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Editorial

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

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Converging evidence from studies on the pathophysiology of schizophrenia links increased mesolimbic dopamine (DA) neuronal activity (*i.e* hyperdopaminergia) to a reduced thalami-cortical glutamate (*i.e* hypoglutamatergia) drive [1-3]. In fact, the activation of postsynaptic DA D_2 receptors, mainly located on the medium size spiny GABA neurons projecting from the nucleus accumbency to the ventral palladium, exert a tonic inhibitory regulation of GABAergic neurotransmission. An increased D_2-mediated tone on nucleus accumbency-ventral palladium medium size spiny GABA neurons leads to a disinhibition of GABAergic neuron projecting from the ventral-palladium 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 substantianigra 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 accumbency, further strengthens this hypothesis.

One of the possible mechanisms underlying the NT-induced regulation of mesocorticolimbicDA pathway has been proposed to be the antagonistic action of the activated NTS1 on D_2 receptor function. The Kd values of the D_2 receptor agonist [^{3}H] NPA binding sites in ventral sections of the rat forebrain, mainly containing the nucleus accumbency and the tuberculumolfactorium, 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]. Micro dialysis findings suggested that this mechanism operates also in vivo in modulating nucleus accumbency neurotransmission. In the nucleus accumbency, 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 accumbency GABA outflow [11] associated with a concomitant and significant $GABA_A$ receptor mediated-reduction of nucleus accumbency DA release.

In vivo micro dialysis studies demonstrate that when NT, at nanomolar concentration by itself ineffective on GABA outflow, is co-perfuse with the D_2 receptor agonist pergolide, it significantly counteracts the pergolide-induced inhibition of GABA outflow, by

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NTS1R activation. On the contrary, the pergolide-induced inhibition of DA outflow is unaffected by the coperfusion with NT [10]. In view of the localization of NTS1Rs and D_2 receptors on cortico-accumbens glutamatergic terminals, it seems likely that the antagonistic NTS1-D_2 receptor-receptor interactions and/or the activation of NTS1R protomer in the putative NTS1/D_2 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-D_2 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 D_2 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].

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