higher cortisol levels [60].

3. Opioid Neuropeptides

3.1. Enkephalin (ENK)

ENKs are endogenous opioid pentapeptides produced in the adrenal medulla and central nervous system. Structurally, there are two different ENK peptides: Leu-ENK (YGGFL) and Met-ENK (YGGFM). These two peptides are derived from a precursor protein called proENK via post-translational proteolytic cleavage. In mammals, five ENK sequences are present in proENK: one copy of Leu-ENK and four copies of Met-ENK. Hence, the proENK gene's activity is magnified when multiple ENK peptides are produced. In general, ENK peptides bind to the delta opioid receptor (DOR) and are involved in pain modulation, neurotransmission, mood regulation, neuroendocrine functions, and movement [61].

- ENK in Depression

Enkephalins, in addition to their analgesic properties, play an important role in stress responses and motivated behaviors. In earlier investigations, participants given a DOR antagonist, which blocks the receptor that ENK normally binds to, exhibited depressive and anxious behaviors. These behaviors were also noted in animals lacking the precursor of ENK (proENK) or DOR [62]. The role of ENK–DOR signaling in modulating depressive behaviors has been studied in multiple brain regions. For instance, rats exposed to foot-shock stress in one study [63] and forced swimming in another study [64] exhibited lower levels of Leu-ENK in the hypothalamus and Met-ENK in the striatum and hypothalamus [64]. Additionally, chronic usage of the antidepressants imipramine and iprindole increased the levels of ENK in NAc in rats, whereas chronic mild stress decreased ENK levels [65]. Furthermore, when given enkephalinase inhibitors in the nucleus accumbens, mice displayed greater resilience to stress in a social interaction test, which was able to reduce depressive-like behaviors. One study looked at the effects of inflicting stress on mice. Overall, these earlier studies point to a critical function for ENK–DOR signaling in the regulation of depressive behaviors and behavioral responses to stress [66].

- ENK in Anxiety

The central nucleus of the CeA contains high concentrations of the endogenous opioid ENK, which may play a role in the regulation of anxiety and fear. Experiments on mice have shown that, when the levels of ENK in the amygdala decrease, the fear, anxiety, and aggressiveness of mice increases. By contrast, increasing the levels of

ENK or reducing its breakdown reduces such behaviors [67]. One study examined the functional role of ENKergic neurons in the BLA by modifying levels of ENK in rats. Findings demonstrated that behavioral abnormalities such as increased anxiety in social interactions occur from the depletion of ENK in the BLA [68]. In another study, a CUS stress model was administered to vulnerable individuals. It is clear that the BLA's ENK expression was not being adequately compensated for. These findings suggest that the adaptability to anxiety and chronic stress is mediated by adaptive mechanisms that allow ENK recovery in the BLA [69].

3.2. Endorphins

Endorphins, also known as the body's natural painkillers, were the first endogenous opioid peptides to be discovered. They are released by the pituitary gland and hypothalamus in response to stress or pain. Endorphins are also strongly linked to states of pleasure, such as those induced by love, laughter, and sex. There are three types of endorphins, with beta-endorphins being the most studied and prevalent. They are best known for their pain-relieving effect and for being associated with exercise-induced euphoria [70]. Endorphins are also known for their functional duality, as they act as hormones in the pituitary gland and as neuromodulators or neurotransmitters in the central nervous system [71].

- Endorphins in Depression

The opioid system is important in mediating social attachment and analgesia, and it may also have an impact on depression. In general, opioid systems can signal reward by releasing endogenous opioids when motivated behavior is displayed. A study examining the brain processes of participants diagnosed with depression found that μ-opioid receptor neurotransmission increases in the anterior cingulate during induced sadness [72]. Beta-endorphin levels, in particular, can be used to diagnose depression, given that individuals with depression exhibit abnormal levels of endorphins. A study observed the effect of the administration of citalopram, an antidepressant, to depressed patients while maintaining a control group of depressed individuals who did not take the medication. Beta-endorphin levels in each group were equal at baseline. After 8 weeks of citalopram treatment, beta-endorphin levels decreased significantly compared to the control group. This indicates a strong correlation between the levels of beta-endorphins and depression [73]. Furthermore, another study examining the relationship between exercise and depression found that regular exercise promotes the release of endorphins, which in turn improved the mood of participants. This suggests that endorphins can be used in therapeutic strategies for depression [74].

- Endorphins in Anxiety

Anxiety disorders are common psychiatric conditions that are chronic and can negatively affect multiple aspects of one's life. The opioid system has an important role in the neural modulation of anxiety. Multiple studies found that exercise contributes to the release and binding of beta-endorphins to their receptor sites in the brain, which promotes reduced anxiety and mood elevation [75]. A study found that phobic anxiety is linked to a significant elevation in patients' plasma beta-endorphin levels. These levels stabilized at normal levels after the anxiety subsided. This is in line with the hypothesis that the homeostatic endorphinergic response to stress and anxiety

functions as an effective mechanism in prolonged exposure therapy for the treatment of phobias [76]. Short-term aerobic exercise has also been shown in multiple studies to help lower anxiety sensitivity, which is the tendency to misinterpret anxiety-related symptoms and worry that they can have severe social, physical, or psychological consequences. Individuals with high anxiety sensitivity might benefit from exposing themselves to the symptoms they fear (such as rapid heartbeat) through regular exercise, thus increasing their tolerance for such symptoms [75].

4. Pituitary Hormones

4.1. Arginine-Vasopressin (AVP)

AVP also known as antidiuretic hormone (ADH), is a nine-amino-acid neuropeptide located in the hypothalamus. It regulates kidney function and water reabsorption. It also regulates blood pressure, osmotic balance, and sodium homeostasis. Several diseases are caused by a disruption in ADH secretion or levels [77]. Furthermore, AVP is thought to play an important role in the pathophysiology of affective disorders, as clinical and postmortem studies have found increased levels of vasopressin in the brain and plasma of depressed and anxious patients [78].

- AVP in Depression

Because it functions as a neuromodulator of the stress response, AVP is heavily involved in mood disorders. For example, AVP levels increase significantly in healthy subjects when they are exposed to severe psychological stressors [78]. Moreover, AVP binds to V1b receptors in the anterior pituitary, which are involved in the activation of the HPA axis. The HPA axis is found to be more active in subjects diagnosed with major depressive disorder, which implies a higher rate of synthesis and release of AVP, driving the axis in such cases instead of CRH. Additionally, patients with major depressive disorder (MDD) have a substantial increase in AVP neurons and V1b receptors [79]. One study enrolled 52 patients with MDD, of whom 18 were hospitalized and 43 were outpatients, to compare AVP levels in healthy and depressed patients. Researchers found that depressed patients had significantly higher concentrations of AVP compared to healthy individuals [80].

- AVP in Anxiety

AVP seems to be involved in daily anxiety-related behavior, as well as anxiety disorders. It is proposed that, if AVP's central release patterns reach an upper limit of a continuum, "normal" anxiety might progress to pathological anxiety, with AVP aiding in this psychopathological process. Additionally, it is believed that genetic susceptibility and dysregulated stress responses contribute to psychopathology. AVP has been shown to play a role in genetic expression in addition to responding to stressful stimuli. In the hypothalamic paraventricular nucleus, an excess of AVP caused by polymorphism was clearly linked to a severe anxiety phenotype [81]. One study found that the AVP receptor V1aR plays a role in regulating anxiety-related behavior and social recognition in mice. Subjects were exposed to stressful and anxiety-inducing stimuli such as an elevated maze, forced swimming, and a lit open-topped box connected to a dark closed box. Mice tended to spend more time in open areas that were well lit, and

they exhibited anxious tendencies when forced to do tasks under pressure or in less illuminated areas. An increase in AVP levels and activation of the V1aR have been linked to increased anxiety in mice [82].

4.2. Adrenocorticotropic Hormone (ACTH)

ACTH is a tropic hormone that regulates cortisol and androgen production. It is produced by the pituitary gland and controlled by the HPA axis. It is associated with many diseases including Addison disease, Cushing disease, and affective disorders such as depression and anxiety [83].

- ACTH in Depression

Because of its effect on the release of the stress hormone cortisol, ACTH has been shown to be extensively involved in mood disorders such as depression. One study compared ACTH levels with the HPA axis. Activity in depressed and healthy subjects found that MDD patients had significantly higher levels of ACTH compared to their healthy counterparts, as well as irregular HPA axis activity [84]. Another study that looked at HPA axis activity during depression enrolled 43 patients with MDD. After 6 weeks of treatments with the antidepressant fluoxetine, ACTH and cortisol levels decreased significantly compared to baseline. Hence, it was postulated that the initial recovery of the HPA axis is mediated by the return of glucocorticoid negative feedback on ACTH levels [85].

- ACTH in Anxiety

Many studies have established a role between anxiety and the release of ACTH. In one study, rat pups were separated from their mothers for 3 h each day for 14 days to examine the effects on adult behavior. Researchers found that maternal separation led to increased ACTH and cortisol levels, as well as abnormal and anxiety-related behaviors in adulthood [86]. According to results of another study, the anxiogenic effects of ACTH peaked while individuals were performing a stressful task. However, it was also shown that chronic administration of the anxiolytic drug chlordiazepoxide decreased ACTH levels, proposing that anxious behaviors result from the action of ACTH in the midbrain and hypothalamus [86][87].

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