

Editorial

Neurotensin NTS1-Dopamine D₂ Receptor-Receptor Interactions in Putative Receptor Heteromers: Relevance for Schizophrenia

Luca Ferraro*, Sarah Beggiano, Maria Cristina Tomasini, Tiziana Antonelli, Sergio Tanganelli and KjellFuxe

Department of Life Sciences and Biotechnology,
University of Ferrara, Italy

*Corresponding author: Luca Ferraro, Department of Life Sciences and Biotechnology, Section of Medicinal and Health Products, University of Ferrara, Via Fossato di Mortara 17-19, 44100 Ferrara, Italy

Received: March 19, 2014; Accepted: March 20, 2014;
Published: March 24, 2014

Converging evidence from studies on the pathophysiology of schizophrenia links increased mesolimbic dopamine (DA) neuronal activity (*i.e.* hyperdopaminergia) to a reduced thalamic-cortical glutamate (*i.e.* hypoglutamatergia) drive [1-3]. In fact, the activation of postsynaptic DA D₂ receptors, mainly located on the medium size spiny GABA neurons projecting from the nucleus accumbens to the ventral pallidum, exert a tonic inhibitory regulation of GABAergic neurotransmission. An increased D₂-mediated tone on nucleus accumbens-ventral pallidum medium size spiny GABA neurons leads to a disinhibition of GABAergic neuron projecting from the ventral-pallidum to the medial dorsal nucleus of the thalamus and, in turn, a reduction of excitatory glutamate thalamocortical projection, which produces some schizophrenia symptoms [1,3]. It has been, therefore, suggested that an increase of the activity of a subset of GABAergic neurons could represent a common neurochemical mechanism of antipsychotic agents; conversely, a reduction of ventral striato-pallidal GABA transmission may underlie the disturbances in affect and cognition associated to psycho stimulant abuse and psychosis [4].

The tridecapeptide neurotensin (NT) is widely distributed in the central nervous system and in the periphery. Its biological actions are initiated by binding to three different receptor subtypes named NTS1R, NTS2R and NTS3R, respectively [5]. Most of the known effects of NT are mediated through NTS1R, which signals preferentially via the Gq protein. The differential regional distribution of NT in the brain, the presence of NT receptors in different brain areas such as cortical, striated and limbic regions, the sodium and calcium dependent NT release and the involvement of NT in several electrophysiological and behavioral responses, suggest that the peptide acts as a neurotransmitter or neuromodulator. NT immunoreactive cell body and terminal systems and NT receptors are found in many parts of the mammalian brain and especially interact with the mesolimbic, mesocortical and nigrostriatal DA neurons.

NTS1 mRNA levels and NTS1 proteins are enriched on the bodies and dendrites of dopaminergic neurons in the substantia nigra and ventral segmental area, as well as within the projection areas of the ascending mesostriatal and mesocorticolimbic dopaminergic pathways [6]. In line with this anatomical distribution, several studies documented the existence of a close functional interaction between NT and DA neurons, and a role for NT in schizophrenia has been hypothesized for over three decades [7]. In line with this view, in the cerebrospinal fluid (CSF) of certain drug-free schizophrenic patients a reduced concentration of NT has been observed and significantly linked to the severity of schizophrenic delusions and hallucinations. More interestingly, in the same patients, CSF NT concentration tends to normalize during a clinically effective antipsychotic drug treatment. Based on these findings, it has been proposed that NT may represent an endogenous antipsychotic compound [8] and, consequently, a NT deficit may be one of the possible neurochemical alterations implicated in the etiology of schizophrenia [8]. Preclinical pharmacological, behavioral and electrophysiological evidence also supports this hypothesis. The central injection of NT produces behavioral effects that are similar to those induced by antipsychotic drugs and, as a consequence, the NT system has been implicated in the mechanism of action of antipsychotic drugs [9]. The observation that acute or chronic administration of either typical or atypical antipsychotic drugs enhances NT mRNA levels, NT tissue content and release in the nucleus accumbens, further strengthens this hypothesis.

One of the possible mechanisms underlying the NT-induced regulation of mesocorticolimbic DA pathway has been proposed to be the antagonistic action of the activated NTS1 on D₂ receptor function. The K_d values of the D₂ receptor agonist [³H] NPA binding sites in ventral sections of the rat forebrain, mainly containing the nucleus accumbens and the tuberculum olfactorium, are significantly increased by low concentrations of NT and its biologically active fragment NT (8-13), without any change in the B_{max} value [10]. Microdialysis findings suggested that this mechanism operates also *in vivo* in modulating nucleus accumbens neurotransmission. In the nucleus accumbens, NTS1R is mainly located on cortical glutamatergic afferents as well as, although to a lower extent, on the cell bodies and dendrites of GABA neurons. The local perfusion with NT in low (10 nM) concentration induces, through NTS1R activation, an increase of nucleus accumbens GABA outflow [11] associated with a concomitant and significant GABA_A receptor mediated-reduction of nucleus accumbens DA release.

In vivo microdialysis studies demonstrate that when NT, at nanomolar concentration by itself ineffective on GABA outflow, is co-perfused with the D₂ receptor agonist pergolide, it significantly counteracts the pergolide-induced inhibition of GABA outflow, by

NTS1R activation. On the contrary, the pergolide-induced inhibition of DA outflow is unaffected by the co-perfusion with NT [10]. In view of the localization of NTS1Rs and D₂ receptors on cortico-accumbens glutamatergic terminals, it seems likely that the antagonistic NTS1-D₂ receptor-receptor interactions and/or the activation of NTS1R protomer in the putative NTS1/D₂ receptor heteromer, increasing glutamate outflow, may counteract the inhibitory tone exerted by DA on ventral striato-pallidal GABA neurons [11]. This mechanism results in the release of glutamate which causes GABA release from the ventral striatal-pallidal GABA neurons and seems to dominate since there exists relatively few NTS1Rs on the accumbency DA terminals. In fact, the resulting increase of nucleus accumbency glutamate outflow, by enhancing GABA release from dendrites and collaterals of the ventral striato-pallidal GABA pathway, could be responsible for the significant reduction of DA release observed in the nucleus accumbency following NT perfusion [11]. This effect indicates that this peptide, by activating the antagonistic NTS1-D₂ receptor-receptor interactions in heteromers located on nucleus accumbency glutamate terminals and on GABA cell bodies and collaterals, produces its potential antipsychotic action. In fact, at the end, these effects of NT may contrast the hyperactivity of DA neurons and the hypoactivity of glutamate terminals that represent one of the possible functional substrate underlying schizophrenia.

These neurochemical findings are consistent with the hypothesis that an enhancement of NT signaling in the nucleus accumbency induced by the D₂ receptor blocking actions of antipsychotic drugs could contribute to the therapeutic effects of such drugs [6-8]. Thus, NT agonists in combination with classical antipsychotic drugs may represent an interesting therapeutic approach for treatment of schizophrenia [11].

References

1. Bencherif M, Stachowiak MK, Kucinski AJ, Lippiello PM. Alpha7 nicotinic cholinergic neuromodulation may reconcile multiple neurotransmitter hypotheses of schizophrenia. *Med Hypotheses*. 2012; 78: 594-600.
2. Carlsson A, Waters N, Carlsson ML. Neurotransmitter interactions in schizophrenia--therapeutic implications. *Biol Psychiatry*. 1999; 46: 1388-1395.
3. Fuxe K, Marcellino D, Rivera A, Diaz-Cabiale Z, Filip M, et al. Receptor-receptor interactions within receptor mosaics. Impact on neuropsychopharmacology. *Brain Res Rev*. 2008; 58: 415-452.
4. Geisler S, Bérod A, Zahm DS, Rostène W. Brain neurotensin, psychostimulants, and stress--emphasis on neuroanatomical substrates. *Peptides*. 2006; 27: 2364-2384.
5. Lambert PD, Gross R, Nemeroff CB, Kilts CD. Anatomy and mechanisms of neurotensin-dopamine interactions in the central nervous system. *Ann N Y Acad Sci*. 1995; 757: 377-389.
6. Nemeroff CB. Neurotensin: perchance an endogenous neuroleptic? *Biol Psychiatry*. 1980; 15: 283-302.
7. Kinkead B, Nemeroff CB. Neurotensin: an endogenous antipsychotic? *Curr Opin Pharmacol*. 2002; 2: 99-103.
8. Cáceda R, Kinkead B, Nemeroff CB. Neurotensin: role in psychiatric and neurological diseases. *Peptides*. 2006; 27: 2385-2404.
9. Li XM, Ferraro L, Tanganelli S, O'Connor WT, Hasselrot U, et al. Neurotensin peptides antagonistically regulate postsynaptic dopamine D2 receptors in rat nucleus accumbency: a receptor binding and micro dialysis study. *J Neural Transm Gen Sect*. 1995; 102: 125-137.
10. Tanganelli S, O'Connor WT, Ferraro L, Bianchi C, Beani L. Facilitation of GABA release by neurotensin is associated with a reduction of dopamine release in rat nucleus accumbens. *Neuroscience*. 1994; 60: 649-657.
11. Boules M, Li Z, Smith K, Fredrickson P, Richelson E. Diverse roles of neurotensin agonists in the central nervous system. *Front Endocrinol*. 2013; 4: 36.