ECRONICON OPEN ACCESS

EC NEUROLOGY
Review Article

How does a Brain Chemical Command Gloom and Bloom?

Raghavendra Rao MV[1]*, MM Karindas[2], Ilie Vasiliev[3], Mahendra Kumar Verma[4], Jerryson A Gidisu[5], Dilip Mathai[6], Srikanth Bhandari[7] and Mubasheer Ali[8]

[1]Scientist-Emeritus, Department of Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India

[2]Professor, Department of Oncology, World Academy of Medical Sciences, Mexico

[3]Professor, Department of Internal Medicine, World Academy of Medical Sciences, Mexico

[4]Assistant Professor, American University School of Medicine, Aruba, Caribbean Islands

[5]President and Council Chairman, Department of cardiothoracic surgery, School of Medicine, Kings and Queens Medical College, Ghana, West Africa

[6]Professor, Dean, Department of Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India

[7]Department of Psychiatry, Asha Hospital, Banjara Hills, Hyderabad, TS, India

[8]Consultant, MD Internal Medicine, Apollo Hospitals and Apollo Tele Health Services, Associate Professor Department of General Medicine, Shadan Medical College, India

***Corresponding Author:** Raghavendra Rao MV, Scientist-Emeritus, Department of Medicine, Apollo Institute of Medical Sciences and Research, Hyderabad, TS, India.

Received: May 27, 2022; **Published:** June 29, 2022

Abstract

Neurotransmitters are the diction of our brain. Exclusively, the brain possesses 183 different neurotransmitters. Very low or absence of most neurotransmitters or their respective receptors can accompany coma or departure from life. Many neurological conditions and mental disorders are due to the improper functioning of neurotransmitters. GABA diminishes heart rate and hypertension. GABA helps to lighten, moderate, calm and fall asleep. GABA stops other neurons from firing. Dopamine bonuses the brain up and transfer fondness of enjoyment. Dopamine is a pleasure chemical (Feel good neurotransmitter), involved, learning and emotion. The feeling comes from adrenalin or epinephrine. Nor-epinephrine alerts the person. Serotonin sets the body's internal clock. Serotonin is a mood neurotransmitter. Glutamate excites neurons to fire and involved in memory. These chemicals are called neuromodulators.

Keywords: *Acetylcholine; Dopamine; Serotonin; GABA; Glutamate; Glycine; Aspartate; Alzheimer's disease; Oxytocin; Epinephrine*

Introduction

More amounts of glutamate can cause excitotoxicity resulting in cellular death [1].

Oxytocin plays a role in social recognition, bonding, and sexual reproduction [2]. Epinephrines are produced in the body in response to pain and intricate in visceral functions [3]. Epinephrine is a stress hormone that is released by the adrenal system but concern as a neurotransmitter [4]. Histamine is a neurotransmitter in the brain and spinal cord [5]. Dopamine is the feel-good neurotransmitter, involved in reward, motivation [6]. Serotonin improves mood and reduce feelings of anxiety [7]. In the central nervous system, beta-endorphins similarly bind mu-opioid receptors and exert their primary action at presynaptic nerve terminals [8,9]. As the brain develops into adulthood, GABA's role changes from excitatory to inhibitory [10]. Serotonin is stored in blood platelets, is released during agitation,

vasoconstriction, where and acts as an agonist to other platelets [11]. Glutamate is involved in learning and memory in the brain [12]. Glutamate, released from a neighbouring synapse creates extra synaptic signalling transmission [13]. The glutamate neurotransmitter plays the principal role in neural activation [14]. GABA can promote the replication and survival of β-cells [15].

Chronological record of significant events

Loewi, first discovered neurotransmitter and Dale, first studied neurochemicals. The function of dopamine, as neurotransmitter, was discovered in 1958 by Arvid Carlsson and Nils-ake Hillarp. The structures of choline set on by Adolf von Baeyer in 1867 [16,17].

Frederick Walker, Dobinson noted that choline injections decreased the hypertension [18].

Rosenblueth developed a theory of two sympathins, sympathin E (excitatory) and sympathin I (inhibitory) [19].

Hermann and Holtz identified the biosynthetic structure for norepinephrine [20].

T. Hayashi in 1952, suggested that glutamate might function as a transmitter [21].

Aspartic acid was first discovered in 1827 by Auguste-Arthur Plisson and Étienne Ossian Henry [22].

Dopamine is not only a precursor of norepinephrine and epinephrine, a neurotransmitter [23].

Major neurotransmitters:

- Glutamate, aspartate, D-serine, Gamma-Amino butyric acid (GABA), glycine (Amino acids)
- Nitric oxide (NO), carbon monoxide (CO), hydrogen sulphide (H_2S) (Gaso transmitter)
- Dopamine (DA), norepinephrine (noradrenaline; NE, (NA), epinephrine (adrenaline), histamine, serotonin (SER, 5-HT) (Monoamines)
- Phenethylamine, *N*-methylphenethylamine, tyramine, 3-iodothyronamine, octopamine, tryptamine, etc (Trace amines)
- Oxytocin, somatostatin, substance P, cocaine and amphetamine regulated transcript, opioid peptides (Peptides)
- Adenosine triphosphate (ATP), adenosine (Purines)
- Dopamine, norepinephrine (noradrenaline), epinephrine (adrenaline) (Catecholamines)
- Acetylcholine (ACh), anandamide (Others).

Acetylcholine

ACh (Acetylcholine) is released from axon terminals of cholinergic neurons. Methyl erases methylate ethanolamine into choline with the labile methyl groups from three successive S-adenosyl methionine molecules [24].

Choline acetylase next transfers the acetyl group from Acetyl-CoA to the alcoholic OH group of choline to change the later to ACh. Acetylcholine in the PNS is produced by: Motor neurons and Parasympathetic. Acetylcholine was first noted. Taveau found that it decreased blood pressure in a small dose.

Dale outlined the effects of acetylcholine at various types of peripheral synapses [25].

Diseases related to acetylcholine

Main features are the presence of plaques in the brain and loss of connection between the neurons, in the brain. Manifestations are severe memory loss, cognitive deficits, problems with recognition, problems with spatial awareness, problems with speaking, reading, or writing and personality or behaviour changes. There is no remedy for Alzheimer's disease. Lower levels of acetylcholine produce Alzheimer's disease. Ache inhibitors can help with language, judgment and memory.

Myasthenia gravis

Characteristically, without acetylcholine, muscles unable to contract. Manifestations of myasthenia gravis are fragility in the arms, legs, hands, or neck, difficulty in swallowing and distress in speaking. Alzheimer's disease AChE inhibitors may also help to relieve manifestations of myasthenia gravis.

Parkinson's disease

People living with Parkinson›s have a very low level of dopamine. Disproportion in levels of acetylcholine, effect in people with Parkinson's disease Scientists discovered that patients with the condition usually have low dopamine levels that allow acetylcholine to take over. As a result of this, muscles become "excited," which starts to symptoms like jerking movements and tremors? This confesses dopamine levels to restore balance and help in relieving some symptoms. These drugs are described as anticholinergics. Other after effects are distraction. Memory loss, delusion and indistinct vision.

Dopamine

Dopamine was synthesized by George Barger and James Ewens [26].

Dopamine's function as a neurotransmitter was first recognized in 1958 by Arvid Carlsson and Nils-Ake Hillarp [27].

Excess leads to schizophrenia. Less quantity leads to tremors and decreased mobility in Parkinson's and ADHD.

Diseases related to dopamine

Dopamine scarcity results in, depression, schizophrenia, hysteria, deceptiveness or illusions and Parkinson's disease. In Parkinson's disease, there is deterioration of the nerve cells in particular parts of the brain and destitution of dopamine in that zone. Damage caused by drug abuse is higher. Addiction people have shown knockdowns in dopamine D2 receptors. Excess glucose and saturated fats can crush dopamine.

Chemistry of amino acids

Some amino acids such as glycine and alanine are converted into carbohydrates in the body. Tyrosine give rise to the hormones adrenaline and thyroxine. Glycine, arginine and methionine may give rise to creatine. Glycine and cysteine are used in producing bile salts. Glycine, aspartate, glutamine and serine are used in purine synthesis. Peptide bonds serially link glutamate, cysteine and glycine to form glutathione. The neurotransmitters, gamma-amino butyrate (GABA) and serotonin are synthesized from respectively glutamate and tryptophan. Serotonin a vaso active amine and neurotransmitter, is synthesized from tryptophan in liver, kidneys, gastrointestinal tract and hypothalamus:

Serine + tetrahydrofolate → glycine.

Glutamate excites neurons and memory. GABA inhibits neurons. Serotonin affects mood, hunger and sleep. Dopamine involved in learning, reward and emotion.

GABA (Gamma amino butyric acid)

GABA is released from some neurons of the corpora quadrigemina, corpus striatum, diencephalon, cerebellum and cerebral cortex. GABA receptors, on the postsynaptic membrane are arranged around a ligand-gated chloride channels across the membrane. This causes the inhibition of neurotransmission across synapse. GABA thus functions as an inhibitory neurotransmitter. Less secretion of GABA produces seizures, tremors and insomnia.

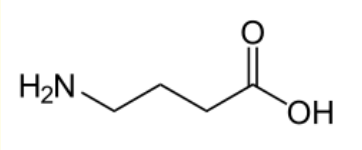

Figure 1

Serotonin

Serotonin is kept in reserve in blood platelets. Less serotonin leads to depression.

Glycine

Glycine is an interference neurotransmitter in the CNS, specifically in the spinal cord, brainstem.

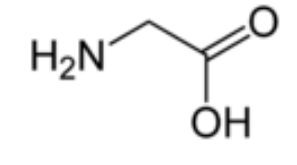

Figure 2

Nitric oxide NO

At lower concentration helps in regulating the circulatory and central nervous system. In females, relaxes uterine smooth muscles, thus risk of premature birth is prevented. At high concentration, fight against infectious organisms and cancer cells. Nitric oxide is synthesized from L-arginine. Nitric oxide acts as on blood vessels potent vasodilator Decreased concentration of nitric oxide leads to hypertension.

Nitric oxide and mood disorders

Serotonin promotes neurogenesis in the hippocampus. Nitric oxide inhibits neurogenesis.

Regulatory substances

Cytokines

These cells can express and release a variety of cytokines, including the IL-1β and IL-6, TNF-α and IFN-γ [28].

Carbon monoxide

It regulates olfactory neurotransmission, smooth muscle cell proliferation and aggregation of platelets.

Co appears to participate in the neurotransmission. In the gastrointestinal nervous system, carbon monoxide serves as a neurotransmitter.

Release of peptide hormones is under the care of CO.

Carbon monoxide was found to block the secretion of both oxytocin and vasopressin from the hypothalamus in animal models.

Endocannabinoids

In India Cannabis was used as an appetite stimulant. Tetrahydrocannabinols (THC) active compound of cannabis joint of Marijuana when smoked 20 to 80 μg of THC reach the brain. Anandamide is a lipid produced endogenously in the brain that could activate cannabinoid receptors and function as a neurotransmitter.

Biosynthesis of endocannabinoids

Endocannabinoid receptors:

- **CB1:**
    - Most abundant GPCRs in the brain.
    - Occur at highest density in the basal ganglia, cerebellum, hippocampus, hypothalamus, ACC and cerebral cortex, particularly the frontal cortex.
- **CB2:**
    - Is predominantly expressed on the surface of white blood cells of the immune system,
    - Small amounts appear to be present in the brainstem.

Endocannabinoids in anxiety and mood

1. Loss of signalling by the endocannabinoid system appears to promote anxiety-like states in animal studies.
2. Role for cannabinoid signalling in forgetting painful memories.

Endocannabinoids in psychosis

Cannabis use often worsens psychosis in schizophrenia and heavy use has been associated with developing schizophrenia.

Effects on brain injury and pain

1. 2-AG appears neuroprotective, reducing brain oedema, infarct size, and cell death while improving functional outcomes.
2. Anandamide also protects--- against brain injury in multiple sclerosis patients.

Effects in the periphery

1. Blood shot appearance of conjunctiva.
2. Treatment of glaucoma.

Neurosteroids

Stimulate axonal growth and promote synaptic transmission:

1. Regulate brain serotonin and dopamine levels,
2. suppress cortisol.

Anxiety disorders

Allopregnanolone stimulates GABA activity with 20 times the strength of benzodiazepines and 200 times the potency of barbiturates.

Psychotic disorders

DHEA has been dispensed to decrease anxiety in schizophrenics, as DHEA and DHEA-S suppress GABA inhibition and heighten the neuronal response at the NMDA and sigma receptors.

Substance abuse

Alcohol regulates GABA receptor and induces de novo steroid synthesis in the brain. Increase in peripheral alcohol levels leads to increase in Pregnenolone, Allopregnanolone and Allo tetra hydro deoxy corticosterone levels in the brain and periphery.

Research on the role of memory disorders and aging

DHEA levels at age 70 are only about 20 percent of their maximum value recorded in the late twenties. In patients with Alzheimer disease, DHEA concentrations have been found to be markedly decreased.

Diseases associated with neurotransmitters

1. Acetylcholine----------Alzheimer's disease
2. Dopamine----------Parkinson's disease, Schizophrenia

3. GABA----------Epilepsy
4. Serotonin----------Migraine, Depression
5. Glutamate----------Migraine, Stroke.

Recent advances in diagnostic technology

Acetylcholine receptor (AChR) antibody test is pre-owned to assist in diagnosing myasthenia gravis (MG). AChR antibodies are two types: 1. AChR unbreakable antibodies. 2. AChR preventive antibodies. Blood test can calculate dopamine levels in the blood, it cannot evaluate how the brain acknowledge to dopamine. Some illness can produce a person's body not to synthesize dopamine transporters. Most of the physicians do not test dopamine levels, but diagnose a person based on the manifestations.

Current altercation

The discovery of levodopa in the by Arvid Carlsson was rightfully awarded with a Nobel Prize in 2001. Up to this date, levodopa remains the most efficacious anti-parkinsonian drug and the cornerstone in the treatment of PD. Recently, it is proved that D-Aspartic acid neurotransmitter is highly useful to fight against neurological diseases like Parkinson's disease, Schizophrenia. Dopamine is helpful to multiply the success of anticancer drugs and radiation therapy.

Breakthrough treatments and management of neurotransmitters

Since GABA is inhibitory transmitter, a low level of GABA deficiency of pyridoxal phosphate would lead to convulsions. Sodium Valproate, which inhibits GABA oxidase, is used in treatment of epilepsy. Some of the most effective therapeutic agents for ADHD are psychostimulants-> methylphenidate and amphetamine: increase both dopamine and norepinephrine levels in brain. GABA is taken orally for relieving anxiety, improving mood, reducing symptoms of premenstrual syndrome (PMS). It is also used for muscle growth, balancing hypertension and palliate pain. Lamotrigine is a glutamate release obstacle/FDA-approved this drug.

Anticholinergic drugs are atropine (Atropen), belladonna alkaloids. Benztropine mesylate (Cogentin), clidinium, cyclopentolate (Cyclogyl), darifenacin (Enablex), dicyclomine and fesoterodine (Toviaz):

1. Amphetamine, Cocaine ----- CNS stimulant
2. Benztropine Benzhexol -------Parkinson's disease
3. Ironized, Tranylcypromine ------Nonselective MAO inhibitors
4. Selegiline---- MAO inhibitors, Parkinson's disease.

Research on the treatment of Parkinson's disease

Ropinirole, pramipexole, apomorphine, selegiline, rasagiline, tolcapone, entacapone, levodopa, the metabolic precursor of dopamine, is the single most percussive agent in the treatment of Parkinson's disease [29].

Commotion in serotonergic mechanisms have been linked to several of the behavioral consequences of Alzheimer's disease [30].

Recent work involving re-uptake inhibition with 5-HT in patients with dementia have suggested improvement in behavioral disturbances [31].

Augmentation of the 5-HT system with a direct-acting agonist in patients with Alzheimer's disease [32].

Research program to the next generation world

Neurons in the nucleus basalis of Meynert (an area that provides cholinergic output to several cortical regions) were found in nonhuman primates to have enhanced firing rates to novel pictures; when those pictures were presented repeatedly, firing decreased [33].

In rats, neurons in the locus coeruleus, present a clear response to sensory stimuli [34].

Novelty would be among a group of highly salient events that elicit a locus coeruleus response in a non-conditioned manner [35].

Dopamine plays an essential role in humans for the coordination of body movements, motivation and reward. Most attention has been paid to dopaminergic involvement in novelty responses [36].

Indeed, several models have focused on how DA stimulates learning and exploration, and promotes planning [37].

Dopaminergic transmission has been addressed in recent years with the comprehensive 'Novelty-related Motivation of Anticipation and exploration by Dopamine (NOMAD)' model [38].

Actual exposure to novel stimuli triggers phasic DA firing, which would, through cascades linked to the D1 and D5 receptors help transform transient synaptic plasticity into long-lasting plasticity [39].

A new way to view brain neurotransmitter

The release of Neurotransmitter is basically resolved by the classical micro dialysis technique. This is principally bringing out to high presentation of liquid chromatography (HPLC).

Artificial neurotransmitters

Nano bot models team delivers artificial neurotransmitters for pharmaceutical exemplification of future mental diseases treatment using medical nanotechnology and sophisticated drug delivery. Artificial neurotransmitter capsule will inject neurotransmitters in micromanage tone, applying electromagnetic antenna.

Artificial synapse that works with living cells created

In 2017, Stanford University researchers presented a new device that mimics the brain's efficient and low-energy neural learning process [40].

Shortened version of large work

Alzheimer's disease is a neurodegenerative condition. A build-up of tangles in the brain, cell death, causes memory loss and cognitive decline.

An opinion arrived at through a process of reasoning

Nitric oxide clearly has a wide range of actions on other molecules large and small and therefore on diverse cellular processes.

Conclusion

Neurotransmitters play a vital role in the causation of many neurological as well as mental illnesses. GABA is an inhibitory neurotransmitter involved in epilepsy. Glutamate is involved in migraine and stroke. Lower Serotonin levels are involved in causation of anxiety disorders and depression. Dopamine is responsible for bipolar disorder and positive and negative symptoms of schizophrenia. It also plays a major role in the development of Parkinsonism. Acetylcholine is involved in Alzheimer's disease. Many drugs used in the treatment of the above conditions target these neurotransmitter receptors and pathways causing either increase or decrease of the neurotransmitter levels in the brain depending on their mechanism of actions. Hence normal functioning of the brain involves balancing of neurotransmitter levels. Apart from their role in brain these brain chemicals have a role in the peripheral systems too.

Bibliography

1. Wang R and Reddy PH. "Role of glutamate and NMDA receptors in Alzheimer's disease". *Alzheimer's Disease* 57.4 (2017): 1041-1048.
2. Magon N and Kalra S. "The orgasmic history of oxytocin: love, lust and labor". *Indian Journal of Endocrinology and Metabolism* 15 (2011): S156-S161.
3. Sprouse-Blum AS., *et al*. "Understanding endorphins and their importance in pain management". *Hawaii Medical Journal* 69.3 (2010): 70-71.
4. Tank AW and Lee wong D. "Peripheral and central effects of circulating catecholamines". *Comprehensive Physiology* 5.1 (2015): 1-15.
5. Nuutinen S and Panula P. "Histamine in neurotransmission and brain diseases". *Advances in Experimental Medicine and Biology* 709 (2010): 95-107.
6. Arias-Carrión O., *et al*. "Dopaminergic reward system: a short integrative review". *International Archives of Medicine* 3 (2010): 24.
7. Albert PR., *et al*. "Serotonin-prefrontal cortical circuitry in anxiety and depression phenotypes: pivotal role of pre- and post-synaptic 5-HT1A receptor expression". *Frontiers in Behavioral Neuroscience* 8 (2014): 199.
8. Miller R. "Miller's Anesthesia". 6th edition. Pennsylvania: Elsevier (2005): 382-386.
9. Brunton L. "Goodman and Gilman's The Pharmacological Basis of Therapeutics". 11th edition. New York: McGraw-Hill (2006): 547-559.
10. Li K and Xu E. "The role and the mechanism of γ-aminobutyric acid during central nervous system development". *Neuroscience Bulletin* 24.3 (2008): 195-200.
11. Schlienger RG and Meier CR. "Effect of selective serotonin reuptake inhibitors on platelet activation: can they prevent acute myocardial infarction?". *American Journal of Cardiovascular Drugs: Drugs, Devices, and Other Interventions* 3.3 (2003): 149-162.
12. McEntee WJ and Crook TH. "Glutamate: its role in learning, memory, and the aging brain". *Psychopharmacology* 111 (4): 391-401.
13. Okubo Y., *et al*. "Imaging extrasynaptic glutamate dynamics in the brain". *Proceedings of the National Academy of Sciences of the United States of America* 107.14 (2010): 6526-6531.
14. Robert Sapolsky. "Biology and Human Behavior: The Neurological Origins of Individuality (2nd edition)". The Teaching Company (2005): 19-20.
15. Purwana I., *et al*. "GABA promotes human β-cell proliferation and modulates glucose homeostasis". *Diabetes* 63.12 (2014): 4197-4205.

16. Kawashima K., *et al*. "Non-neuronal cholinergic system in regulation of immune function with a focus on α7 nAChRs". *International Immunopharmacology* 29.1 (2015): 127-134.

17. Mott FW and Halliburton WD. "VII. The physiological action of choline and neurine". *Philosophical Transactions of the Royal Society of London. Series B, Containing Papers of a Biological Character* 191 (2001): 211-267.

18. Hunt R and Taveau M. "On the physiological action of certain choline derivatives and new methods for detecting choline". *British Medical Journal* 2 (1906): 1788-1791.

19. Hayashi T. "A physiological study of epileptic seizures following cortical stimulation in animals and its application to human clinics". *The Japanese Journal of Physiology* 3.1 (1952): 46-64.

20. Herman Blaschko. "A half-century of research on catecholamine biosynthesis". *Journal of Applied Cardiology* (1987): 171-183.

21. Dorkins HR. "Suxamethonium-the development of a modern drug from 1906 to the present day". *Medical History* 26.2 (1982): 145-168.

22. Dale HH. "The action of certain esters and ethers of choline, and their relation to muscarine". *Journal of Pharmacology and Experimental Therapeutics* 6.2 (1914): 147-190.

23. Barondes SH. "Better Than Prozac". New York: Oxford University Press (2003): 39-40.

24. Bacq ZM. "Chemical transmission of nerve impulses". In Parnham MJ, Bruinvels J (editions.). Discoveries in Pharmacology, Volume 1. Amsterdam: Elsevier (1983): 49-103.

25. Fahn S. "The history of dopamine and levodopa in the treatment of Parkinson's disease". *Movement Disorders* 23.3 (2008): S497-508.

26. Benes FM. "Carlsson and the discovery of dopamine". *Trends in Pharmacological Sciences* 22.1 (2001): 46-47.

27. Watkins JC. "l-glutamate as a central neurotransmitter: looking back". *Biochemical Society Transactions* 28.4 (2000): 297-309.

28. S Parasuraman. Associate Professor, Faculty of Pharmacy, AIMST University. Malaysia.

29. Fardan Quadeer. "Dopamine- an important neurotransmitter in the CNS, regulates various physiological and pathological processes in the body". *Health and Medicine* (2016).

30. Quirion R., *et al*. "Neurotransmitter and receptor deficits in senile dementia of the Alzheimer type". *Canadian Journal of Neurological Sciences* 13 (1986): 503-510.

31. Nyth AL and Gottfries CG. "The clinical efficacy of citalopram in treatment of emotional disturbances in dementia disorders. A Nordic multicentre study". *British Journal of Psychiatry* 157 (1990): 894-901.

32. Lawlor BA., *et al*. "A pilot placebo controlled study of chronic m-CPP administration in Alzheimer's disease". *Biological Psychiatry* 30 (1991): 140-144.

33. Meeter M., *et al*. "Mode shifting between storage and recall based on novelty detection in oscillating hippocampal circuits". *Hippocampus* 14 (2004): 722-741.

34. Aston-Jones G and Cohen JD. "An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance". *Annual Review of Neuroscience* 28 (2005): 403-450.

35. Nieuwenhuis S., *et al*. "Decision making, the P3, and the locus coeruleus-norepinephrine system". *Psychological Bulletin* 131 (2005): 510-532.

36. Lisman JE and Grace AA. "The hippocampal-VTA loop: controlling the entry of information into long-term memory". *Neuron* 46 (2005): 703-713.

37. Suri RE., *et al*. "Modeling functions of striatal dopamine modulation in learning and planning". *Neuroscience* 103 (2001): 65-85.

38. Duzel E., *et al*. "Novelty related motivation of anticipation and exploration by dopamine (NOMAD): implications for healthy aging". *Neuroscience and Biobehavioral Reviews* 34 (2010): 660-669.

39. Stanford University, Science daily (2020).

40. Hyman SE. "Neurotransmitters". *Current Biology* 15.5 (2005): R154-158.

Volume 14 Issue 7 July 2022