Journal of Experimental and Basic Medical Sciences 2021;2(1):62-75

Review

Peptide Hormones and Neurodegenerative Diseases

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ABSTRACT

Hormones are classified as steroid, protein, peptide and polypeptide hormones according to their chemical structures. Peptide and polypeptide hormones: Oxytocin, leptin, ghrelin, corticotropin-releasing hormone, gonadal regulating hormone, vasopressin, cholecystokinin. The pharmaceutical industry has generally made great efforts to develop complex peptide hormone products, and studies have been conducted on different uptake pathways of peptide hormones in psychiatric diseases. Psychiatric disorders, on the other hand, are disorders that change an individual's behavior and lifestyle as a result of the mental and mental problems experienced by the individual. In this review, the effects of peptide hormones on psychiatric diseases such as autism spectrum disorder, attention deficit and hyperactivity disorder (ADHD), depression and anxiety disorder, and the applicability of peptide hormones as therapy will be discussed.

Keywords: Anxiety, attention deficit and hyperactivity disorder (ADHD), autism spectrum disorder (ASD), depression, oxytocin, peptide hormones, psychiatric disorders.

Hormones according to their chemical structure; are divided into an amino acid derivative (amine), peptide-polypeptide structure, protein, glycoprotein, and steroid hormones. Peptide and polypeptide hormones; Hormones such as oxytocin, hormones secreted from the hypothalamus, Antidiuretic hormone (ADH), insulin, glucagon, secretin, gastrin can be given as examples. The structures of most hormones in our body are peptide and polypeptide. Polypeptides consisting of a hundred or more amino acids are called proteins, and polypeptides consisting of a hundred and fewer amino acids are also called peptides.

The endoplasmic reticulum of endocrine cells produces protein and peptide hormones. The first step is to create a preprohormone with no biological action. These prohormones form a small protein called prohormone in the endoplasmic reticulum and are transported in secretory vesicles to be packaged into the Golgi apparatus. Prohormones are broken down by enzymes in the vesicles into smaller and biologically active hormones and non-activated parts. As a result of stimulation of endocrine cell surface receptors with the ligand, the amount of cyclic adenosine monophosphate (cAMP) increases, protein kinases are activated and hormones are secreted. The solubility of peptide hormones in water allows them to reach target tissues easily.[1]

There are seven endocrine glands and hormones are secreted from these endocrine glands. The pituitary gland, which is one of the endocrine glands, is divided into three anterior, middle, and posterior lobes. Six main peptide hormones and less important hormones are secreted from the frontal lobe. These hormones: Somatotropic hormone (STH), Growth hormone (GH), Adrenocorticotropic hormone (ACTH), Thyroid-stimulating hormone (TSH), Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), Luteotropic hormone (Prolactin - LTH), Melanophore-stimulating hormone from the middle lobe (pars intermedia), from the posterior lobe; Antidiuretic hormone and Oxytocin hormone are secreted.

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Cite this article as: Aybüke Yayla M, Arda B, Çağlar Ö, Erbaş O. Peptide Hormones and Neurodegenerative Diseases. JEB Med Sci 2021;2(1):62-75.

doi: 10.5606/jebms.2021.75639

Received : March 15, 2021
Accepted : March 31, 2021
Published online : May 31, 2021

- Thyroid-stimulating hormone (TSH); by affecting the thyroid gland, it releases thyroxine (T4) and triiodothyronine (T3) secreted from this gland. It regulates the rate of intracellular chemical reactions in the body.
- Prolactin: provides the development of the mammary glands during pregnancy together with the estrogen hormone. Provides milk production in breast tissue after birth.
- Luteinizing hormone (LH); secretes testosterone from Leydig cells in males and ovary in females. LH secretion is controlled by a gonadotropin-releasing hormone that is feedback regulated with hormones such as progesterone, estrogen, and testosterone.
- Follicle-stimulating hormone (FSH); provides sperm production in the testicles in males, and the growth of follicle cells in the ovaries during the menstrual cycle in females, and the release of estrogen hormone from follicle cells.
- Antidiuretic hormone (ADH); decreases urinary water excretion by increasing the reabsorption of water from the kidneys.
- Oxytocin hormone (OXT); ensures the contraction of the uterus muscle during delivery, and milk comes from the mammary glands of the mother for the baby to suck after birth.[1,2]

Oxytocin, one of the peptide hormones, is a neuropeptide that plays a role in the bonding of mother and baby, bonding of couples, and social behavior. It acts as a hormone in peripheral circulation and as a neurotransmitter in the central nervous system.[3,4] It is produced in the supraoptic and paraventricular nuclei of the hypothalamus and stored in the posterior lobe of the pituitary gland. From here, it is released into the peripheral circulation, contracting the uterus during labor, and is discharged from the milk ducts during breastfeeding.[5] In the central nervous system, oxytocin is released from neurons extending from the paraventricular nucleus to the amygdala, hippocampus, and nucleus accumbens, resulting in behavioral and psychological effects. There is one oxytocin receptor (OXTR) that has been identified to date. This receptor is distributed in gender and the species-specific manner in the brain and body. Mammary glands, uterine myometrium, gastrointestinal system, heart muscle, and vascular endothelium are the places where OXTR is found in the body. In the brain, the cortex, hippocampus, nucleus accumbens, hypothalamus, limbic system, basal ganglia, medial preoptic area, olfactory bulbus are the areas where this receptor is densely located. OXTR is from the family of G-protein coupled receptors, the receptor binds to two different G-proteins. After oxytocin binds to the receptor, different intracellular processes come into play depending on the location of the receptor in the body. Also, the number of OXTR increases and decreases in some periods of life such as birth and postpartum. Dynamic changes in OXTR expression and activation of different processes within the cell bring along individual differences in the oxytocin system.[6,7] Numerous studies in humans and animals have revealed that oxytocin plays a role in social behavior.[8-10] It is known that the administration of oxytocin increases eyesight in humans[9] and is also effective in understanding the emotions of others and recognizing faces.[10] Another effect of oxytocin is that it reduces anxiety and creates a sense of trust by suppressing stress-induced cortisol release.[8-12]

A double-blind placebo-controlled study in humans found that oxytocin is given intranasally to couples before discussion decreased cortisol levels and anxiety while increasing positive communication.[13] Oxytocin provides the suppression of the fear response via GABAergic neurons in the amygdala.[14] In addition, oxytocin suppresses the autonomic symptoms that occur during the fear response by inhibiting the stimulation of the brainstem.[12-15] However, it has been reported that oxytocin has a role in wound healing and pain relief due to its anti-inflammatory effect.[16,17]

PSYCHIATRIC DISORDERS

Psychiatric disorders occur in the early stages of development or childhood before development. It is a neurodevelopmental disorder that causes personal, social skills, academic or professional dysfunctions. Examples of these disorders are mental development disorder, communication disorders, autism spectrum disorder, attention deficit and hyperactivity disorder, bipolar disorder, schizophrenia, depression, anxiety disorders, obsessive-compulsive spectrum disorder, eating disorders, sleep disorders, and sexual identity depression.[18]

In this review, autism spectrum disorder (ASD), attention deficit and hyperactivity disorder (ADHD), depression, and anxiety disorders are discussed.

AUTISM SPECTRUM DISORDER

Autism spectrum disorder is a neurodevelopmental disorder that begins to show symptoms in the first years of life, characterized by developmental delays and deviations in mutual social interaction, language, and communication, repetitive stereotypes of behavior and interests.[15] In clinical studies, ASD was found to be 4-6 times more in boys than girls, and 2-3 times more in boys than in the population sample.[17-19]

Symptoms in autism spectrum disorder are grouped under two main headings: When we first examine the deficiencies in social communication and social interaction; avoidance of eye contact, inability to use body language and difficulty in understanding, limitation in facial expressions and non-verbal communication, interest and emotion sharing, and inadequate social interaction and emotional reactions. Secondly, when we examine repetitive behaviors and limited activities; Behaviors such as repetitive or obsessive motor behavior, attachment to routines, abnormally obsessive and constant interests in terms of intensity, being overactive or unresponsive to certain sensory stimuli such as sound, texture, or smell are observed.[17] ASD is linked to mutations in some voltage-gated and ligand-gated ion channels that are important in the stimulation of neurons and calcium ion signaling pathways. During development, abnormalities in neuronal excitation can also occur due to changes in neurotransmitter systems. Among such systems, some evidence supports the lack of GABAergic inhibition in autism. GABA is considered to be an important excitatory neurotransmitter causing depolarization of neurons and Ca2+ influx through voltage-gated Ca2+ channels during early development. A deficiency in GABA function can lead to disturbances in the developing brain, which can cause some neurodevelopmental disorders such as ASD. When studies were conducted to develop drugs for the treatment of ASD, it was claimed that a drug called Bumetanide, which was previously developed for the treatment of edema, can also be used in the treatment of ASD symptoms and has been shown in some studies. Bumetanide inhibits the triggering of nerve cells in the adult brain and restricts their communication. It enables the nerve cells to communicate by triggering them during early development. In this way, it contributes to the natural development of the brain by supporting the network formation of nerve cells.[19-21]

THE RELATIONSHIP BETWEEN OXYTOCIN HORMONE AND AUTISM SPECTRUM DISORDER

When studies investigating the effect of oxytocin hormone on deficiencies in social interaction seen in autism were examined, it was observed that oxytocin increased eye contact in two of three studies.[22,23] The effects of oxytocin on emotion recognition in individuals with autism also found that oxytocin infusion was significantly effective in recognizing the emotional content of speech in placebo-controlled studies. While the acute effects of oxytocin given intranasally (nasal drug administration) were evaluated in one of two studies using the mind-reading test in the eyes, adult patients who were given oxytocin for six weeks were evaluated in the other study. In both studies, oxytocin was shown to significantly improve test performance over placebo.[24,25] The effect size was found to be higher in studies where oxytocin was used for a long time.[25] Contrary to these results, in a study conducted on children with autism, participants received a single daily i.n. dose for 4 days. oxytocin was given. In this study, no significant difference was found between oxytocin and placebo groups in the facial emotion recognition test.[22] In both studies evaluating the effects of oxytocin on general functionality in autism, no significant improvement in overall disease severity compared to placebo was found.[22-25] When studies evaluating the effectiveness of oxytocin in autism were examined in terms of side effects, it was seen that oxytocin was generally well tolerated and that there was no side effect that would require medical intervention. Also, in terms of safety, it was found that there was no difference in the way oxytocin is given (i.v. or i.n.).[26] When studies on the effectiveness of oxytocin in autism are examined, it is noteworthy that there are conflicting results. Methodological and personal biological differences may have caused discrepancies between results. According to placebo-controlled studies, the magnitude of the effect of oxytocin on the main symptoms of autism is moderate.[27]

AUTISM SPECTRUM DISORDER TREATMENT

The main goal of pharmacotherapy is to increase the child's adaptive skills and ensure their participation in individual education.[28] In randomized controlled trials with children and adolescents, Risperidone

and Aripiprazole have been shown to have positive effects on overreaction and aggression.[29,30] With this treatment, irritability, aggression, self-destructive and repetitive behaviors improve in the vast majority of cases. These two drugs are in the class of atypical antipsychotics, but drugs in a similar group may not have the same effect. These drugs have many side effects, but metabolic side effects should be closely monitored, especially in long-term use.[31]

SSRIs (selective serotonin reuptake inhibitors) can reduce repetitive behavior, but the findings are inconsistent.[32] Methylphenidate (MPH), atomoxetine, and guanfacine used in ADHD treatment can be used in the treatment of comorbid ADHD in patients with ASD. However, drug side effects are more common in individuals with ASD, and response to treatment is lower.[33] It is estimated that 30 to 70% of patients diagnosed with ASD receive at least one drug treatment.[34]

In a longitudinal study conducted on patients between the ages of 0-24 who were recently diagnosed with ASD in England, it was found that 29% of the patients were prescribed drugs, the most commonly prescribed drugs were hypnotics (9.7%) and stimulants (7.9%) and antipsychotics (7.3%).[35]

When we look at the mechanism of action of stimulated drugs; Stimulant drugs such as Ritalin and Concerta target the dopamine-active transporter gene. These stimulant drugs bind to the dopamine-active carrier and block the transporter. Increases extracellular dopamine and norepinephrine levels. When the ratio of dopamine in the brain increases, impulsivity, and hyperactivity are seen in ADHD decrease.[36]

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder is a neuropsychiatric disorder that begins in childhood and is characterized by inattention, hyperactivity, and impulsivity inappropriate for the age of the person.[37] It is the most common neurobehavioral disorder in primary school-age children, negatively affects normal development and functionality in academic and social fields.[38,39] In a comprehensive meta-analysis study conducted in recent years, it has been shown that the average prevalence of ADHD in the world is 5.29%, and it is seen more in boys than in girls.[40] According to many scientific studies, there is a consensus in the literature that ASD and ADHD are seen frequently together, so the diagnosis of ASD for ADHD is not an exclusion criterion within the scope of DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition).[41] Although ADHD and ASD are two clinically different disorders, genetic, cognitive, and neurobiological impairments/losses show that they have some intersections. Social problems arising from impulsivity, which is one of the main symptoms of ADHD, are very common. Social problems are also one of the main symptoms of ASD. Again, rapid reactions in social communication and misinterpretation of social cues, which are common in ADHD, are also seen in ASD. In a scientific study, it was found that individuals with ADHD have autistic features such as difficulty in reading emotional facial expressions.[42] Although the underlying mechanism is different, impairments in executive functions related to goal-oriented behaviors and planning are seen in both ADHD and ASD. The fact that chromosome 16p13 is between the responsible genes in both ASD and ADHD cases indicates a common genetic link.[43]

Those showing symptoms of attention-deficit; cannot follow the instructions from beginning to end, they have difficulty concentrating on the work or game they are doing, they lose the materials needed for work and activities at home or school, they seem not to listen when you speak, they overlook the details, they appear disorganized, they have difficulty doing things that require mental effort for a long time and they run away from them, they are forgetful, their interest is easily diverted.[44]

Those showing symptoms of hyperactivity; they cannot sit even though they should sit, they have difficulty playing quietly, they run and climb out of place, they talk a lot, they often answer before the question is completed, they always deal with something, they have difficulty waiting their turn, they intervene in events or conversations and interrupt them.[44]

Some disorders are extremely common simultaneously with ADHD. Two-thirds of the patients have another concomitant disorder; 30-50% have behavioral disorders, 20-25% have anxiety disorders, 15-20% have mood disorders, 10-25% have learning difficulties.

Finding another disorder simultaneously requires applying different treatment approaches together. It is necessary to check whether there is any other accompanying disorder in the child diagnosed with ADHD.

Differential diagnoses from other psychiatric diseases:

- Depression (depression in children may present with symptoms different from adults, such as restlessness, irritability, hyperactivity, attention problems, and therefore mimic the ADHD clinic).
- Anxiety disorders (symptoms such as anxiety, restlessness can be confused with ADHD).
- Learning difficulties, mental retardation (this possibility should come to mind only if there are attention problems brought to the school as a complaint by the teacher and there is a history of school failure; teachers can often be confused with 'attention deficit' with the problems related to the child's learning difficulties).
- Bipolar Affective Disorder (confused with ADHD, since it is more common in children with a 'continuous mania' state and progresses with symptoms such as irritability, increased psychomotor activity, and too much speech)

The most striking factor that may be important for ADHD in this development is that the inhibitory effect increases parallel to the decrease in dopamine concentration in the brain with age. The concentration of dopamine metabolites has increased in the cerebrospinal fluid of many ADHD boys. This situation supports the developmental delay hypothesis.

The concept of 'executive functions' can be useful in explaining ADHD symptoms. The concept of executive functions emerged as a result of studies with patients with frontal damage. The executive function concept includes skills such as starting, maintaining, suppressing, prioritizing, organizing, and developing strategies. In summary, the symptoms of individuals with frontal damage are similar to those of ADHD cases. Closed circuits involving the prefrontal cortex, basal ganglia, and thalamus play an important role in executive functions. These circuits are regulated by monoaminergic neurotransmitters, and especially dopamine.[44]

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ATTENTION DEFICIT HYPERACTIVITY DISORDER TREATMENT

Methylphenidate (MPH), which shows a central effect on dopamine by blocking the reuptake of catecholamines through a noradrenergic route, is one of the first-line psychostimulant drugs in the pharmacological treatment of ADHD.[41,45] The most important side effect of MPH is the moderate increase in heart rate and blood pressure.[46,47] In a double-blind randomized study, MPH was found to increase heart rate.[48]

MPH is also effective in the dopaminergic system in the central nervous system. It increases extracellular dopamine levels by inhibiting the dopamine transporter. It is thought to produce dopaminergic effects, particularly in the prefrontal cortex and striatum regions.[49]

MPH is the most commonly researched agent in the treatment of ADHD and has been shown to have a very good efficacy and safety profile in studies conducted to date.[50] It has been demonstrated that tolerance to the most common side effects of MPH such as anorexia, irritability, and headache developed in a very short time. There is no consensus on the response to MPH in cases with ADHD + ASD. According to a limited number of studies, it has been reported that the use of MPH improves ADHD symptoms in patients with ASD.[51]

In another scientific study, in a review evaluating the treatment algorithm in cases with ADHD and ASD, it was revealed that the use of MPH increases side effects and is not beneficial. In conclusion, more comprehensive controlled studies are needed to determine the different factors that play a role in the etiology and the effective treatment strategies to be applied in this group, which constitutes an important clinical subtitle among childhood neurodevelopmental diseases.[52]

THE RELATIONSHIP BETWEEN OXYTOCIN HORMONE AND ATTENTION DEFICIT HYPERACTIVITY DISORDER

In a scientific study conducted on children with ADHD, serum oxytocin levels were found to be lower in the ADHD group than healthy controls. When the ADHD cases using and not using medication were compared, the oxytocin level was found to be significantly higher in the drug-using group. In addition, oxytocin levels were found to be negatively correlated with the total symptom score and the attention deficit score.[53] It has been reported that giving oxytocin to the mother for induction of labor in the perinatal period increases the risk of developing ADHD in the future of the baby.[54] The number of studies investigating the role of oxytocin in the etiology of ADHD is very limited, and to the best of our knowledge, there are no studies on its use for therapeutic purposes.[54]

THE EFFECT OF METHYLPHENIDATE ON GROWTH HORMONE IN THE TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

Stimulant drugs have been used in ADHD treatment for a long time. It has a negative effect on growth hormone.[55] However, the effect of stimulants on growth may also be due to the effect of growth hormone on the cartilage (cartilage tissue). GH stimulates the liver production of somatomedin C, which stimulates cartilage growth in the bone structure. Studies have shown that long-term use of stimulants does not affect somatomedin C levels.[55,56] In studies on this subject, it has been reported that MPH moderately reduces the expected height and weight in the early period, and this side effect decreases over time.[55] In most of the studies evaluating the growth rate in terms of height during the use of MPH; It was reported that the growth rate was negatively affected in the early period of the treatment, however, this rate became normal in the later periods of the treatment.[55] It has been reported that disruptions in height increase are highest in the first 6 months of treatment, however, normalized between 30 and 42 months of treatment. In another study, it was reported that 2-year MPH treatment caused a delay in expected height, a few months of interruption to drug therapy accelerated growth, and growth delay was balanced.[57] Children who received 5-year MPH or Amphetamine therapy and had delays in height were reported to have reached the expected growth curve on measurements 2 years after cessation of treatment.[58] Although the use of MPH has been proven to cause adverse effects on body weight, these effects have been reported to decrease over time and do not affect final height and weight in adults.[55] In a scientific study conducted with boys diagnosed with ADHD, it was reported that the dose used had a clear effect on height and that the delay in height growth increased with the increase of the MPH dose.[59]

THE EFFECTS OF METHYLPHENIDATE ON LEPTIN HORMONE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

Leptin is a peptide hormone released from adipose tissue, effective on energy balance, appetite, immune and neuroendocrine functions. Leptin is mainly secreted by fat cells. It was discovered to be the product of the ob/ob gene on the long arm (7q31) of chromosome 7. It is therefore also referred to as the "ob protein".[60,61]

One of the main functions of leptin is to suppress appetite on the central nervous system, especially the hypothalamus. However, they are reported to have very important roles in the regulation of metabolism, sexual development and reproduction, hematopoiesis, immune system, and gastrointestinal functions.[62] Physiological effects of leptin; appetite, energy intake, and consumption are on the neuroendocrine axes and the immune system. Glucocorticoids, insulin, prolactin, tumor necrosis factor-alpha, interleukin-1, and glucose increase the release of leptin. Thyroid hormones, growth hormone (GH), somatostatin, free fatty acids, cold exposure, catecholamines reduce leptin release.[63,64]

In the studies conducted, it has been suggested that it may be an impaired appetite center under the abnormal eating behaviors encountered in individuals with ADHD. The relationship between leptin, which is an important regulatory hormone of the appetite center, and ADHD was investigated due to the high frequency of being overweight and obese in individuals with ADHD.[65] As a result of this study, it has been reported that leptin, which was found low, plays an important role in individuals with ADHD who have decreased cognitive functions and have social difficulties, and that it can be used as a biomarker in individuals with ADHD showing this feature.[66,62]

In a study conducted in 2007, it was investigated whether there is a relationship between appetite

suppression, which is the most common side effect of MPH treatment, which is the first choice in ADHD treatment, and leptin, which is an appetite suppressor.[67] In the study, leptin levels of male, newly diagnosed ADHD patients (before and after short-acting MPH treatment) and a sociodemographic matched control group aged 6-12 were compared. It was stated that leptin levels before the treatment were higher in the ADHD group compared to the control group, but there was no statistical difference. There was no difference in leptin levels between ADHD patients after MPH treatment and ADHD patients before MPH treatment.

In a study investigating the effect of MPH treatment on appetite and appetite-related hormone levels, it was reported that there was no difference between pre-treatment ADHD and the control group in terms of appetite and appetite-related hormone levels of 30 newly diagnosed children and adolescents with ADHD and 20 healthy control groups.[68]

In another scientific study, the pre-treatment leptin levels were found to be similar in the ADHD group and the healthy control group, and when the leptin values in the control group were compared by controlling the BMI (body mass index) after the treatment, the leptin values were significantly lower in the ADHD group compared to the healthy controls. was detected. As a result, it appears that new studies are needed to explain the relationship between leptin and anorexia due to MPH use.[69]

THE EFFECTS OF METHYLPHENIDATE ON GHRELIN HORMONE IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

Ghrelin is a hormone that stimulates growth hormone (GH) release by activating the growth hormone-releasing receptor. Ghrelin also plays a role in energy homeostasis by stimulating appetite, hunger, and food intake.[70,71]

Ghrelin is a hormone that acts directly on the central nervous system and affects behavioral, neuroendocrinal, cognitive, and neuropsychological processes.[72] In the article published in 2010, it was emphasized that Ghrelin may be associated with ADHD symptoms of inattention and hyperactivity by affecting dopaminergic pathways in the brain.[73]

However, there are a limited number of studies that we can have an idea about the relationship between Ghrelin and ADHD. In a study conducted in 2014, it was reported that there was no difference before and after treatment when Ghrelin levels were measured after the initiation of treatment and after two months of treatment in 33 boys aged 6-12 years.[72]

One study found that there was no difference in Ghrelin levels between the ADHD group and the healthy control group before MPH treatment.[74] After 2 months of MPH treatment, ghrelin treatment was found to be significantly higher in patients with ADHD. This study emphasized that Ghrelin is related to the neurobiological mechanism underlying MPH-related loss of appetite and weight loss. No difference was observed between the medication-free ADHD diagnosed and the healthy control group.[68,72] However, unlike other studies, the study found that the pre-treatment ADHD group had significantly higher ghrelin levels than the control group.[69] In the same study, after 3 months of MPH treatment, after treatment in the ADHD group, the Ghrelin level significantly decreased compared to the pre-treatment. Also, a higher rate of decrease in Ghrelin levels was observed in those with anorexia in the ADHD group compared to those without.[74]

According to a study, it was observed that Ghrelin levels decreased after treatment in the ADHD group. In addition, the fact that there is a positive correlation between Leptin and Ghrelin hormone levels in both pre-treatment and post-treatment groups, and the decrease in both hormone levels after treatment, although not statistically significant, support the literature information that Leptin increases Ghrelin release.[75] However, although there is no significant weight difference after the treatment, the fact that the percentile (growth curve) of the expected weight gain is not known suggests that there may have been a loss of adipose tissue. Loss of adipose tissue may be a reason for the observed decrease in Leptin and Ghrelin levels.

DEPRESSION

When healthy people react emotionally, such as distress, sadness, or grief, to unwanted or disappointing events, these emotions are called depressive feelings. Depressive feelings are a normal part of life. What distinguishes the malaise and moodiness of daily life from depression is the severity and duration of the symptoms in depression. To diagnose depression, the onset of depression is observed when the person's complaints continue for at least two weeks, significant impairment in

social and occupational functioning, and recurrent episodes in most depressive individuals.[76] Depression is not a single disorder, but a cluster of many subgroups. Psychiatric disorders are named with different classification systems. The most accepted classification system in the world is DSM IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition), which is the classification system of the American Psychiatric Association. Depression subgroups according to DSM IV; Major depressive disorder, dysthymic disorder, depression in bipolar disorder, depression due to a general medical condition, depressive adjustment disorder, depressive disorders not otherwise named. The disorder that cannot be named otherwise is also its subgroups; They are divided into premenstrual dysphoric disorder, minor depressive disorder, and recurrent brief depressive disorder.[77]

As a brain disease, depression is a cluster of symptoms in which impaired emotion, thought, behavior, and bodily functions occur as a reflection of impaired brain functions and disorders. Not all symptoms can coexist in every patient. The main symptoms of depression include pessimistic and sad mood, pessimistic thought content, hopelessness, feelings of helplessness, inability to enjoy life, loss of interest, intolerance, forgetfulness, and distraction, lack of energy, sleep, and appetite disorder. In the emotional state, unhappiness, sadness, and pessimism prevail, and anxiety and fears can also be found. There may be feelings of inner restlessness and tension. While there may be crying accompanying the sad mood, some patients complain of not being able to cry. Excessive anger can be seen. One cannot enjoy life. He doesn't want or get bored with the activities he used to enjoy. There is a feeling of emptiness and everything can feel meaningless. With the loss of motivation, it becomes difficult to set and focus on the future goal. There may be negative thoughts about the future. Adverse events in the past often come to mind, and the feeling of regret may intensify. In the present tense, the patient feels worthless, inadequate, or guilty, and has difficulty trusting himself and the environment. Sensitivity increases. Loneliness can be felt. Thinking slows down, causing speech to slow down and decrease. Energy drops, the person gets tired quickly. There may be common body aches. It can be difficult to fall asleep. Even if he falls asleep, there may be interruptions in sleep during the night or waking up tired and not falling back in the morning. Conversely, susceptibility to sleep and prolonged sleep may also occur. There may be a decrease in appetite and weight loss, as well as a need to overeat. Learning something new becomes difficult. Forgetfulness occurs and attention may be impaired. In severe cases, the person can make plans to hurt himself or cause harm. There may be suicidal thoughts/plans.[77]

Regardless of where it is done, all studies show that depression is seen twice as often in women than in men. Although differences between genders are present in all age groups, this difference is more pronounced in the young and middle age group than in the children and the elderly group. Although the reason for this difference between the genders is not known precisely, there are various opinions on this issue. Among the possible reasons, the first thing that comes to mind is the endocrine system. However, it has been shown that the risk of depression increases only in the postpartum and premenstrual periods, and there is no such risk for the menopause period. Studies conducted on this subject indicate that the difference between genders cannot be explained through the endocrine system for now.[78] The average age of onset for depression is 40. The age of onset is between 20 and 50 in the vast majority of cases. Most studies have suggested that depression is less likely to occur in children and the elderly.[79]

BIOLOGICAL EFFECTS

Serotonin (5-HT, 5-hydroxytryptamine), dopamine, noradrenaline, and similar chemicals are responsible for the communication between nerve cells in the brain. Serotonin stimulates all areas of the brain. The limbic brain regions (hippocampus, amygdala, temporal lobes) and the nuclei (thalamus) that play a role in sensory transmission are the most intensely stimulated areas. The neurotransmitter most involved in depression is serotonin. Increasing the amount of serotonin present in the synaptic cleft due to the decrease in 5-HT reuptake in the platelets of depressed patients causes an increase in serotonergic neural conduction.[80]

Noradrenaline originates in half of its cells from the locus coeruleus (LC) in the dorsal pons. It is detected in high concentrations in the hypothalamus and limbic system (amygdala, hippocampus); It is found in most neurons of the sympathetic nervous system and is involved in most body functions.[81] It is attributed to the low level of norepinephrine metabolism, increased tyrosine hydroxylase activity, and decreased norepinephrine carrier density in patients with depression.

Dopamine is found in the ventral mesencephalon in the brain. Dopamine activity is decreased in patients whose role in depression is psychomotor slowing. This dopamine activity is increased with an antidepressant.[80]

TREATMENT

Psychotherapies can be applied to positively change the behavior, cognition, and emotions of depressed people. These types of therapy are; cognitive behavioral therapy, behavioral activation therapy, interpersonal psychotherapy, problem-solving therapy, and non-directive counseling.[82] In addition to psychotherapies, antidepressants are used to treat depression.[83] Antidepressant drugs; monoamine oxidase inhibitors (MAOI), tricyclic antidepressants (TSA), selective serotonin reuptake inhibitors (SSRI), selective noradrenergic reuptake inhibitors (NRI), noradrenaline and dopamine reuptake inhibitors (NDGI), serotonin and noradrenaline reuptake inhibitors (SNRIs) They act as enzyme or receptor inhibitors and reuptake inhibitors, including noradrenergic and serotonergic antidepressants (NaSSA), serotonin 2A antagonists/serotonin reuptake inhibitors (SAGI).[84]

PEPTIDE HORMONES AND DEPRESSION

Corticotropin releasing hormone (CRH)

Corticotropin-releasing hormone (CRH) is a 41 amino acid peptide isolated in 1981. Due to its strategic distribution in the CNS (central nervous system), it has been seen as the basis of autonomic, endocrine, immune, and behavioral factors in mammalian response to stress, and studies have been conducted on this subject. CRF1 and CRF2 (corticotropin-releasing factor 1 and 2) receptor abnormalities are thought to play a role in the pathophysiology of anxiety, depression, eating disorders as well as cardiac and inflammatory diseases.[85]

Studies on the role of CRH in major depressive disorder indicate that there is CRH hypersecretion. When CRH is administered to experimental animals, it has been shown to cause events such as hypercortisolism and major depression-related anorexia, decreased libido.[86,87] In major depressive disorder, there is increased activity in the hypothalamic-pituitary-adrenal axis. As a result of the changes in this axis; Hypercortisolemia, CSF (cerebrospinal fluid) increase in CRH concentration, resistance to cortisol suppression occurs in the dexamethasone (corticosteroid drug) suppression test. In one study, as a result of IV (intravenous-vascular access) or SC (subcutaneous-subcutaneous injection) CRH administration, a response was obtained in the form of an increase in ACTH, β-endorphin, β-lipotropin, and cortisol in the normal subject, while the subject meeting the depression criteria were found to have increased cortisol, ACTH and there was no increase in beta-endorphin levels. ACTH response improves with clinical improvement. Two theories have been developed for the decreased ACTH response to this CRH in depression; According to the former, there is down-regulation of pituitary CRH receptors due to hypothalamic CRH hypersecretion. According to the second hypothesis, the sensitivity of the pituitary to glucocorticoid negative feedback has changed.[88]

Gonadal regulatory steroids (GnRH)

Gonadal regulatory steroids (GnRH) are neuromodulators found in the hypothalamus that regulate sexual behavior as inhibitors or excitatory. It is thought to contribute to the development of the central nervous system as well as to the general control of excitability and anxiety. Irregularities in the hypothalamic Pituitary-gonadal axis are thought to be effective on the endogenous depression and postpartum depression of women in peri and post-menopause. Supporting this, the antidepressant effect of estrogen has been observed in some women.[89]

In the etiology of depression, decreased prolactin secretion, FSH, LH, and testosterone levels in men have also been reported with the administration of tryptophan.[90]

Arginine vasopressin and oxytocin

Arginine vasopressin (AVP) and oxytocin are neuropeptides synthesized in the supraoptic and paraventricular nucleus membrane of the hypothalamus consisting of 9 amino acids.[91] AVP is a hormone that may play a role in the pathophysiology of affective disorders due to its role in adjusting the effects of norepinephrine. AVP is thought to play a role in attention, memory, and learning. The release of AVP is increased by stress, pain, exercise, morphine and nicotine use, and barbiturates; decreases with alcohol intake. Inappropriate vasopressin release may occur spontaneously in some psychiatric diseases for unclear reasons. Increases in central vasopressin are associated with a history of aggressive behavior in humans.[90]

The suprachiasmatic nucleus, which plays an

important role in the regulation of circadian rhythm, and vasopressin, one of its major neuropeptides, have been the focus of attention due to the prevalence of circadian rhythm disturbances in patients with depression. In a controlled study (11 patients - 8 depression, 3 bipolar - 11 controls) on this subject, it was hypothesized that AVP-immunoreactive neurons should decrease in patients with suprachiasmatic nucleus depression, but it was observed that these neurons did not decrease or even increased after the study. Besides, in support of the hypothesis, it has been observed that there is a disorder in the synthesis and release of AVP in depressive cases.[92]

Cholecystokinin (CCK)

It has been suggested that cholecystokinin is a possible neuromodulator of panic attacks, a type of anxiety disorder.[93] CCK-A and CCK-B receptor types in the central nervous system of cholecystokinin have been described.[94,88] The fact that CCK-B receptor antagonists such as CCK-4 and pentagastrin induce panic attacks in humans.[95,96] Studies suggesting that CCK-B receptor antagonists exert anxiolytic effects in experimental animals support the argument that cholecystokinin is a neuromodulator for anxiety disorders.[97,98]

Few articles have been published pointing to the relationship of cholecystokinin with depression. These studies are mostly related to the regulation of antidepressant-like activities of opioids (chemical substances acting like morphine) via CCK-B receptors. Blocking of CCK-B receptors has been shown to increase the antidepressant activities of opioids. A similar effect has not been achieved by the blockade of CCK-A receptors.[99,100]

ANXIETY

Anxiety; experienced in the face of an identifiable or unidentified situation that contains danger to the organism; It is characterized by a sense of anxiety and accompanying physical arousal symptoms. Physiologically, symptoms such as palpitations, difficulty in breathing, rapid breathing, tremors in the hands and feet, excessive sweating, as well as psychological symptoms include distress, extreme excitement, feeling, and fear of a sudden bad event. Physical symptoms such as interpersonal communication disruption, frequent tremors, palpitations, dry mouth, and muscle tension were evaluated as pathological.[101]

Anxiety disorders according to DSM-IV; general medical condition-related anxiety disorders are classified as panic disorder, substance-related anxiety disorder, generalized anxiety disorder, obsessive-compulsive disorder, social phobia, specific phobia, acute stress disorder, post-traumatic stress disorder, mixed anxiety depressive disorder, anxiety disorders not otherwise named.[18,96]

It is an extreme and pervasive state of anxiety accompanied by a variety of somatic symptoms that causes significant impairment of social or occupational functions or significant stress to the patient.[102]

In stressful and fearful situations, the oxytocin system is stimulated, causing oxytocin release in both the central nervous system and the peripheral nervous system.[103,104] In a study conducted, a positive relationship was found between plasma oxytocin level and trait anxiety level in women;[105] Another study found an inverse relationship between plasma oxytocin levels and anxiety levels in men.[106] When oxytocin is given for three weeks in patients with generalized anxiety disorder, a decrease in symptoms has been observed.[107] Oxytocin is thought to reduce anxiety, and this hormone is thought to have anxiolytic (anxiety-relieving drugs) properties.[108] As a result, it can be said that plasma oxytocin level has an anxiolytic effect according to gender.

RESULT

In this review, the relationships between psychiatric disorders (Autism spectrum disorder, Attention deficit, and hyperactivity disorder, depression, anxiety disorder) and peptide hormones (oxytocin, ghrelin, leptin, corticotropin regulating hormone, gonadal regulating hormone, vasopressin, cytokine) were examined. The definitions of psychiatric diseases, stress, anxiety, and many symptoms prioritize most diseases, triggering the disease as a result of problems in the regulation of the receptors, and genetic and environmental factors also cause these diseases. The drugs used in the treatment of psychiatric diseases and the mechanism of action of these drugs were examined. The mechanism of action of methylphenidate used in the treatment of ADHD, methylphenidate delayed growth hormone, there was no similarity in its relationship with Leptin hormone, delayed Ghrelin hormone, and caused the loss of appetite.

Depression is treated with either psychotherapy or medications. Dopamine activity in the brain of sick individuals is increased by an antidepressant.

Vasopressin, one of the peptide hormones, appears to play a role in attention and learning. Depressed patients may display aggressive behavior as a result of impaired synthesis and release of vasopressin. Irregularities in the gonadal regulatory steroids hormone may be associated with an anxiety disorder.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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