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Neurotransmitters and hair loss

Aylin Kayaaltı[1], Oytun Erbaş[2]

[1]*Institute of Experimental Medicine, Gebze-Kocaeli, Turkey*
[2]*Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey*

ABSTRACT

Neurotransmitters are important in regulating the body's functions. They transmit messages between neurons and are a part of the nervous system. They have a variety of impacts on human behavior, psychology, and thought processes. Furthermore, they have roles in our skin which is important for stem cells. Hair stem cells are affected by many factors, including hormones and neurotransmitters. If the release of neurotransmitters or hormones is disrupted, the hair and stem cells are affected quickly. This dysfunction might cause hair loss. Hair loss is one of the most common problems experienced by people all over the world and can be caused by a variety of factors. Further research is needed in order to find a cure.

Keywords: Hair loss, nervous system, neurotransmitters.

The nervous system regulates the organs, sensations, motions, and physical and psychological processes. Nerve cells, also known as neurons, and their neurotransmitters have important roles in this system. Neurons that release neurotransmitters activate nerve impulses. Transmission between two neurons occurs in a small gap between neurons, which is called the synaptic cleft. Electric signals traveling through the axons are converted into chemical signals through the release of neurotransmitters and cause a response in the receiving neuron.[1]

Neurons synthesize neurotransmitters, also known as chemical messengers or chemical transmitters, and vesicles, located in the axon's terminal end, called presynaptic terminal neurotransmitter stores. Signals are transmitted by neurotransmitters from nerve cells to lots of different target cells such as glands, muscles, or other nerves. Neurotransmitters are necessary for the regulation of functions such as heart rate, breathing, sleep cycles, appetite, digestion, muscle movement, and concentration. There is no single type of receptor for any neurotransmitter. On the contrary, lots of different receptor proteins are activated by a given neurotransmitter. Neurotransmitters, when attached to the target cell, trigger an action in that cell. Neurotransmitters are broken down after delivering the messages. Removing the neurotransmitters is necessary for enabling the postsynaptic cell to engage in another cycle of releasing neurotransmitters, generation of a signal, and binding. This annihilation occurs in three ways: diffusion, degradation of the enzyme, and reuptake.[2,3]

Neurotransmitters can be categorized in many ways. They can be categorized into seven titles according to their structures: amino acids, gasotransmitters, monoamines, trace amines, peptides, purines, and catecholamines. They can be categorized according to their effects in three titles: excitatory, inhibitory, and modulatory. Regulation of neurotransmitters' release is controlled by other neurotransmitters, which means they regulate each other. Imbalances or disruptions in this

Correspondence: Aylin Kayaaltı. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.
e-mail: aylin.kylt3@gmail.com

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system can cause many diseases or mental disorders such as insomnia, Parkinson's disease, depression, attention-deficit/hyperactivity disorder, anxiety, dramatic changes in weight and addictions, autism, obsessive-compulsive disorder, amyotrophic lateral sclerosis, memory loss, and hair loss.[4,5]

Hair loss, also known as baldness or alopecia, is a disorder that occurs as a result of interruption in the body's cycle of hair production. Alopecia affects almost half of the men and women in the world, so it is a prevalent problem. It affects the scalp mostly, but it can occur anywhere on the body. Its severity could change from a small area to the entire body.[6,7]

Hair loss can come in a variety of forms. These can be categorized as androgenetic alopecia (AGA), telogen effluvium (TE), anagen effluvium (AE), alopecia areata (AA), tinea capitis, and male or female pattern hair loss. The most common form of hair loss is AGA. The result of the combination of hormones and heredity causes the development of this condition. Alopecia can be temporary or permanent. Temporary hair loss is caused by some reasons such as illness, iron deficiency, stress, cancer treatment, drugs, surgery, or weight loss.[6,8]

Hair loss has quite effects on the patient's quality of life. It is distressing, but it is not life-threatening or deadly. Patterns of hair loss can be obvious like bald patches that occur in AA or more subtle like diffuse hair loss that occurs in TE. Hair loss has some treatments, and one of these is using the drugs minoxidil (MNX) and oral finasteride (FNS).[9] According to a study by Avcı et al.,[10] hair growth in mice is stimulated by using low-level therapy, and it is a possible way of treatment. Additionally, the neurotransmitter norepinephrine (NE) promotes hair follicle growth in an organotypic skin culture model, according to a study by Kong et al.[11] A study published in the scientific journal of the American Academy of Neurology claimed that baldness induced by dopamine treatment may be reversible.[12]

In this review, neurotransmitters, their roles and effects, hair loss, reasons and types of hair loss, and its treatments are introduced, and finally, neurotransmitters' effects on hair loss are discussed.

NEUROTRANSMITTERS

The exact number of neurotransmitters in humans is unknown, but more than 200 have been discovered and more are still being discovered. The research on the gap between neurons, synaptic cleft, led to histological examinations. The synaptic cleft was discovered by O'Brien.[13] The existence of the gap suggested that neuronal communication occurs through chemical messengers traversing the synaptic cleft. Loewi,[14] a German pharmacologist, approved that communication between neurons occurs by releasing chemicals.

Neurotransmitters are released for many different reasons and purposes. Crossing the synaptic gap and binding to the site on the other neuron occurs after release. Neurotransmitters and receptors act as a key-and-lock system. Categories of some neurotransmitters, their names, and effects are shown in Table 1. Neurotransmitters' functions on the receiving neuron can be categorized into three topics such as excitatory, inhibitory, and modulatory. The possibility of the neuron firing an action potential is increased by excitatory neurotransmitters and decreased by inhibitory neurotransmitters. Numerous neurons are affected by modulatory neurotransmitters, also known as neuromodulators, at the same time. Other chemical messengers' effects are influenced by modulatory neurotransmitters as well. Neurotransmitters are removed after the signals are received by degradation, diffusion, and reuptake. The structure of neurotransmitters is changed by enzymes so that it can't be recognized by the receptor during degradation. Neurotransmitters drift away from the receptor during degradation. Finally, in reuptake, all of the neurotransmitter molecules are taken back up by the axon of the neuron that released it.[15,16]

HAIR LOSS

The growing hair undergoes three cycles, anagen, catagen, and telogen. The anagen phase, also known as the growing phase, is usually responsible for more than 80% of the hair on someone's head, and it is possible that the anagen phase lasts from two years to eight years. In the catagen phase, also known as the transition phase, shrinking of the hair follicles occurs, which takes about two to three weeks. In the telogen

Table 1. Categories, names, and effects of neurotransmitters

Category	Name	Effects
Amino acids	Gamma-aminobutyric acid (GABA)	GABA is a naturally occurring amino acid, an inhibitory neurotransmitter due to the effects of blocking or inhibiting brain signals, decreasing the activity of the central nervous system, and playing a role in the regulation of anxiety.[17]
	Glutamate	Glutamate, which is a metabolic precursor for GABA, is an excitatory neurotransmitter that plays a role in neural circuits involved with synaptic plasticity and cognitive functions such as memory and learning.[18,19]
Peptides	Oxytocin	Oxytocin is a peptide hormone and neurotransmitter. It plays a role in social recognition, sexual activity, reproduction, bonding, and childbirth.[20]
	Endorphins	Endorphins, which are the body's natural painkillers, inhibit the transmission of the pain signals and create an energized and euphoric feeling. They are produced in response to pain and can be triggered by some activities such as aerobic exercise. [21]
Purines	Adenosine triphosphate (ATP)	Adenosine triphosphate has major roles in peripheral nerves as a neurotransmitter. It can be considered to be the energy currency of life. It plays a role in autonomic control, sensory transduction, and communication with glial cells.[22,23]
	Adenosine	This naturally occurring chemical acts as a neuromodulator in the brain. It has a prominent role in the cardiovascular system and is involved in suppressing, arousing, and improving sleep.[24]
Acetylcholine	Acetylcholine	Acetylcholine is an excitatory neurotransmitter that plays a role in both the nervous and peripheral nervous systems. It is associated with motor neurons. It has important roles in memory, muscle movements, and learning. Low levels of it are linked with some problems with memory and thinking such as Alzheimer's disease.[25]
Monoamines	Epinephrine	Epinephrine, also known as adrenaline, is both a hormone and a neurotransmitter. It is a stress hormone that is released by the adrenal system. It increases the heart rate and breathing and gives energy to the muscles. It helps the brain to make quick decisions in the face of danger.[26,27]
	Norepinephrine	Norepinephrine plays a role in alerting the body's fight or flight response. It stimulates adrenergic receptors which cause vasoconstriction of the radial smooth muscle of the iris, arteries, veins, or urinary bladder.[28,29]
	Histamine	Histamine plays a role in metabolism, allergic reactions, temperature control, sleep-wake cycle control, and regulating various hormones. It is produced as a part of the response of the immune system against pathogens.[30]
	Dopamine	Dopamine is commonly known as a pleasure or reward neurotransmitter because it is released during pleasurable activities. It is important for the coordination of movements, memory, and learning. Its deficiency can cause Parkinson's disease.[31,32]
	Serotonin	Serotonin is an inhibiting neurotransmitter and a hormone that plays a role in regulating mood, anxiety, depression, sleep, appetite, and sexuality. Selective serotonin reuptake inhibitors (SSRIs) which are a type of antidepressant medication are used for treating depression, anxiety, or panic attacks.[33,34]

phase, also known as the resting phase, shedding of the hair follicles occurs, which takes about two to four months.[35]

It is known that there are many types of hair loss. One of the most common AGA, which includes male and female pattern hair loss. In females, AGA generally does not cause total baldness. Thinning of the hair all over the head occurs, and the hairline does not recede. In males, the loss of hair is in a well-defined pattern, beginning above both temples. The hairline recedes to the 'M' shape with time. Thinning of the hair also occurs at the crown, near the top of the head, and usually causes complete or partial baldness.[36,37]

FEMALE PATTERN HAIR LOSS

Female pattern hair loss (FPHL) is a common reason for hair loss in women that increases with age. According to a study by Ludwig,[38] Female pattern hair loss is classified into three grades. Grade I is the start of a small amount of thinning. Grade II involves the widening of the affected area and increased thinning. Grade III is thinning of the see-through area at the top of the scalp of females. Both androgen-dependent

and androgen-independent mechanisms possibly contribute to the phenotype.[37-39]

Hair loss in women has some signs such as visible daily hair loss on the brush, on the floor, on pillows, in the shower, or the sink, noticing patches of missing hair, including a wider area on the top of the head, seeing scalp skin through hair, a smaller ponytail, and noticable hair breakage. Females who have just given birth or have had chemotherapy, females using certain medications or harsh chemicals, females with genetic tendencies, females older than 40, and menopausal females are more inclined to be affected. Two different things can happen during menopause: growth of hair where it did not before and the start of hair thinning. Levels of estrogen and progesterone decrease and that ensures the increase of androgens and male hormones.[40-42]

Some treatment options are available for FPHL.[41] Firstly, there are two pharmacological options: androgen-independent and androgen-dependent. Minoxidil, which is categorized as androgen-independent, affects the hair cycle, causes premature termination of the telogen phase, and prolongs the anagen phase. There may be side effects such as redness, itching, dryness, or hair growth on areas where it is not wanted. Finasteride, spironolactone, flutamide, and cyproterone acetate are in the androgen-dependent type. Abnormalities in the genitalia of the male fetus can be caused by these medications. Finasteride suppresses androgen activity by restricting total circulating androgen activity and works by inhibiting the 5α-reductase II enzyme. There may be some side effects such as headaches, hot flashes, decreased sex drive, and breast tenderness. Blocking of androgen receptors and inhibition of gonadotropin-releasing hormone (GnRH) are the effects of cyproterone. It may cause side effects such as menstrual disturbances, weight gain, depression, breast tenderness, and gastrointestinal upsets. Spironolactone, a diuretic, inhibits the production of androgen and it may help regrow hair in women. Its possible side effects are fatigue, irregular menstruation, electrolyte imbalances, breast tenderness, and spotting between periods. Flutamide, a potent antiandrogen, is mostly used for treating advanced prostate cancer and hirsutism, and it acts via androgen receptor antagonism. A second option is surgical treatments such as hair transplantation, in which a thin strip of hair from one part of the patient's scalp is removed and is implanted in an area where the missing hair is, and scalp reduction which involves bringing hair-bearing skin closer together by removing the central scalp affected by the alopecia.[40-44]

MALE PATTERN HAIR LOSS

The most common type of hair loss in men is male pattern hair loss (MPHL), also known as AGA. Almost half of the men in the world experience this problem by the age of fifty, but it can occur in puberty as well, and the risk increases with age. Genetics has a significant role in it; according to many observations, the combination of hereditary factors and hormones causes AGA in men.[45,46]

The classical pattern of male hair loss begins at the hairline. The hairline gradually recedes and forms an 'M' shape. Eventually, the hair becomes shorter, finer, and thinner. It creates a pattern that looks like a horseshoe or U-shape around the sides of the head. A team of investigators from Columbia, Rockefeller, and Stanford Universities have found a gene called APCDD1 that causes progressive hair loss via hair follicle miniaturization in childhood. They have also found that a signaling pathway controlling hair growth is inhibited by APCDD1 in mouse models, but it has not been linked to hair growth in humans. This pathway, also known as the Wnt signaling pathway, was targeted by laboratory researchers for stopping and initiating mices' hair growth, but it did not appear to be involved in humans' hair loss. This is an important finding because it is proof that humans and mice do not have the same hair growth patterns. Treatments and research for MPHL or other forms of hair loss will be affected by the discovery of this gene.[47,48]

Many studies have tried to create an ideal MPHL classification throughout the years. These are Hamilton, Norwood-Hamilton, Adapted Norwood-Hamilton, and Basic and Specific. Three variables are important in MPHL classification: detail, practicality, and reproducibility.[49]

There are some treatments for MPHL. For example, MNX is a vasodilator that is also used to treat high blood pressure. When used to treat hair loss, it dilates blood vessels and provides more blood flow to the hair follicles, and it is applied

directly to the scalp. Secondly, oral FNS is a synthetic compound that blocks the conversion of testosterone to dihydrotestosterone which is the most potent androgen affecting the human hair growth cycle, with adverse effects in male pattern hair loss. Thirdly, platelet-rich plasma can be used as a non-pharmacologic treatment for treatment-refractory patients. Hair transplants, wigs, or hats are some other options.[46,49]

TELOGEN EFFLUVIUM

Telogen effluvium is a common cause of temporary hair loss and is a scalp disorder characterized by diffuse, non-scarring shedding of hair, and it was first described by Kligman[50] in 1961. In TE, stress or shock results in more hairs transitioning to the telogen phase. Typically, in this condition, about 30% of the hairs stop growing and go into the resting phase before falling out. So if a person has TE, they lose an average of 300 hairs a day instead of 100.[51,52]

Telogen effluvium can be classified into two groups as acute and chronic according to the duration of the disease. Chronic TE lasts more than six months and often presents in females with thick and moderately long hair; this is because they notice the shed hair more than those with finer or shorter hair. Telogen effluvium does not cause complete baldness, although it may unmask a tendency to genetic balding like in FPHL or MPHL. Acute TE lasts less than six months, and patients who have acute TE present with increased hair loss while washing, combing or brushing hair. These patients often have a concern about baldness.[52,53]

Some causes for TE are drugs, psychological and emotional stress, hyper and hypothyroidism, systemic amyloidosis, hepatic failure, chronic renal failure, inflammatory bowel disease, lymphoproliferative disorders, severe protein, fatty acid, and zinc deficiency, chronic starvation, calorie restriction, and ultraviolet light. There are some treatments and therapeutic options for TE, such as inhibition of catagen, induction of anagen in telogen follicles, inhibition of exogen, MNX, FNS, and topical and systemic corticosteroids.[53,54]

ANAGEN EFFLUVIUM

Anagen effluvium is a form of non-scarring alopecia that arises during the anagen or growth stage of the hair cycle and is generally associated with chemotherapy. After chemotherapy ends, hair usually grows back on its own. Major hair loss may be encountered in extreme cases. Anagen effluvium is equally prevalent among males and females. It does not have sex or regional predilection. There are many causes of AE, such as chemotherapy drugs, radiotherapy, malnutrition, iron deficiency, chronic infections, or oral contraceptives. Suggested treatments for AE are topical MNX solution, scalp cooling during chemotherapy, and cosmetic camouflage of the eyebrows.[55,56]

ALOPECIA AREATA

Alopecia areata, also known as spot baldness, is a common autoimmune disorder where the body's immune system attacks healthy tissues, including hair follicles, and causes hair to fall out in small patches, which may be unnoticeable. However, these patches might connect and then become noticeable. Sudden hair loss may occur on the scalp, eyebrows, eyelashes, face, or other parts of the body. The disease might cause psychological stress. Most people are otherwise healthy. It sometimes leads to complete hair loss in a patch or the entire scalp, which can prevent hair from growing back, but hair regrows spontaneously in many cases. Alopecia areata is not contagious and frequently occurs in people affected by family members, suggesting heredity as a factor.[59,60]

Alopecia areata is not easily treated, and treatment for all cases is not accepted universally. However, Japanese and British treatment guidelines have suggested topical immunotherapy.[59] Intralesional, topical, or systemic corticosteroids are also used in patients with AA.[60] Some other medications such as MNX or anthralin are used for promoting hair growth or affecting the immune system.[61]

TINEA CAPITIS

Tinea capitis, also known as ringworm of the hair or herpes tonsurans infection, is a fungal infection that causes a red ring-shaped rash when it appears on the trunk, extremities (hands, feet, toenails), groin, or face. It is a contagious disease, so people can be affected by an object, a person, or an animal

that contains infectious fungi. The disease is primarily caused by dermatophytes in the genera trichophyton and microsporum that invade the hair shaft. Tinea capitis predominantly affects preadolescent children, with incidence peaking between the ages of three and seven years. It can also affect adults, particularly those who are immunocompromised.[62,63]

Since it does not penetrate the root of the hair follicle, tinea capitis always requires at least four weeks of medication. Griseofulvin was used to treat tinea capitis. However, it is not available in some countries today. Terbinafine, itraconazole, and fluconazole are new antifungal agents as effective as griseofulvin. However, these are less effective on the genus microsporum. Using topical agents such as ketoconazole, povidone-iodine, and selenium sulfide shampoos may reduce spore transmission.[63,64]

NEUROTRANSMITTERS' EFFECTS ON HAIR LOSS

It has been demonstrated that psychological factors cause hair loss, and stress may promote hair loss as a cofactor. Higher brain centers activate the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axis in response to psychological stress. Our skin is a neuroendocrine regulated by many factors such as hormones, neurohormones, neurotransmitters, and SAM and HPA axis, and it expresses elements of these axes, including proopiomelanocortin (POMC), corticotropin-releasing hormone (CRH), CRH receptor 1 (CRHR1), and adrenoreceptors. Neurons are induced by stress-induced signals to produce and release CRH. Then CRH binds to CRH-R1, and the release of POMC-derived adrenocorticotropic hormone is induced, which stimulates glucocorticoid synthesis and secretion. The release of neurotransmitters epinephrine and NE from the adrenal medulla is increased by the activation of the SAM axis and stimulates the sympathetic norepinergic nerves to promote further NE secretion. According to a study by Kong et al.,[11] normal hair growth is promoted by signals from the sympathetic nervous system, which stimulates the proliferation of keratinocytes in the epithelium and hair follicles, and initiation of the hair follicle in cultured neonatal skin is promoted by NE.

Compared with the general population, people with hair loss have an increased prevalence of psychiatric disorders, including a major depressive episode, an anxiety disorder, social phobia, or a paranoid disorder. Nervous disorders such as depression may be the result and the reason for hair loss. There are three important neurotransmitters that play a role in depression: serotonin, NE, and dopamine. Irregularities in these neurotransmitters may cause depression, which can cause hair loss at the edges. According to a study by Crowe et al.,[65] understanding the hyperinnervation of the underlying vessels in rabbit skin might be of importance in solving the hair loss problems.

In conclusion, neurotransmitters are known to play a variety of roles and have a variety of consequences in the body. As a result, they can be employed to treat various disorders, which is a promising development. Hair loss is one of these disorders, and it is a condition that could affect anyone. It exists in a range of forms, each of which is dependent on a variety of factors. Scientists are working to develop a cure for this disorder, and neurotransmitters show promise. This potential allows us to explore and find remedies for hair loss, which may also be the solution to psychiatric diseases such as depression or anxiety, since losing hair causes individuals to be despondent. Further research on the subject may allow the treatment of patients suffering from a variety of diseases.

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