
Preface

A Historical Perspective of the Study of Dopamine and Its Receptors

Dopamine was first synthesized in 1910 at the Wellcome laboratories in London, England, by two chemists, George Barger and Arthur James Ewins. In the same year, Sir Henry Dale, British physiologist and pharmacologist, reported that dopamine had very weak sympathomimetic activity suggesting at that time an insignificant physiological role for this amine. Up to 1952, dopamine was referred by its original name, 3,4-dihydroxyphenylethylamine. In fact on that year, it was Sir Henry Dale, then a Physiology and Medicine Nobelist, who first coined the word dopamine from the contraction of 3,4-*dihydroxyphenylethylamine*. Pioneering work spanning from the early 1910s to the late 1930s unraveled the discovery of L-DOPA (also known as levodopa), a naturally occurring isomer of the amino acid 3,4-dihydroxyphenylalanine and the enzyme DOPA decarboxylase, which allowed paving the way for the still in force principles of the catecholamine biosynthetic pathway. Up to the late 1950s, dopamine's role was solely confined to that of a precursor generated from L-DOPA decarboxylation to serve as a critical intermediary in the synthesis of the sympathomimetic active catecholamines, norepinephrine and epinephrine. Seminal biochemical, histoimmunochemical, and radioligand studies done notably from the late 1950s to the late 1970s in the laboratories of Arvid Carlsson (2000 Physiology and Medicine Nobelist), Oleh Hornykiewicz, Paul Greengard (2000 Physiology and Medicine Nobelist), Maynard H. Makman, Pier Franco Spano, Leslie Iversen, Solomon Snyder, Philip Seeman, and others gave credence to a role of dopamine beyond that of just being a mere intermediary in the biosynthesis of norepinephrine but also on its own a true biogenic amine neurotransmitter involved in a plethora of physiological effects in brain and peripheral tissues. Importantly, work done in the late 1950s and the early 1960s by Oleh Hornykiewicz and Arvid Carlsson also hinted to an important role of a deregulated dopamine activity in the etiology of Parkinson's disease and schizophrenia. Furthermore, these studies strengthened the view that dopamine played a critical role in the signal transduction via two receptor subtypes. Initially, the view was that one subtype, D₁, was linked to the stimulation of adenylyl cyclase and cAMP production while the other subtype, D₂, exhibited high affinity for antipsychotics but was not linked to adenylyl cyclase. Molecular cloning studies in the late 1980s and the early 1990s uncovered the existence of a gene family coding for dopamine receptor proteins larger than anticipated.

Nowadays, it is well established that dopamine actions are chiefly mediated through the binding and activation of six cell surface seven-transmembrane proteins that belong to the large family of G protein-coupled receptors or GPCRs. The dopaminergic GPCRs are catalogued in two major classes: D₁-class (D₁ and D₅) and D₂-class (D_{2short/long}, D₃, and D₄) receptors. These receptors can regulate locomotion, cognition, reward, natriuresis, vascular tone, gastrointestinal motility, heart function, and respiratory activity. Besides Parkinson's disease and schizophrenia, impaired activity of dopamine and its receptors is also implicated in the etiology or phenotypic expression of several other hallmark human brain illnesses

and conditions such as Huntington's disease, attention deficit and hyperactivity disorder, and substance abuse. Whether the disorders arise from death of neurons in substantia nigra pars compacta (Parkinson's disease) or striatum (Huntington's disease), or impairment in dopamine reuptake (cocaine addiction), a large body of studies suggest that these conditions likely culminate in compromised signal transduction through dopamine receptors.

Consistent with this view, drugs targeting dopamine receptors are currently used in clinical settings to manage and treat symptoms of diseases associated with impaired dopamine activity. However, these drugs are not magic bullets as they also cause undesirable side effects or are unable to alleviate all disease symptoms linked to dopamine dysfunction. To address these issues, important facets of dopamine receptor biology remain to be further addressed at the functional and mechanistic levels: drug selectivity, high-resolution structure predictions, subtype-specific signaling properties, posttranslational modifications, and receptor gene expression. Potentially, a better understanding of dopamine receptor functionality will help in developing new pharmacological tools to improve our knowledge of in vivo roles played by each receptor subtype and synthesis of prospective lead compounds for drug discovery.

The primary objective of this *Neuromethods* book is to lay an interface between updated classical methods and new emerging technologies heretofore not available to new or seasoned researchers, who are keen to further our understanding of dopamine receptor biology. The book is divided into five sections dedicated to experimental approaches investigating different facets of dopaminergic signal transduction: epigenetic and posttranscriptional analysis, computational and biochemical techniques, visualization and imaging methods, molecular and cell biological tools, and behavioral assessment. The book provides insightful step-by-step protocols and methodological reviews that readers will find useful. Furthermore, this book will be a complement to existing literature experimental protocols to study dopamine function.

In closing, I would like to express my sincere gratitude to all scientists who took time to contribute a chapter in spite of their busy schedule. I want also to thank Boyang Zhang, Michael Beazely, Jean-Claude Béique, Diane Lagace, and Kursad Turksen for their help and valuable advice during the editing of this book. Finally, I want to thank Wolfgang Walz, the series editor, and Patrick Marton from Springer New York for their encouragements and support during the making of this book.

Ottawa, ON, Canada

Mario Tiberi

Dopamine Receptor Technologies

Tiberi, M. (Ed.)

2015, XIV, 379 p. 63 illus., 26 illus. in color., Hardcover

ISBN: 978-1-4939-2195-9

A product of Humana Press