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Review article

Serotonergic modulation of the activity of mesencephalic dopaminergic systems: Therapeutic implications

Philippe De Deurwaerdère[a,*], Giuseppe Di Giovanni[b,c,**]

[a] Centre National de la Recherche Scientifique, Unité Mixte de Recherche 5293, 33076 Bordeaux Cedex, France
[b] Department of Physiology & Biochemistry, Faculty of Medicine and Surgery, University of Malta, Malta
[c] Neuroscience Division, School of Biosciences, Cardiff University, Cardiff, UK

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ABSTRACT

Since their discovery in the mammalian brain, it has been apparent that serotonin (5-HT) and dopamine (DA) interactions play a key role in normal and abnormal behavior. Therefore, disclosure of this interaction could reveal important insights into the pathogenesis of various neuropsychiatric diseases including schizophrenia, depression and drug addiction or neurological conditions such as Parkinson's disease and Tourette's syndrome. Unfortunately, this interaction remains difficult to study for many reasons, including the rich and widespread innervations of 5-HT and DA in the brain, the plethora of 5-HT receptors and the release of co-transmitters by 5-HT and DA neurons. The purpose of this review is to present electrophysiological and biochemical data showing that endogenous 5-HT and pharmacological 5-HT ligands modify the mesencephalic DA systems' activity. 5-HT receptors may control DA neuron activity in a state-dependent and region-dependent manner. 5-HT controls the activity of DA neurons in a phasic and excitatory manner, except for the control exerted by 5-HT_{2C} receptors which appears to also be tonically and/or constitutively inhibitory. The functional interaction between the two monoamines will also be discussed in view of the mechanism of action of antidepressants, antipsychotics, anti-Parkinsonians and drugs of abuse.

Contents

Abbreviations: 5-HT_{2C} receptor, serotonin2C receptor; DRN, dorsal raphe nucleus; MRN, medial raphe nucleus; DA, Dopamine; 6-OHDA, 6-hydroxydopamine; HFS, high frequency stimulation; NAc, Nucleus Accumbens; STN, subthalamic nucleus; EPN, entopeduncular nucleus; GPCRs, G-protein coupled receptors; GPi, internal globus pallidus; GPe, external globus pallidus; SN, substantia nigra; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; VTA, ventral tegmental area; mPFC, medial prefrontal cortex; GAD, glutamic acid decarboxylase; TH, tyrosine hydroxylase; PLC, phospholipase C; PLA_2, phospholipase A_2; BOLD, blood oxygen dependent level; OCD, Obsessive Compulsive Disorders; 5-HT, 5-hydroxytryptamine (serotonin); EPS, extrapyramidal side effects; NE, norepinephrine (noradrenaline); HIP, hippocampus; TH, tyrosine hydroxylase; VMAT, vesicular monoamine transporter; GABA, γ-Aminobutyric acid; Ih, hyperpolarization-activated cation current; DOPAC, 3,4-dihydroxyphenylacetic acid; 5-HIAA, 5-hydroxyl-indolacetic acid; pCPA, para-chlorophenylalanine; 5,7-DHT, 5,7-dihydroxytryptamine; EPSP, excitatory post-synaptic potentials; IPSP, inhibitory post-synaptic potentials; SSRI, selective serotonin reuptake inhibitor; MDMA, 3,4-methylenedioxy-methamphetamine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-Methyl-D-aspartate; APD, antipsychotic; TTX, tetrodotoxin; DAT, dopamine transporter; SERT, serotonin transporter; NET, norepinephrine transporter; PKA, protein kinase A; GAD, glutamic decarboxylase; GPCR, G-protein coupled receptor; IP, inositol phosphate; cAMP, cyclic AMP; RT-PCR, reverse transcriptase polymerase chain reaction.

* Corresponding author.
** Corresponding author at: Department of Physiology & Biochemistry, Faculty of Medicine and Surgery, University of Malta, Malta.
E-mail addresses: deurwaer@u-bordeaux.fr (P. De Deurwaerdère), giuseppe.digiovanni@um.edu.mt (G. Di Giovanni).

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1. Introduction

The interaction between serotonin (5-HT) and dopamine (DA) systems in the brain has been investigated by neurobiologists, psychiatrics, neurologists and pharmacologists for at least four decades. Knowledge of this subject seems crucial to a better understanding of the mechanisms of action of several psychoactive drugs currently on the market, but especially to drug discovery. The field of antipsychotic drugs is probably a good illustration of the pertinence of the 5-HT/DA interaction in drug design. Notably, the therapeutic benefit of atypical antipsychotics in terms of fewer extrapyramidal side effects and larger efficacy in reducing psychosis has been related to their ability to block 5-HT$_{2A}$ receptors more efficiently with respect to DA-D$_2$ receptors (Deutch et al., 1991; Meltzer, 1999a; Meltzer and Huang, 2008; Meltzer et al., 1989b). Although this property is still a matter of debate, such a consideration has raised great interest regarding the contribution of the 5-HT system in the mechanism of action of DA drugs in humans. Nowadays, the other pharmacological properties of these atypical antipsychotic drugs (i.e., 5-HT$_{1A}$, 5-HT$_{2C}$, 5-HT$_3$, 5-HT$_6$ affinity) have been studied and have led to a better knowledge of the 5-HT/DA interaction. Similarly, a closer look at the mechanism of action of drugs of abuse and dopaminomimetics has disclosed several pieces of information on this interaction. In particular, the best medication in Parkinson's disease (PD) for almost 50 years has been the exogenous administration of the metabolic precursor of DA, L-3,4-dihydroxyphenylalanine (L-DOPA). An increasing body of evidence indicates that 5-HT neurons directly and indirectly mediate the actions of L-DOPA, leading to the development of 5-HT-based compounds to counteract the unwanted motor, mood and psychotic outcomes of L-DOPA therapy (Bastide et al., 2015; Carta et al., 2007, 2008; Jenner et al., 1983; Melamed et al., 1996; Pact and Giduz, 1999; Zoldan et al., 1996). The influence of the 5-HT system in the control of DA neuron activity appears as a pivotal factor in the motor, mood and cognitive effects of DA therapies.

The precise nature of the interactions between 5-HT and DA has been difficult to elucidate, in that both inhibitory and excitatory roles for 5-HT have been suggested and shown (Di Giovanni et al., 2008b; Fink and Gothert, 2007; Kapur and Remington, 1996; Soubrie et al., 1984). The discrepancies among the studies are related to the numerous parameters studied, the existence of 5-HT responses mediated or not by 5-HT receptors, the existence of several 5-HT receptor subtypes (Di Matteo et al., 2008a; Navailles and De Deurwaerdere, 2011) and the release of other co-transmitters (Trudeau, 2004). In addition, the interaction between the two monoaminergic systems appears to be region-dependent