DOCTORAL THESIS

Localization of GABA receptors in the rat basal ganglia

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Localization of GABA Receptors in the Rat Basal Ganglia

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Abstract

Gamma-aminobutyric acid (GABA) is one of the most important inhibitory neurotransmitters in the rat basal ganglia. $GABA_B$ receptors are the first heteromeric metabotropic receptors found in the brain and it is one of the most important types of GABA receptor that mediate GABA neurotransmission. A functional $GABA_B$ receptor is known to be composed of two subunits, namely the $GABA_BR1$ and $GABA_BR2$ subunits. The novelty of the present study was to provide one of the first comprehensive studies about the precise cellular and subcellular localization of two subunits of the $GABA_B$ receptor in identified subpopulations of neurons in the normal rat basal ganglia. In the confocal microscope, immunoreactivity for $GABA_BR1$ was detected in the neuropilar elements as well as in the perikarya of neurons in the neostriatum. Many of the $GABA_BR1$-immunoreactive perikarya resembled the morphology of medium spiny neurons. In addition, other $GABA_BR1$-immunoreactive neurons were characterized by double immunofluorescence. Over 90% of the parvalbumin- and choline acetyltransferase-immunoreactive striatal interneurons and about 80% of the nitric oxide synthase-immunoreactive interneurons displayed $GABA_BR1$ immunoreactivity. In contrast, immunoreactivity for $GABA_BR2$ was primarily found in the neuropil of the neostriatum. Double labeling revealed that those perikarya that expressed immunoreactivity for parvalbumin, choline acetyltransferase, nitric oxide synthase, glutamate receptor two, *N*-methyl-*D*-aspartate receptor one, or $GABA_A\alpha1$ receptor respectively, did not express $GABA_BR2$ immunoreactivity. These results indicate that there is a differential expression of $GABA_BR1$ and $GABA_BR2$ immunoreactivity in different subpopulations of striatal neurons. The striatal neurons may therefore suggest to process less $GABA_B$ receptor in their fully functional assembly. In the normal rat substantia nigra, over 90% of tyrosine hydroxylase-immunoreactive dopaminergic neurons in the substantia nigra pars compacta were found to display immunoreactivity for $GABA_BR1$. Less $GABA_BR1$ immunoreactivity was detected in neurons of the substantia nigra pars reticulata. In addition, the tyrosine hydroxylase-immunoreactive dopaminergic neurons and the parvalbumin-immunoreactive GABAergic neurons in the substantia nigra pars reticulata were also found to display moderate $GABA_BR2$ immunoreactivity. These results demonstrate that there is also a distinct pattern of localization of $GABA_BR1$ and $GABA_BR2$ immunoreactivity in different subpopulations of the rat substantia nigra. A functional $GABA_B$ receptor may be expressed by the dopaminergic neurons in the substantia nigra pars compacta. It is less clear whether neurons in the substantia nigra pars reticulata express a functional $GABA_B$ receptor. In the electron microscope, $GABA_BR1$ and $GABA_BR2$ immunoreactivity was found in dendritic elements as well as in axonal elements in the neostriatum and the globus pallidus. These results confirm that neurons in the neostriatum and the globus pallidus may display both $GABA_B$ receptor subunits, although neurons may express a much higher level of $GABA_BR1$ than $GABA_BR2$ subunit. Last but not least, immunoreactivity for $GABA_BR1$ and $GABA_BR2$ was found to be increased in the substantia nigra but not in the neostriatum of the 6-hydroxydopamine-lesioned rat, an animal model of Parkinson's disease. These results indicate that expression of $GABA_B$ receptors in the neostriatum and the substantia nigra is differentially affected by dopamine denervation. These findings may have important implications in treatment of Parkinson's disease.

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