


# Bridging the Gap: Understanding the Significance of Catecholamines in Neurochemistry and Recent Advances in their Detection

Arnab Bhattacharya, PhD

Independent Researcher, Agartala, India; abinitio03@gmail.com

 <https://orcid.org/0000-0001-7949-1081>

<https://doi.org/10.57098/SciRevs.Biology.2.1.3>

Received April 04, 2023. Accepted April 30, 2023.

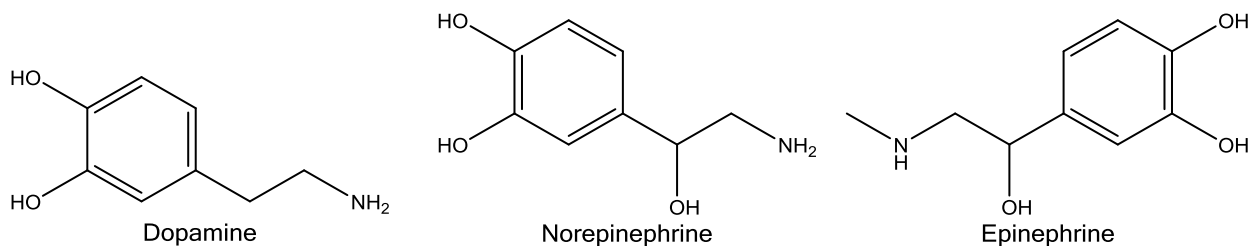
**Abstract:** The neurochemistry of catecholamines plays a crucial and complex role in human memory, behavior, and cognition, while affecting other organs such as the lungs, heart, liver, and skin. Dopamine, norepinephrine, and epinephrine are three closely-related catecholamines that have been widely studied over the last seven decades for development of medications for life-threatening diseases. Other studies have also suggested a link between drug abuse and catecholamine levels. The determination of catecholamine levels in different parts of the human body has also been a hot topic for research in these years. HPLC, spectrophotometry, fluorescence, electrochemistry and other techniques have been used to quantify catecholamines in mostly in biological samples like serum and urine, although in vivo studies are also possible. This article attempts to present the research on catecholamines from the perspectives of their bodily functions, development of medications for diseases related to these, and the techniques used for their detection and quantification.

## Introduction

The development of brain and the central nervous system (CNS) has been one of the decisive factors in the evolution of humans. Alongside the CNS, the evolution of the autonomic nervous system (ANS) has resulted in a complex and sophisticated set of behaviors. Among the multitude of functions that the human brain and other parts of the CNS perform in conjunction with the ANS, emotional responses are perhaps the most challenging to study from an objective perspective because the triggers for joy, happiness, misery, fear, greed, love, faith, doubt, and many more emotions differ from person to person. Recent advances in understanding the brain neurochemistry have revealed that one of the most crucial neurochemical systems deals with neurotransmission, which can further be classified into cholinergic and aminergic [1]. The first type of

transmission involves acetylcholine (ACh), whereas the second involves the dopamine (DA), norepinephrine (NE), and serotonin.

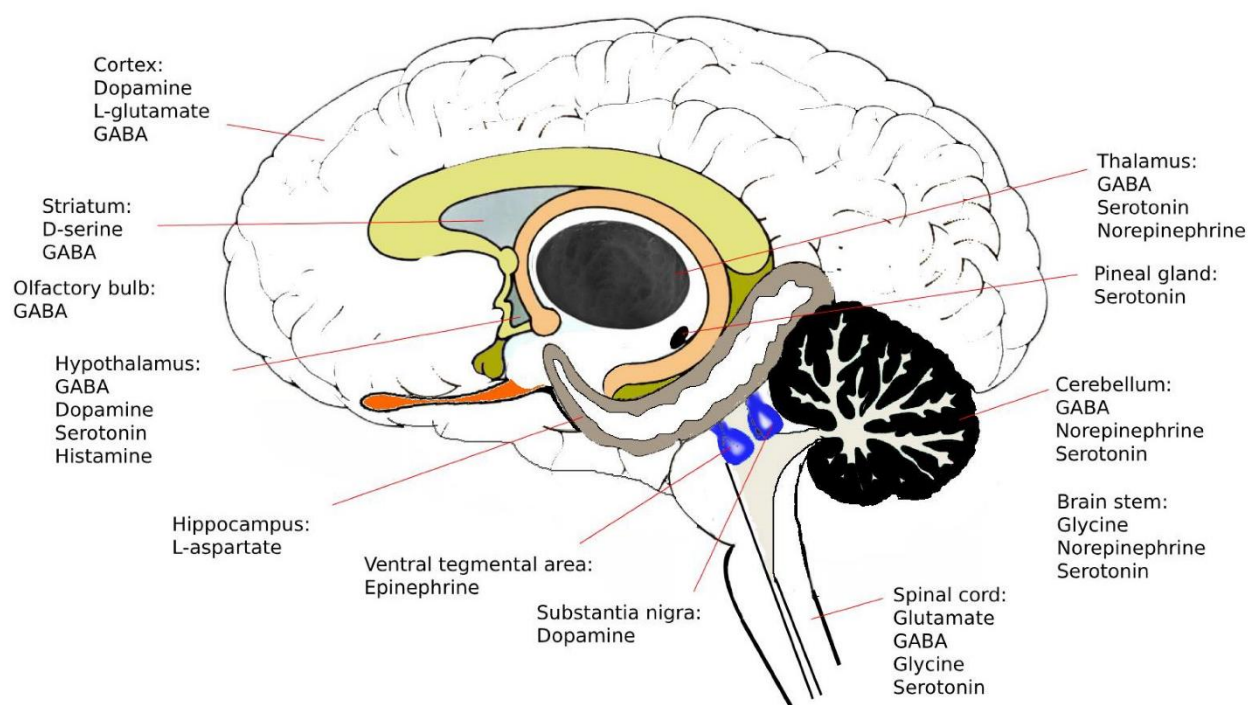
DA and NE are clubbed with a similar molecule, epinephrine (EP), as all three have a catechol moiety as the common fragment in their chemical structures (Figure 1). DA as an input neuronal substance plays roles in the CNS, including a wide range of functional tasks, such as motivation, reward processing, and movement control [2, 3]. NE and EP though very similar in structures, the latter has a methyl group at the amine position; this difference tunes these molecules sometimes toward closely-related and sometimes quite different bioactivities [4].



**Figure 1:** Chemical structures of Dopamine (DA), Norepinephrine (NE), and Epinephrine (EP)

Produced mainly by the adrenal glands, EP performs the dual roles of a hormone and neurotransmitter. EP is primarily involved in the "fight or flight" response, triggering increases in heart rate and blood pressure, as well as bronchodilation and increased metabolic rate. It also has a role in the regulation of glucose metabolism and immune function. NE plays a vital role in regulating arousal,

attention, and mood, as well as triggering the sympathetic response to stress, such as elevation in heart rate and blood pressure. One of the reasons for varied functions is that multiple sites in the brain produce these chemicals aimed at specific purposes. These are often produced alongside other neurotransmitters (Figure 2).



**Figure 2:** Neurotransmitters produced at different regions of human brain. Reproduced from "A Review of Neurotransmitters Sensing Methods for Neuro-Engineering Research" by Niyonambaza et al. under the terms and conditions of the Creative Commons Attribution (CC BY) license.

With such closely-related functions that directly impact human experience of life, the catecholamines have attracted studies from various perspectives. This article summarizes the recent research on catecholamines in terms of their presence and functions in the human body, their role in drug abuse, and

methods for their detection and quantification in human clinical samples.

### Perspectives of research on catecholamine formation and functions in human body

The synthesis of catecholamines is a complex process with multiple steps. Researchers at present fairly understand the mechanism in detail. Since the 1960s, numerous studies on catecholamines have been a result of the technical upgradation that occurred in that era. Till then, the primary focus of the researchers in this field was to better understand the function and regulation of the sympathoadrenal system by quantifying the NA levels in samples such as chromaffin cells from adrenal medulla. Research on the storage and synthesis conditions picked up further pace in the 1970s with the discovery of dopamine- $\beta$ -hydroxylase (D $\beta$ H), an enzyme that converts DA to NE. The enzyme was found to be bound within the NE storage vesicles, that is, terminal varicosities of sympathetic neurons [5, 6]. Among many compounds that facilitate catecholamines synthesis, tyrosine-3-monooxygenase (tyrosine hydroxylase, TH) and its cofactor tetrahydrobiopterin are important because their role can affect how the catecholamine imbalance may result in neuropsychiatric diseases like Parkinson's Disease. The role of TH end product inhibition was once thought to be solely responsible for NA biosynthesis [7]. The end product inhibition was later proven to be an exception rather than a norm in later research [8]. A 2006 review paper by Nagatsu highlights the role of TH in regulating catecholamine biosynthesis and the genetic makeup of humans that propel this process [9]. Studies on non-human models have significantly improved the scope of our understanding of the role of catecholamines in the brain and nervous system. Research on mutant mice have provided evidence for the importance of DA in postnatal motor control and emotional learning, whereas NA has been found to be active in long-term learning that leads to conditioning [10]. Especially, the excitability of pyramidal neurons in cerebral cortex have been found to be modulated by norepinephrinergic neurons; this finding suggests that inactivity of norepinephrinergic neurons can lead to damage of the cerebral cortex and long-term memory loss. Another non-human model study on catecholamine chemistry demonstrated that sheep display maternal-fetal stress transfer [11]. This study provided evidence for the indirect transfer of psychosocial stress due to the decrease in uterine blood flow (UBF) and increase in fetal anaerobic metabolism. The decrease in UBF was found to be related to the increase in maternal NE concentration,

and subsequently increase in fetal NE concentration, leading to anaerobic metabolism of the fetus. Among the research on non-human catecholamine chemistry, the most interesting would perhaps be that of plants. A review from 2007 emphasizes that catecholamine activity in plants ranges from the growth and development by regulating carbohydrate metabolism, affecting various hormones, providing protection against pathogens, serving as building blocks of alkaloids, and being involved in nitrogen detoxification. Interestingly, like animals, plants too have been reported to secrete catecholamines during stress [12].

Interaction of catecholamines with cellular receptors have been studied *in silico* using software to understand their binding affinity with adrenergic receptors. The research suggests that based on such interaction studies, experimental myocardial infarction can be induced to cure ailments like muscular, neurological, and cardiovascular disorders that result from altered catecholamine concentrations [13]. Catecholamines have also been explored from the viewpoint of the impact of exercise in humans. Speed of cognition has been reported to increase as a result of catecholamines produced through moderate-intensity exercise which activates adrenergic neurons in the vagal/NTS afferent pathway. The dopamine-rich neurons were found to be positively affected for excitability. This viewpoint has however been challenged citing blood brain barrier for catecholamines and from that angle, though a link between catecholamine concentration and cognitive ability is accepted, the cause-effect relationship between the two is contested [14]. Liver disorders in humans have recently been linked to catecholamine concentrations, as the number of publications regarding this have been on the rise [15]. Liver fibrosis, fatty liver diseases, liver cancers, and many associated diseases have been reported with focus on adrenergic and dopaminergic receptor expression in the liver cells. EP activates or inhibits metabolic enzymes involved in hepatic gluconeogenesis and glycogenolysis. The positive impact of catecholamines on the liver cells extends to liver regeneration. Myocardial disorders like cardiomyopathies can be triggered by catecholamines, as reported by Kumar et al. in 2021. In this review, the authors explored the role of catecholamines from the perspective of endocrinologists [16]. The role of catecholamine oxidation products in stress-induced heart diseases

has been studied in light of the relationship between catecholamines and glucocorticoids. excessive catecholamine concentration has been found to be the reason for functional hypoxia/ischemia, coronary insufficiency, and overload of  $\text{Ca}^{2+}$  ions. These in turn, cause oxidative stress, energy defects, loss of electrolytes and other intracellular content. All these finally lead to myocardial damage [17]. A clinical research on Alzheimer's disease patients in 2022 suggests the damage of noradrenergic and dopaminergic neurons. In this study, Henjum et al. concluded that patients with Alzheimer's disease have higher levels of NE and EP in their cerebrospinal fluid [18]. However, the changes in these levels over time may not follow a linear pattern, indicating that they may not have a high predictive or diagnostic value. In symptomatic Alzheimer's disease, the levels of these two transmitters may increase due to synaptic damage, as they are positively correlated with the CSF levels of neurogranin.

### Catecholamines in drug abuse and medicinal use

The requirement of fresh research on these catecholamines is essential in the modern-day world where stress levels are high. This is especially urgent because DA drug abuse has been on the rise. Hacking the brain's reward system via drugs has been on the rise and recent studies have shown that conditioned stimuli, that is, exposure to stimuli related to the drug leads to an increase in DA concentration in dorsal striatum, thus firing the motivation to consume the drug. The long-term drug abuse, in contrast, actually is inversely related to the DA concentration [5]. In a research published in 2021, Fitzgerald provides insights into how many drugs may end up as DA, EP, or NE after passing through

various biochemical steps. Especially, drugs that acutely boost the signaling of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, come out as NE and EP. The excess of these neurotransmitters leads to rapid breathing, sweating, high blood pressure and other symptoms. The author suggests that if indeed such pathways are established whereby psychedelics, alkaloids, and other drugs can be broken down to these catecholamines, it would further enhance our understanding of their natural biosynthesis [20]. Recent research on disulfiram which blocks dopamine  $\beta$ -hydroxylase, an enzyme for NE biosynthesis, has shown that NE can be linked to DA signaling and drug addiction [21]. With this understanding, further insights into the neurochemistry of action of psychostimulants, opiates, alcohols can be explored in terms of how DA-NE balance affects their abuse. Both cocaine and amphetamine are DA reuptake inhibitors, whereas the latter also acts as a DA releaser. L-DOPA acts as a DA agonist, whereas haloperidol, and many antipsychotics act as DA antagonists. The parallels for NE are tricyclic antidepressants that act as NE reuptake inhibitors and ephedrine that acts as NE releaser [1]. Adrenergic receptors actively impact smooth muscle contraction in organs such as the bronchi and thus, EP can perform a special role as  $\beta(2)$ -Adrenoceptor agonist and be potent in reversing the airway constraints. Therefore, EP has been used as a medication for asthma, and in fact, in murine models, the administration of EP has led to complete abolishment of the disease [22]. Table 1 summarizes some of the important catecholamine-research based drugs that have been developed since the 1960s.

**Table 1.** Some important drugs developed out of catecholamine research

Generic Name	Introduced	Clinical applications	Mechanism of action
Propranolol	1965	Hypertension, Cardiac arrhythmias, Heart failure	$\beta$ -Adrenoceptor antagonist
Haloperidol	1967	Schizophrenia, Schizoaffective disorder, Bipolar disorder	$\text{D}_2$ receptor antagonist
Clonidine	1974	ADHD, Migraine, Hypertension	$\alpha_1$ -Adrenoceptor agonist
Reboxetine	1997	Depressive disorder	NE-selective reuptake inhibitor
Pramipexole	1998	Parkinson's disease	Dopamine $\text{D}_2/\text{D}_3$ receptor agonist
Atomoxetine	2002	ADHD	NE-selective reuptake inhibitor
Guanfacine	2015	ADHD	$\alpha_2$ -Adrenoceptor agonist

### Methods for detecting and measuring the levels of catecholamines in human samples

Catecholamine neurotransmitter sensing is a challenging field of research on three accounts: (1) The extremely low concentrations in which these are present in the body; (2) The fluctuating nature of their concentration because of the reward, motivation, and stress levels; (3) The closeness of their chemical structures. With these constraints, researchers over the years have figured out some methods that may be suitable for the detection and quantification of DA, EP, and NE in various bio-fluids. The design principles for chemical sensing of catecholamines make use of fluorescence resonance energy transfer, photo-induced electron transfer (PET), photo-induced charge transfer, electrostatic interactions, excimer formation, ligand exchange method, catalytic and molecular beacon, fluorescence polarization, and fluorescent chemodosimetry [23]. According to a review paper by Gorbunova et al. published in 2019, approximately 42% of all the methods used for catecholamine determination are based on high performance liquid chromatography (HPLC), followed by those based on electrochemistry (30%), spectrophotometry (13%), fluorescence spectroscopy (9%), and immunoassays (3%) [24]. This data fits perfectly with the sudden rise in the number of research papers in the late 1980s dealing with catecholamine determination as the availability of HPLC till then was not widespread. The interesting data regarding the use of spectrophotometric techniques is that despite advancement in equipment, determination of catecholamines in adrenal glands is limited to only 5% whereas urine (9%) and serum (19%) samples have been used much frequently for this purpose. However, pharmaceuticals (57%) have been mostly tested for their catecholamine content. The luminescence techniques have been found to be better suited for *in vivo* determination as 6% of these studies worked in the brain, whereas 23% and 18% in urine and serum, respectively. Among other techniques, the highest number of successful studies involving Raman

spectroscopy have been for DA (67%) followed by that for NE (17%) and EP (16%). Other methods like single-photon emission computed tomography (SPECT), surface enhanced Raman spectroscopy (SERS) have also been reported for catecholamine determination. DA has been frequently quantified till the nanomolar levels using PET, SERS, colorimetric and electrochemical techniques, EP and NE determination has been confined mostly to the micromolar levels using these techniques [25].

### Conclusions

Catecholamine neurochemistry is one of the most complex and pivotal for human cognition, behavior, and memory. In addition, the levels of DA, NE, and EP impact various types of bodily functions in brain, lungs, heart, liver, and skin. As in humans, other animals too require these for various functions. Animals such as sheep and mice have been extensively studied to understand the role of these chemically similar molecules with focus on how the knowledge can be transformed into synthesizing artificial molecules that mimic or inhibit or promote these biomolecules. The result of research on this field that started gaining momentum since the 1960s, has been the development of many medications for life-threatening diseases. Parallel research has also been going on in understanding how drug abuse leads to imbalance in their levels and the possibility of many psychedelics and other addiction drugs being broken down into catecholamines in the biochemical pathways. As the research data since the 1960s suggest, the advent of HPLC has provided a major boost in quantifying the catecholamines in biological samples such as serum and urine. With modern instruments in place, fluorescence, chemiluminescence, and electrochemiluminescence are emerging as promising techniques for imaging their activity in the brain and CNS. Further research is still required in this field as many gaps in understanding the storage, activity, and impact of DA, NE, and EP remain.

### References

1. Buck, R. *Emotion: A Biosocial Synthesis*, 1st ed.; Cambridge University Press, 2014. <https://doi.org/10.1017/CBO9781139049825>.
2. Di Chiara, G. Chapter VI Dopamine, Motivation and Reward. In *Handbook of Chemical Neuroanatomy*; Elsevier, 2005; Vol. 21, pp 303–394. [https://doi.org/10.1016/S0924-8196\(05\)80010-7](https://doi.org/10.1016/S0924-8196(05)80010-7).

3. Gepshtein, S.; Li, X.; Snider, J.; Plank, M.; Lee, D.; Poizner, H. Dopamine Function and the Efficiency of Human Movement. *Journal of Cognitive Neuroscience* 2014, 26 (3), 645–657. [https://doi.org/10.1162/jocn\\_a\\_00503](https://doi.org/10.1162/jocn_a_00503).
4. Goldstein, D. S. Adrenaline and Noradrenaline. In *eLS*; John Wiley & Sons, Ltd, Ed.; Wiley, 2010. <https://doi.org/10.1002/9780470015902.a0001401.pub2>.
5. Noradrenaline Storage Particles in Splenic Nerve. *Phil. Trans. R. Soc. Lond. B* 1971, 261 (839), 313–317. <https://doi.org/10.1098/rstb.1971.0062>.
6. Bisby, M. A.; Fillenz, M. The Storage of Endogenous Noradrenaline in Sympathetic Nerve Terminals. *The Journal of Physiology* 1971, 215 (1), 163–179. <https://doi.org/10.1113/jphysiol.1971.sp009463>.
7. Spector, S.; Gordon, R.; Sjoerdsma, A.; Udenfriend, S. End-Product Inhibition of Tyrosine Hydroxylase as a Possible Mechanism for Regulation of Norepinephrine Synthesis. *Mol Pharmacol* 1967, 3 (6), 549–555. [https://doi.org/10.1016/S0065-2571\(71\)80042-0](https://doi.org/10.1016/S0065-2571(71)80042-0)
8. Stanford, S. C.; Heal, D. J. Catecholamines: Knowledge and Understanding in the 1960s, Now, and in the Future. *Brain and Neuroscience Advances* 2019, 3, 239821281881068. <https://doi.org/10.1177/2398212818810682>.
9. Nagatsu, T. The Catecholamine System in Health and Disease -Relation to Tyrosine 3-Monooxygenase and Other Catecholamine-Synthesizing Enzymes-: – Relation to Tyrosine 3-Monooxygenase and Other Catecholamine-Synthesizing Enzymes—. *Proc. Jpn. Acad., Ser. B* 2006, 82 (10), 388–415. <https://doi.org/10.2183/pjab.82.388>.
10. Kobayashi, K. Role of Catecholamine Signaling in Brain and Nervous System Functions: New Insights from Mouse Molecular Genetic Study. *Journal of Investigative Dermatology Symposium Proceedings* 2001, 6 (1), 115–121. <https://doi.org/10.1046/j.0022-202x.2001.00011.x>.
11. Rakers, F.; Bischoff, S.; Schiffner, R.; Haase, M.; Rupperecht, S.; Kiehnkopf, M.; Kühn-Velten, W. N.; Schubert, H.; Witte, O. W.; Nijland, M. J.; Nathanielsz, P. W.; Schwab, M. Role of Catecholamines in Maternal-Fetal Stress Transfer in Sheep. *American Journal of Obstetrics and Gynecology* 2015, 213 (5), 684.e1–684.e9. <https://doi.org/10.1016/j.ajog.2015.07.020>.
12. Kulma, A.; Szopa, J. Catecholamines Are Active Compounds in Plants. *Plant Science* 2007, 172 (3), 433–440. <https://doi.org/10.1016/j.plantsci.2006.10.013>.
13. Kalaivannan, S.; Vinoth Kambali, T.; Prabhu, S.; Visvanathan, S.; Karpagam, N. Interaction Studies on Catecholamines to Cellular Receptors Using in Silico Approach. *ARTRES* 2017, 19 (C), 29. <https://doi.org/10.1016/j.artres.2017.06.001>.
14. Commentaries on Viewpoint: Reappraisal of the Acute, Moderate Intensity Exercise-Catecholamines Interaction Effect on Speed of Cognition: Role of the Vagal/NTS Afferent Pathway. *Journal of Applied Physiology* 2016, 120 (6), 659–660. <https://doi.org/10.1152/jappphysiol.01055.2015>.
15. Lelou, E.; Corlu, A.; Nessler, N.; Rauch, C.; Mallédant, Y.; Seguin, P.; Aninat, C. The Role of Catecholamines in Pathophysiological Liver Processes. *Cells* 2022, 11 (6), 1021. <https://doi.org/10.3390/cells11061021>.
16. Kumar, A.; Pappachan, J. M.; Fernandez, C. J. Catecholamine-Induced Cardiomyopathy: An Endocrinologist's Perspective. *Reviews in Cardiovascular Medicine* 2021, 22 (4), 1215. <https://doi.org/10.31083/j.rcm2204130>.
17. Adameova, A.; Abdellatif, Y.; Dhalla, N. S. Role of the Excessive Amounts of Circulating Catecholamines and Glucocorticoids in Stress-Induced Heart Disease. *Can. J. Physiol. Pharmacol.* 2009, 87 (7), 493–514. <https://doi.org/10.1139/Y09-042>.

18. Henjum, K.; Watne, L. O.; Godang, K.; Halaas, N. B.; Eldholm, R. S.; Blennow, K.; Zetterberg, H.; Saltvedt, I.; Bollerslev, J.; Knapskog, A. B. Cerebrospinal Fluid Catecholamines in Alzheimer's Disease Patients with and without Biological Disease. *Transl Psychiatry* 2022, 12 (1), 151. <https://doi.org/10.1038/s41398-022-01901-5>
19. Volkow, N. D.; Fowler, J. S.; Wang, G.-J.; Swanson, J. M.; Telang, F. Dopamine in Drug Abuse and Addiction: Results of Imaging Studies and Treatment Implications. *Arch Neurol* 2007, 64 (11), 1575. <https://doi.org/10.1001/archneur.64.11.1575>.
20. Fitzgerald, P. J. Many Drugs of Abuse May Be Acutely Transformed to Dopamine, Norepinephrine and Epinephrine In Vivo. *IJMS* 2021, 22 (19), 10706. <https://doi.org/10.3390/ijms221910706>.
21. Weinschenker, D.; Schroeder, J. P. There and Back Again: A Tale of Norepinephrine and Drug Addiction. *Neuropsychopharmacol* 2007, 32 (7), 1433–1451. <https://doi.org/10.1038/sj.npp.1301263>.
22. Thanawala, V. J.; Forkuo, G. S.; Al-Sawalha, N.; Azzegagh, Z.; Nguyen, L. P.; Eriksen, J. L.; Tuvim, M. J.; Lowder, T. W.; Dickey, B. F.; Knoll, B. J.; Walker, J. K. L.; Bond, R. A.  $\beta_2$ -Adrenoceptor Agonists Are Required for Development of the Asthma Phenotype in a Murine Model. *Am J Respir Cell Mol Biol* 2013, 48 (2), 220–229. <https://doi.org/10.1165/rcmb.2012-0364OC>.
23. Pradhan, T.; Jung, H. S.; Jang, J. H.; Kim, T. W.; Kang, C.; Kim, J. S. Chemical Sensing of Neurotransmitters. *Chem. Soc. Rev.* 2014, 43 (13), 4684–4713. <https://doi.org/10.1039/C3CS60477B>.
24. Gorbunova, M. V.; Gutorova, S. V.; Berseneva, D. A.; Apyari, V. V.; Zaitsev, V. D.; Dmitrienko, S. G.; Zolotov, Y. A. Spectroscopic Methods for Determination of Catecholamines: A Mini-Review. *Applied Spectroscopy Reviews* 2019, 54 (8), 631–652. <https://doi.org/10.1080/05704928.2018.1470980>.
25. Niyonambaza, S. D.; Kumar, P.; Xing, P.; Mathault, J.; De Koninck, P.; Boisselier, E.; Boukadoum, M.; Miled, A. A Review of Neurotransmitters Sensing Methods for Neuro-Engineering Research. *Applied Sciences* 2019, 9 (21), 4719. <https://doi.org/10.3390/app9214719>.

### Conflicts of Interest

The author declares no conflict of interest.