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Presynaptic Dopamine D2 Receptors Modulate [^{3}H]GABA Release at StriatoPallidal Terminals via Activation of PLC → IP3 → Calcineurin and Inhibition of AC → cAMP → PKA Signaling Cascades

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Abstract—Striatal dopamine D2 receptors activate the PLC → IP3 → Calcineurin-signaling pathway to modulate the neural excitability of En+ Medium-sized Spiny GABAergic neurons (MSN) through the regulation of L-type Ca^{2+} channels. Presynaptic dopaminergic D2 receptors modulate GABA release at striatopallidal terminals through L-type Ca^{2+} channels as well, but their signaling pathway is still undetermined. Since D2 receptors are Gi/o-coupled and negatively modulate adenylyl cyclase (AC), we investigated whether presynaptic D2 receptors modulate GABA release through the same signaling cascade that controls excitability in the striatum or by the inhibition of AC and decreased PKA activity. Activation of D2 receptors stimulated formation of [^{3}H]IP_1 and decreased Forskolin-stimulated [^{3}H]cAMP accumulation in synaptosomes from rat Globus Pallidus. D2 receptor activation with Quinpirole in the presence of L 745,870 decreased, in a dose-dependent manner, K^+-induced [^{3}H]GABA release in pallidal slices. The effect was prevented by the pharmacological blockade of Gi/o βγ subunit effects with Gallein, PLC with U 73122, IP3 receptor activation with 4-APB, Calcineurin with FK506. In addition, when release was stimulated with Forskolin to activate AC, D2 receptors also decreased K^+-induced [^{3}H]GABA release, an effect occluded with the effect of the blockade of PKA with H89 or stimulation of release with the cAMP analog 8-Br-cAMP. These data indicate that D2 receptors modulate [^{3}H]GABA release at striatopallidal terminals by activating the PLC → IP3 → Calcineurin-signaling cascade, the same one that modulates excitability in soma. Additionally, D2 receptors inhibit release when AC is active. Both mechanisms appear to converge to regulate the activity of presynaptic L-type Ca^{2+} channels.

Key words: D2 receptors, striatopallidal, PLC, adenylyl cyclase.

INTRODUCTION

Loss of dopamine in the basal ganglia leads to Parkinson Disease (PD). In the basal ganglia, the largest structure is the neostriatum, where more than 90% of cells are Medium-sized Spiny GABAergic neurons (MSN) (Parent and Hazrati, 1995). These neurons are segregated into two populations that project to different nuclei and that are modulated by dopamine via different signaling mechanisms. One population expresses dopamine D1 receptors and Substance P (SP+) and projects to the output nuclei of the basal ganglia (Substantia Nigra pars reticulata (SNr), and Globus Pallidus internus (GPi) or the entopeduncular nucleus in the rat). The other population expresses D2 receptors and Enkephalin (Enk+), and they have efferents to the external Globus Pallidus (GPe, Globus Pallidus (GP) in the rat) (Gerfen and Surmeier, 2011). The D1 class of dopamine receptors (D1 and D5 subtypes) is generally coupled to Gs/olf proteins that stimulate adenylyl cyclase (AC) and in turn increase cAMP-dependent Protein Kinase Activity (PKA). The D2 class (D2, D3, and D4 subtypes) is generally coupled to the Gi/o-proteins, which inhibit AC, thus reducing PKA activity (Missale et al., 1998; Beaulieu and Gainetdinov, 2011)

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Abbreviations: AC, adenylyl cyclase; ACSF, Artificial CerebroSpinal Fluid; MNS, Medium-sized Spiny GABAergic neurons; PD, Parkinson Disease; PKA, Protein Kinase Activity.

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