Satellite Symposium - Dopamine: New trends in receptor research and therapeutic implications

Dopamine receptor diversity: perspectives from new molecular and pharmacological developments.
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Five distinct dopamine (DA) receptors, named D1-D5, are expressed in the central nervous system where they control motor function, emotional states, and endocrine physiology. The D1 and D2 receptors are most abundant, and play an important role in control of voluntary movement. Expression patterns of the D3, D4, and perhaps D5 receptors, however, suggest that they may be appropriately located to mediate the effects of DA on affective, emotional, and cognitive function. In this introduction I will discuss the molecular and pharmacological aspects of DA receptor diversity ranging from nucleotide sequences to behavioral aspects of DA involvement in the development of selective D4 receptor agonists and antagonists, as well as a new monoclonal antibody to the human D4 receptor. My aim is to provide a short overview of this rapidly expanding area of research with important implications for both human behavior and human diseases including Parkinson's and schizophrenia.

A POTENTIAL ROLE OF 5-HT2 AND D2 RECEPTOR INTERACTION IN THE ATYPICAL ANTIPSYCHOTIC ACTION OF THE NOVEL SUCCIMIDE DERIVATIVE, PEROSPIRONE (SM-9018).

Patients with schizophrenia show diverse symptoms including the positive symptoms (e.g., hallucination and delusion), negative symptoms (e.g., apathy and social withdrawal) and dysphoric mood disturbances (e.g., anxiety and depression). Based on the hypothesis that dysfunction of the central serotonergic, as well as the dopaminergic, system is involved in the etiology of schizophrenia, we have developed the novel succimide derivative, perospirone, as the serotonin-dopamine antagonist (SDA)-type antipsychotic agent. This presentation will review the pharmacological profile of perospirone in comparison with other typical and SDA antipsychotics and discuss the potential role of 5-HT2 and D2 receptor interaction in the atypical antipsychotic actions of SDAAs based on our findings with selective 5-HT2 antagonists. Our study revealed that perospirone, like other SDAs, differs from the typical antipsychotics by exhibiting 1) putative anxiolytic and/or antidepressant actions in various animal models, 2) reduced extrapyramidal side effects (EPS) liability (e.g., catalepsy and bradykinesia induction), 3) lower propensity to block the striatal D2 receptors as revealed by the c-fos expression and dopamine turnover and 4) weaker actions in inducing supersensitivity of dopamine receptors after repeated treatments (e.g., oral dyskinesia model). The 5-HT2 antagonists mimicked the action of perospirone in animal models of mood disorder, and could attenuate the EPS induction, striatal c-fos expression and dopaminergic sensitization associated with the D2 antagonist treatments. These findings suggest that the blockage of 5-HT2 receptors may contribute to broad efficacy profile of SDAs (i.e., antipsychotic and mood stabilizing actions) and may counteract the striatal D2 receptor blockade by antipsychotics to reduce EPS.

DOPAMINE RECEPTOR SUPERSENSITIVITY.
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Dopamine (DA) receptor supersensitivity (DARSS) is a phenomenon that is represented by disproportionate generation (inhibition) of second messengers and/or exaggerated behavioral responses to an agonist. Using rats in which DA D1- or D2-complex receptors were sensitized during ontogeny, we used behavioral indices to demonstrate that some D1 agonist-induced effects (vacuous chewing) are dependent on the (a) presence of serotonin (5-HT) nerves, (b) supersensitization of 5-HT2 receptors, and (c) functional muscarinic receptors. The haloperidol-induced high level of vacuous chewing in DA-lesioned rats is found to be more readily attenuated by 5-HT2-blockers, than D1- or D2-blockers. DA D1-associated quinpirole-induced yawning is modulated by substances acting at nicotinic receptors. These and associated findings by others lead to the suggestion that DARSS is a phenomenon that may be related to a facilitated neural pathway, not necessarily to a process that is restricted to neurons on which DA receptors reside.

Dopamine and reward
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Not received
In vertebrate retinae, dopamine (DA) plays an important role in the transition from scotopic to photopic vision. At the cellular level, release mechanisms have been well described, but knowledge of DA removal from the extracellular space is scarce in the retina. We have used an antiserum against a dopamine transporter (DAT) to identify sites involved in DA reuptake in fish and marmoset retinas. DAT-immunoreactivity (DAT-ir) was investigated using a rat monoclonal DAT antibody generated against the N-terminus of the human DAT. Cryosections of paraformaldehyde fixed tissue were used for DAT-immunohistochemistry. In marmoset retinae, DAT-ir was observed in a prominent single band of processes in the distal sublayer of the inner plexiform layer, less pronounced in a small strip at the level of the IPL in the proximal retina. The distribution of DAT-ir coincides with the pattern of ramification of tyrosine hydroxylase-ir. A partial colocalization of DAT-ir with TH-ir is noted for the OPL and horizontal cell region labelling in the distal retina and for S5 of the IPL in the proximal retina. The distribution of DAT-ir in the inner plexiform layer of marmoset retinae coincides with the pattern of ramification of tyrosine hydroxylase-ir. A partial mismatch between immunocytochemical distribution of DAT and TH in fish retina is recognised for the DAT-staining of S2 and S4 of the IPL, indicating that additional cells may have the dopamine carrier. The staining pattern of DAT-ir in fish retina suggests a neuronal and glial localisation of the monoamine transporter, and supports the hypothesis of a heterogeneous system for the termination of the dopaminergic transmission.

**MULTIPLE ROLES OF DOPAMINE IN RETINAL FUNCTION**

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Dopamine is a neurotransmitter and neuromodulator that is secreted from retinal amacrine and interplexiform cells. The mode of action of dopamine differs from that of classical neurotransmitters in that it can diffuse long distances within the retina from its site of release to receptors on target cells. Dopamine acts on all neuronal cell types in the retina, including photoreceptor, horizontal, bipolar, amacrine and ganglion cells, as well as on the retinal pigment epithelial cells. Dopamine appears to play numerous roles in retinal and ocular function, and a few examples of these roles will be reviewed. During development, retinal dopamine has been implicated in ocular growth and development, and decreases of dopaminergic activity have been associated with development of experimental myopia in birds and primates. Dopamine regulates various aspects of rhythmic metabolism in the photoreceptor pigment epithelial complex, including photoreceptor disk shedding, photomechanical movements, and regulation of melatonin biosynthesis by photoreceptor cells. Retinal dopamine also appears to be involved in output pathways that regulate the synthesis of melatonin in the pineal gland. These actions of dopamine are mediated through dopamine receptor subtypes and cyclic AMP signaling pathways. In addition, dopamine receptors in retina may also regulate calcium signaling pathways via a variety of coupling mechanisms.