EDITORIAL

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Dopamine Interaction with other Neurotransmitter Systems: Relevance in the Pathophysiology and Treatment of CNS Disorders

Giuseppe Di Giovanni

Department of Physiology and Biochemistry, University of Malta, Msida MSD 2080, Malta

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Correspondence
Department of Physiology & Biochemistry, Faculty of Medicine and Surgery, University of Malta. Msida MSD 2080, Malta.
Tel.: +356 23402776;
Fax: +356 21310577;
E-mail: giuseppe.digiovanni@um.edu.mt

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Decades ago, in the late 1950s, dopamine (DA), a highly conserved catecholaminergic neurotransmitter, was discovered in the mammalian brain [1]. The first role identified for DA was in the control of movement. Degeneration of DA neurons within the substantia nigra pars compacta (SNc) and the consequential DA depletion in the striatum were indeed shown by Oleh Hornykiewicz to be the cause of neurological symptoms in Parkinson's disease (PD) [2]. This discovery and the subsequent use of L-DOPA in such patients [3], which represents one of the most successful stories in neuropharmacology, has generated such intense research that this little cluster of DA neurons has become the most studied in the brain today. DA neurons represent a tiny proportion of the total neuronal population in the central nervous system (CNS) but, through their highly divergent branching networks of fibers, these few cells influence large territories of the brain. The majority of brain DA cells resides in the ventral part of mesencephalon. Essentially, they are restricted to two nuclei, the ventral tegmental area of Tsai (VTA) and the lateral SNc. Nevertheless, cells expressing tyrosine hydroxylase (TH), the rate-limiting enzyme in the biosynthesis of catecholamines, have also been described in the striatum of rodents, monkeys and even humans [4]. DA neurons in the midbrain are spontaneously active and show regular, irregular and bursting patterns of activity that are an essential component of the DA release process. DA neuronal activity can be modulated by diverse life events, ranging from exposure to drugs, stress, or unpredictable rewards. Strikingly, it has been shown that DA neuronal discharge is altered in an animal model of depression and can be corrected by desipramine treatment [5]. The new field of optogenetics has furthered our understanding of the causal role of DA cell action potential patterns in driving behavioral changes [6], opening a second exciting electrophysiological era for the dopaminergic neurons. Use of this new technique, together with the subsequent advances gained by associated research will be beneficial for patients with various neurological and psychiatric disorders, including PD.

It is evident that the discovery of DA as a neurotransmitter in the brain marked a turning point in modern neuroscience. Not only has it elucidated our understanding of brain function in both health and disease, it has also helped link theories of brain chemistry and higher brain function, thus playing a vital part in the development of biological psychiatry. The importance of DA's role in all aspects of human behavior, including cognition,

addiction and mood regulation has been shown in the over 110,000 papers published in this burgeoning field. DA neurones have also a fundamental role in almost all brain pathological processes such as schizophrenia, depression, drug addiction, attention deficit hyperactivity disorders (ADHD) and PD [7]. Indeed, DA cells are *sui generis* cells and very delicate, and for some unknown reason are prone to degenerate and are very sensitive to oxidative stress and inflammation [8]. Recently, great progress has been made in the understanding of the ontogeny of DA cells and the possible important application of this knowledge in cell replacement strategy for PD. In addition, new evidence for possible *de novo* DA neurogenesis has given a glimmer of hope for a new theurapetical approach for DA neurodegenerative diseases [9].

Despite all of the past research on DA, many details are missing on how DA acts to produce its effects in the brain. This is due to the complexity of DA actions; also, in these first 50 years of DA research the emphasis has been on investigating DA in isolation from other transmitter systems. Nonetheless, DA does not act like a fast ionotropic neurotransmitter such as acetylcholine, glutamate or GABA but rather modulates other neurotransmitter systems. Activation of DA receptors alone does not induce large postsynaptic currents but modifies the cell's excitability or the neurotransmitter's release, depending on the DA receptor subtype activated. Therefore, there is a need for a more integrated research approach that will lead to greater understanding and improve treatment of diseases involving DA dysfunctions.

With this in mind, this special issue of "CNS Neuroscience & Therapeutics" offers as updated a picture as possible of the intriguing interaction between DA and other neurotransmitters in the brain, in normal and in pathological conditions.

The special issue contains 10 reports by eminent authors with special expertise in the field. The collection starts by looking at the DA interactions with the "small-molecule neurotransmitters," such as acetylcholine, norepinephrine, glutamate, serotonin, and adenosine. Then, it continues with the interaction with neuropeptide neurotransmitters/neuromodulators such as opioids, cannabinoids, and oxytocin. The two last contributions are on dopaminergic modulation by the gaseous molecule of nitric oxide and steroids.

The 10 articles included deal extensively with the latest knowledge on dopaminergic neurotransmission. They also particularly provide further insight on DA's role in the integration of information in the production of a relevant response. Research on dopaminergic mechanisms has yielded great scientific rewards and clinical benefits so far. More is promised in the future and there are grounds for increasing optimism. Technical developments and passionate scientists will shed new light on the role of this neurotransmitter in the brain. Boosting DA research in this new holistic approach will help in finding new pharmacological treatments for several psychopathological states that are not merely DA disorders. This will allow us to alter brain DA for patients' benefit and also to avoid negative effects. I hope that this Special Issue will be a useful guide for future research.

Finally, I would like to acknowledge the authors as well as all the reviewers and Thomas Gaston at Wiley who made possible the realization of the present Special Issue.

Conflict of Interest

The author declares no conflict of interest.

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