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Invited review

Purinergic signaling in Parkinson's disease. Relevance for treatment

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ABSTRACT

Purinergic signaling modulates dopaminergic neurotransmission in health and disease. Classically adenosine A_1 and A_{2A} receptors have been considered key for the fine tune control of dopamine actions in the striatum, the main CNS motor control center. The main adenosine signaling mechanism is via the cAMP pathway but the future will tell whether calcium signaling is relevant in adenosinergic control of striatal function. Very relevant is the recent approval in Japan of the adenosine A_{2A} receptor antagonist, istradefylline, for use in Parkinson's disease patients. Purine nucleotides are also regulators of striatal dopamine neurotransmission via P2 purinergic receptors. In parallel to the alpha-synuclein hypothesis of Parkinson's disease etiology, purinergic $P2X_1$ receptors have been identified as mediators of accumulation of the Lewy-body enriched protein alpha-synuclein. Of note is the expression in striatum of purinergic-receptor-containing heteromers that are potential targets of anti-Parkinson's disease therapies and should be taken into account in drug discovery programs.

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Contents

1. Introduction

Dopamine (DA) was first implicated for Parkinson's disease (PD) in 1959 (Carlsson, 1959) and reduced levels of DA in postmortem brains of PD patients were reported in 1960 (Ehringer and Hornykiewicz, 1960). PD mainly develops through degeneration of the nigro-striatal DA neurons (Anden et al., 1964; Dahlstroem and Fuxe, 1964; Fuxe, 1965; Fuxe et al., 1966, 2006). Dopamine

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produced and released by these neurons impact on receptors in medium-sized spiny GABA neurons of the caudate putamen, which is a major area in the CNS for the control of movements. Consequently, patients with PD have severe motor symptoms such as tremor, rigidity and hypokinesias, leading to difficulties in undertaking voluntary movements. The first clinical trials with dopamine replacement therapy, using the DA precursor L-3,4 dihydroxyphenylalanine (L-DOPA), were made in 1961–1964 (Birkmayer and Hornykiewicz, 1962, 1964). The clinical break-through came with the high dosage therapy of L-DOPA (Cotzias et al., 1969, 1967). Soon afterwards piribedil (2-[4-(1,3-benzodioxol-5-ylmethyl)piperazin-1-yl]pyrimidin-1-ium methanesulfonate) was used in human therapy seemingly acting as dopamine receptor agonist (Corrodi et al., 1971; Chase et al., 1974; Jenner et al., 1973). Fuxe in 1979 provided the first review on the potential of synthetic dopamine agonists in CNS research and as therapeutic agents (Fuxe, 1979).

The L-DOPA is converted into dopamine that engages specific dopamine G-protein-coupled receptor (GPCR) subtypes (D_1 to D_5). Early studies in animal models of PD (Ungerstedt, 1971) and in patients showed that the post-synaptic machinery in the striatum, e.g., the signaling pathways engaged by dopamine G-protein-coupled receptors, were intact except in advanced (demented) PD cases (Cotzias et al., 1969, 1967; Nishino et al., 1993). Prolonged L-DOPA treatment leads to a dysbalance of striatal circuits of motor control and leads to involuntary movements (L-DOPA-induced dyskinesias). Modulation of L-DOPA action is required to attain a more effective anti-PD therapy, especially to prevent further neurodegeneration and/or the appearance of L-DOPA-induced dyskinesias.

Adenosine (Ado) is a purine nucleoside whose systematic name is 6-amino-9-ß-D-ribofuranosyl-9H-purine. It was identified as a regulator of dopaminergic neurotransmission based on studies with adenosine receptors antagonists in the hemiparkinsonian rat model (Fuxe and Ungerstedt, 1974); the potency of methylxanthines such as caffeine in enhancing L-DOPA action best correlated to their potency to block Ado receptors (Fredholm et al., 1976). Ado may be released or produced at the site of action but it is also a volume-transmission (VT) regulator, i.e., by diffusion in the extracellular and the cerebrospinal fluids (CSF) it may target distant high-affinity Ado receptors in the neuron-glia networks (Fuxe et al., 2007a, 2010a).

The field of purine nucleotides as signaling molecules was pioneered by Burnstock (see for historical review (Burnstock, 2006)). The major transmitter/modulator is here ATP mediating its actions via P2X ionotropic receptors and P2Y GPCRs (Burnstock, 2013). ATP participates in fast synaptic transmission via the P2X receptors (Edwards et al., 1992). VT is also a mode of communication for ATP. It is of special interest for this review that P2 receptors can participate in enhancing DA release from the nigrostriatal and mesolimbic DA neurons (Zhang et al., 1995; Krugel et al., 2001a, 2001b). P2Y receptors can therefore have potential in the therapy of PD.

2. Adenosine as neuromodulator

Ado may appear as a novel neurotransmitter as it is present in synaptic vesicles (Corti et al., 2013) and evidence for direct action, via potential-dependent pathway of adenosine release from cerebellar slices, was obtained in mice lacking ecto-5'-nucleotidase, the enzyme that converts AMP to Ado (Klyuch et al., 2012). Due to its pleiotropic nature and the fact that extracellular ATP degrades to Ado, the nucleoside may appear in the extracellular space by a variety of mechanisms.

Extracellular ATP mainly originates from corelease with neurotransmitters (GABA, glutamate, acetylcholine or DA); in mesolimbic nerve terminals, ATP and DA are cotransmitters (Burnstock, 2013). Significant amounts of extracellular Ado in brain parenchyma are due to the breakdown of ATP released from nerve and astroglia cells, which express cell surface ectonucleotidases whose catalytic site faces the extracellular space (Zimmermann, 2000). Ultimately, ecto-5'nucleotidase converts extracellular AMP to extracellular Ado. Also equilibrating Ado transporters in the plasma membrane can contribute to extracellular Ado levels (Peng et al., 2005). Extracellular diffusion, i.e. volume transmission (VT) (Del Arco et al., 2003; De-Miguel and Fuxe, 2012; Fuxe et al., 2012), allows Ado to activate specific receptors on both nerve and glial cells. Ado acts on four specific GPCRs, A_1, A_{2A}, A_{2B} and A_3. In striatum two Ado receptors have been extensively characterized: A_1 and A_{2A} which couple to Gi/o and Gs proteins, respectively.

Astroglia is a quantitatively relevant source of extracellular ATP and adenosine (Hines and Haydon, 2014). One mechanism for astroglial ATP release is exocytosis as indicated from a number of studies (Zhang et al., 2007; Newman, 2003). A pioneering paper by Haydon and colleagues (Pascual et al., 2005) showed that astrocytic purinergic signaling coordinates synaptic networks. Using inducible transgenic animals that express in astrocytes a dominant-negative SNARE (soluble NSF (N-ethylmaleimide-sensitive fusion) protein attachment protein receptor) domain, it is possible to block the release of active compounds from astroglia. In this model the lacking astroglia exocytosis, reduced extracellular Ado levels resulted upon boosting synaptic glutamate transmission. Subsequently, using this model in combination with use of Ado A_1 receptor antagonists, evidence was obtained that astrocytes, via the extracellular ATP-Ado pathway, can increase the drive for sleep; activation of A_1 regulates *inter alia* synaptic glutamate release (Halassa et al., 2009). Astrocyte Ado VT-mediated neuromodulation can have a major impact on the brain circuits through integration of synaptic and VT signals, which involves receptor–receptor interactions in heteroreceptor complexes (Fuxe et al., 2013). However, it should be noted that feedback inhibition of excitatory activity is mediated by neuronal Ado release, and not by astrocytic ATP release (Lovatt et al., 2012). This may represent a rapid negative and neuroprotective feedback to avoid excessive excitatory neuronal activity leading to exhaustive energy depletion and nerve cell death. This mechanism is complimentary to the astroglial adenosine mechanism discussed earlier.

It is of substantial interest that astrocytic ATP may be also released into the extracellular space as a VT signaling molecule through pannexin channels permeable to ATP and other molecules of less than 1.5kD (Dahl and Muller, 2014; Jackson et al., 2014). The pannexin1 channel not only allows ATP efflux along a concentration gradient but is also activated by ATP from the extracellular side via P2Y and P2X receptors, especially $P2X_7$ receptors (Locovei et al., 2007, 2006). This positive feedback is normally counteracted by a negative one, i.e. by direct inhibition of the Pannexin1 channel by higher concentrations of ATP (Qiu and Dahl, 2009; Qiu et al., 2012). When the negative feedback is insufficient to stop the cascade, the overall system activates caspase-1 and -3 within the inflammasome (multiprotein oligomer involved in innate immunity) (Martinon et al., 2002). Apoptotic cell death develops due to caspase-mediated events and disappearance of ion gradients across the plasma membrane (Jackson et al., 2014; Chekeni et al., 2010). It is also suspected that the negative feedback involves Ado VT and activation of Ado receptors. These receptors can e.g., inhibit pannexin1 channel activity via allosteric interactions in heteroreceptor complexes containing Ado, P2X and/or P2Y receptors and the pannexin1 channels. A_{2A}-$P2Y_1$, A_{2A}-$P2Y_2$, A_{2A}-$P2Y_{12}$, A2A-$P2Y_{13}$ and A_1-$P2Y_1$ heteroreceptor complexes have been already identified (Yoshioka et al., 2001; Borroto-Escuela et al., 2014). This possibility would be in line with the neuroprotective actions of Ado