G. Di Giovanni, V. Di Matteo & E. Esposito (Eds.)
Progress in Brain Research, Vol. 172
ISSN 0079-6123

CHAPTER 1

Serotonin–dopamine interaction: an overview

Ennio Esposito[1,*], Vincenzo Di Matteo[1] and Giuseppe Di Giovanni[2]

[1]*Istituto di Ricerche Farmacologiche "Mario Negri", Consorzio "Mario Negri", Via Nazionale, 66030 Santa Maria Imbaro, Chieti, Italy*
[2]*Dipartimento di Medicina Sperimentale, Sezione di Fisiologia Umana, "G. Pagano", Università di Palermo, Corso Tuköry 129, 90134 Palermo, Italy*

Abstract: Central serotonergic and dopaminergic systems play a critical role in the regulation of normal and abnormal behaviours. Moreover, recent evidence suggests that the dysfunction of dopamine (DA) and serotonin (5-hydroxytriptamine, 5-HT) neurotransmission might underlie the pathophysiology of neuropsychiatric disorders, including depression, schizophrenia, attention deficit hyperactivity disorders, drug abuse, Gilles de la Tourette's syndrome and Parkinson's disease.

Keywords: serotonin; dopamine; serotonin receptors; substantia nigra; ventral tegmental area; neuropsychiatric disorders

The interaction between the two amines in the brain, in normal and pathological conditions, is an intriguing research field and a better understanding will provide new pharmacological approaches for the treatment of several neuropsychiatric disorders. An extensive scientific literature has investigated the role of serotonin (5-hydroxytriptamine, 5-HT) in the control of central dopamine (DA) systems, and their dysfunction in pathological conditions. In neuropsychiatric disorders, the involvement of 5-HT and DA has been indicated and singled out and new therapeutic approaches suggested. Nevertheless, the interaction between 5-HT and DA systems is far from being completely revealed.

The interaction between 5-HT and DA in the brain is a research topic that has raised the interest of many scientists working in the field of neuroscience since the first demonstration of the presence of monoamine-containing neurons in the mid-1960s. Thus, a seminal work by Fuxe (1965) reported the presence of 5-HT-containing terminals in both the substantia nigra (SN) and the ventral tegmental area (VTA). It was subsequently found that serotonergic nerve terminals originating from the dorsal raphe nucleus (DRN) innervated both the SN and the VTA (Steinbusch, 1981), whereas 5-HT fibres arising from median raphe nucleus (MNR) innervated the VTA but not the SN (Fibiger and Miller, 1977; Azmitia and Segal, 1978). Based on those anatomical studies, several investigators began to study the behavioural, biochemical and electrophysiological relevance of the neuroanatomical findings. Further impetus was given to this research by the increasing evidence that most psychotropic drugs, including antidepressants, antipsychotics, opioids, anxiolytics and psychostimulants, exerted their pharmacological actions by interfering with serotonergic and dopaminergic transmission. An

*Corresponding author. Tel.: +39 0872 570274;
Fax: +39 0872 570416; E-mail: esposito@negrisud.it

DOI: 10.1016/S0079-6123(08)00901-1

almost parallel and concomitant progress was made in the identification, characterization and cloning of 5-HT receptor subtypes (Boess and Martin, 1994).

Early studies showed that experimental manipulations aimed at decreasing central 5-HT function, such as selective nerve lesions by neurotoxin, inhibition of 5-HT synthesis or 5-HT receptor blockade, tended to potentiate the behavioural and neurochemical effects of drugs such as amphetamine and related compounds, enhancing the dopaminergic transmission, thus leading to the conclusion that central serotonergic systems inhibit DA functions (Samanin and Garattini, 1975). The interest of our laboratory in investigating 5-HT/DA interaction sprang from these early studies. Our approach was based on in vivo electrophysiological and neurochemical techniques. The experimental data gathered over a period of almost 20 years lead to the conclusion that several 5-HT receptor subtypes, including the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_3 and 5-HT_4 receptors, act to facilitate neuronal DA function and release, while the 5-HT_{2C} receptor mediates an inhibitory effect of 5-HT on the basal electrical activity of dopaminergic neurons and on DA release.

A detailed analysis and discussion of the above-mentioned data are reported in this book. Of particular interest is the finding that 5-HT_{2A} and 5-HT_{2C} receptors exert opposite actions on dopaminergic activity, although they belong to the same receptor family, and share almost identical cellular transduction mechanisms. One possible mechanism of this opposite action is the intermediation of a γ-aminobutyric acid (GABA)-ergic neuron in the inhibitory effect of 5-HT_{2C} receptors on DA function. Based on this hypothesis, 5-HT_{2A} receptor stimulation would cause a direct excitation of DA-containing neurons, whereas activation of 5-HT_{2C} receptors would indirectly inhibit these neurons by stimulating a GABA-containing interneuron (Di Giovanni et al., 2001; Di Matteo et al., 2001). However, although early neuroanatomical data showing that 5-HT_{2C} receptors are restricted to GABA-containing neurons in the SN (Eberle-Wang et al., 1997) strengthened this hypothesis, it was recently found that in the VTA, 5-HT_{2C} receptor protein is expressed on both DA and GABA-containing neurons (Bubar and Cunningham, 2007). Thus, there are several possible anatomical sites of 5-HT/DA interaction: it may be at the level of brainstem where SN and VTA are located, and/or at the level of projection areas of nigrostriatal and mesocorticolimbic dopaminergic systems, including the striatum, the nucleus accumbens and the prefrontal cortex. The interaction might be either direct (i.e. mediated by 5-HT receptors located on the cell body and/or on nerve terminals of DA neurons) or indirect (i.e. by 5-HT receptors located on interneurons impinging on DA neurons and/or by short or long feed-back loops originating from innervated brain areas).

It is interesting to note that a number of behavioural studies are consistent with electrophysiological and neurochemical findings, in that 5-HT_{2C} receptor antagonists were found to potentiate the effects of several psychostimulant drugs including cocaine, nicotine and amphetamine-like compounds, whereas 5-HT_{2A} receptor antagonists had the opposite effect (Bubar and Cunningham, 2008). Moreover, 5-HT_{2C} receptor agonists reduce the locomotor and rewarding effects of several drugs of abuse, including nicotine, ethanol, cocaine and amphetamine-like drugs. It is noteworthy that the locomotor and rewarding effects of cocaine were clearly potentiated in 5-HT_{2C} receptor null mutant mice (Rocha et al., 2002). Therefore, an important aspect of 5-HT/DA interaction relates to the possibility of using 5-HT_{2C} receptor agonists in the therapy of addictive disorders. In this respect, it is important to note that several new selective and potent 5-HT_{2C} receptor agonists have been developed, which might be useful to treat disturbances of consummatory behaviours such as overeating and drug addiction, which are now considered related disorders. An intriguing aspect of this problem is the recent finding that the tumour suppressor enzyme PTEN (phosphatase and tensin homologue deleted on chromosome 10) directly interacts with a region in the third intracellular loop (3L4F) of 5-HT_{2C} receptors in the rat VTA. PTEN limits agonist-induced 5-HT_{2C} receptor phosphorylation via its protein phosphatase activity. Systemic or intra-VTA application of the

interfering peptide Tat-3L4F is capable of disrupting PTEN coupling with 5-HT_{2C} in the rat VTA, resulting both in a suppression of the increased firing rate of VTA dopaminergic neurons induced by Δ^9-tetrahydrocannabinol (THC), the psychoactive ingredient of marijuana, and in a blockade of the conditioned place preference induced by THC and nicotine (Ji et al., 2006). This represents a very good example of integration of classical pharmacology with up-to-date molecular biology techniques.

Another important characteristic of the 5-HT_{2C} receptor subtype is that it undergoes post-transcriptional editing. Thus, the 5-HT_{2C} receptor is the only seven transmembrane domain receptor to date found to undergo the post-transcriptional process of mRNA editing, which generates unique isoforms of proteins in a cell- and/or tissue-specific manner. mRNA transcripts of the rat and human 5-HT_{2C} receptor undergo adenosine-to-inosine editing events at five sites which encompass amino acids 156–160 within the putative second intracellular domain of the encoded human receptor, resulting in the production of fourteen 5-HT_{2C} receptor isoforms (Berg et al., 2005). There is increasing evidence that some of these isoforms might be linked to a higher probability of developing depression and psychosis.

The chapters of this book are devoted to the analysis of the relevance of 5-HT/DA interaction in learning and memory, the sleep/wake cycle, attention and impulsivity, and the pathophysiology of several neuropsychiatric disorders, including depression, schizophrenia and other psychotic disorders, drug abuse, Gilles de la Tourette's syndrome, attention deficit hyperactivity disorders (ADHD), Parkinson's disease, Alzheimer's disease, diskynesias and motor tics. The detailed knowledge of 5-HT/DA interaction would also help in understanding the mechanism of action of most psychotropic drugs, including antidepressant, antipsychotic and anti-addictive drugs that is thought to be mediated, at least in part, via the 5-HT system. 5-HT research is now more than 50 years old, and it has generated a wealth of therapeutic agents, some of which have had a major impact on disease management. Not surprisingly, 5-HT receptors and transporters continue to be a major focus of CNS drug discovery. In fact, of the top CNS drugs by total sales, most modulate 5-HT neurotransmission (Segest, 2007). Furthermore, the selective 5-HT reuptake inhibitors (SSRIs) are among the most widely prescribed drugs for treating depression and a variety of other disorders including anxiety and social phobia. But we are a long way from a serotoninergic therapeutic intervention for other neuropsychiatric diseases.

5-HT receptor research has generated detailed information on the molecular biology and regional and cellular localization of these receptors. A major challenge now is to utilize this knowledge to develop receptor-specific drugs and use the information gained to better treat central nervous system disorders. In addition, further clarification of the role of 5-HT transmission in the pathophysiology of neuropsychiatric disorders is required, since the overall picture is still confusing. It is likely that 5-HT_{2C} ligands are promising candidates (Di Giovanni et al., 2006; Rosenzweig-Lipson et al., 2007). Moreover, there are also many avenues that remain unexplored, so there are undoubtedly further advances to be made. The intensive research in medicinal chemistry will help this field of investigation. In fact, more selective ligands for 5-HT receptors are currently produced. In the future, the use of such selective ligands, especially agonists of 5-HT receptors, would certainly be helpful in determining their functional importance and their involvement in the pathogenesis of diseases, not exclusively of the CNS. This has a particular relevance for those disorders such as Parkinsons's disease that are still fatal and for which at present there is no cure (Esposito et al., 2007; Di Giovanni, 2008). However, it should be kept in mind that although selective receptor ligands are an important and indispensable research tool, they rarely happen, in practice, to be drugs. Many questions need to be answered before we can truly understand how these 5-HT receptors regulate DA neuronal activity in the brain. The challenge ahead is to build on this foundation and keep up this engaging adventure: the interaction between 5-HT and DA systems is far from being completely revealed.

References

Azmitia, E.C. and Segal, M. (1978) An autoradiographic analysis of the differential ascending projections of the dorsal and median raphe nuclei in the rat. J. Comp. Neurol., 179: 641–659.

Berg, K.A., Harvey, J.A., Spampinato, U. and Clarke, W.P. (2005) Physiological relevance of constitutive activity of 5-HT_{2A} and 5-HT_{2C} receptors. Trends Pharmacol. Sci., 26: 625–630.

Boess, F.G. and Martin, I.L. (1994) Molecular biology of 5-HT receptors. Neuropharmacology, 33(3/4): 275–317.

Bubar, M.J. and Cunningham, K.A. (2007) Distribution of serotonin 5-HT_{2C} receptors in the ventral tegmental area. Neuroscience, 146(1): 286–297.

Bubar, M.J. and Cunningham, K.A. (2008) Prospects for serotonin 5-HT_2R pharmacotherapy in psychostimulant abuse (Chapter 16 of this book).

Di Giovanni, G. (2008) Will it ever become possible to prevent dopaminergic neuronal degeneration? CNS Neurol. Disord. Drug Targets, 7(1): 28–44.

Di Giovanni, G., Di Matteo, V., La Grutta, V. and Esposito, E. (2001) *m*-Chlorophenylpiperazine excites non-DA-ergic neurons in the rat substantia nigra and ventral tegmental area by activating serotonin-2C receptors. Neuroscience, 103: 111–116.

Di Giovanni, G., Di Matteo, V., Pierucci, M., Benigno, A. and Esposito, E. (2006) Serotonin involvement in the basal ganglia pathophysiology: could the 5-HT2C receptor be a new target for therapeutic strategies? Curr. Med. Chem., 13(25): 3069–3081.

Di Matteo, V., De Blasi, A., Di Giulio, C. and Esposito, E. (2001) Role of 5-HT_{2C} receptors in the control of central dopamine function. Trends Pharmacol. Sci., 22: 229–232.

Eberle-Wang, K., Mikeladze, Z., Uryu, K. and Chesselet, M.-F. (1997) Pattern of expression of the serotonin$_{2C}$ receptor messenger RNA in the basal ganglia of adult rats. J. Comp. Neurol., 384: 233–247.

Esposito, E., di Matteo, V., Pierucci, M., Benigno, A. and Di Giovanni, G. (2007) Role of central 5-ht2c receptor in the control of basal ganglia functions. In: Di Giovanni G. (Ed.), The Basal Ganglia Pathophysiology: Recent Advances. Transworld Research Network, Trivandrum, pp. 97–127.

Fibiger, H.C. and Miller, J.J. (1977) An anatomical and electrophysiological investigation of the serotonergic projection from the dorsal raphe nucleus to the substantia nigra in the rat. Neuroscience, 2: 975–987.

Fuxe, K. (1965) Evidence for the existence of moniamine neurons in the central nervous system. IV. Distribution of monoamine nerve terminals in the central nervous system. Acta Physiol. Scand., 247(Suppl.): 39–85.

Ji, S.P., Zhang, Y., Van Cleemput, J., Jiang, W., Liao, M., Li, L., Wan, Q., Backstrom, J.R. and Zhang, X. (2006) Disruption of PTEN coupling with 5-HT_{2C} receptors suppresses behavioral responses induced by drugs of abuse. Nat. Med., 12(3): 324–329.

Rocha, B.A., Goulding, E.H., O'Dell, L.E., Mead, A.N., Coufal, N.G., Parsons, L.H. and Tecott, L.H. (2002) Enhanced locomotor, reinforcing, and neurochemical effects of cocaine in serotonin, 5-hydroxytryptamine 2C receptor mutant mice. J. Neurosci., 22: 10039–10045.

Rosenzweig-Lipson, S., Dunlop, J. and Marquis, K.L. (2007) Agonists as an innovative approach for psychiatric disorders. Drug News Perspect., 20(9): 565–571.

Samanin, R. and Garattini, S. (1975) The serotonergic system in the brain and its possible functional connections with other aminergic systems. Life Sci., (8): 1201–1209.

Segest, S. (2007) CNS Market Trends, 2007 to 2010. URCH Publishing, London.

Steinbusch, H.W.M. (1981) Distribution of serotonin-immunoreactivity in the central nervous system of the rat-cell bodies and terminals. Neuroscience, 6(4): 557–618.