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Review

In vivo imaging of synaptic function in the central nervous system I. Movement disorders and dementia

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ABSTRACT

This review gives an overview of those in vivo imaging studies on synaptic neurotransmission, which so far have been performed on patients with movement disorders and/or dementia. Thereby, the focus is on disease-related deficiencies within the functional entity of the dopaminergic, serotonergic, cholinergic, glutamatergic, GABAergic or opioid synapse. In vivo investigations have yielded highly consistent results on the dysfunction of synaptic constituents in the majority of diseases covered by this overview. Findings show presynaptic dysfunctions in idiopathic as well as early-onset Parkinson's disease with decreases in striatal dopamine synthesis (57 out of a total of 59 reports on both types of Parkinson's disease), storage (nine out of nine reports), release (two out of three reports) and transporter binding (95 out of 95 reports). In contrast, the "Parkinson plus" syndromes multiple system atrophy and progressive supranuclear palsy are characterized by both pre- and postsynaptic deficiencies with reductions in striatal dopamine synthesis (11 out of a total of 11 reports on both types of "Parkinson plus" syndromes), storage (four of four reports), and transporter binding (27 out of 27 reports) as well as D_1 (two out of two reports) and D_2 receptor binding (34 out of 36 reports). This does not hold for the "Parkinson plus" syndromes dementia with Lewy bodies and corticobasal degeneration. For these diseases, for the time being, firm evidence of alterations in D_1 and/or D_2 receptor binding is lacking. In patients with Huntington's disease, mainly postsynaptic dysfunctions with reductions of striatal D_1 (six out of six reports) and D_2 receptor binding (15 out of 15 reports) were observed. Alzheimer's disease is characterized by both pre-and postsynatic deficiences of the cholinergic system with decreases of cortical acetylcholine storage (one out of two reports) and both musarinic (seven out of 10 reports) and nicotinic cholinergic receptor binding (three out of six reports). Moreover, reductions in cortical (one out of three reports) and limbic 5-HT_{1A} (three out of three reports) and cortical (four out of four reports) and limbic 5-HT_{2A} receptor binding (one out of two reports) were observed. Moreover, there is evidence for a cortical (four out of six reports) and cingulate (three out of three reports) increase of peripheral benzodiazepine receptor binding indicative of microglial activation. In the majority of investigations on patients with Alzheimer's disease, no alterations of presynaptic dopamine function were found, whereas all other forms of dementia including corticobasal degeneration, dementia with Lewy bodies, Parkinson's disease dementia and frontotemporal dementia were characterized by presynatic dopaminergic deficiencies with reductions in striatal dopamine synthesis (10 out of a total of 10 reports on these types of dementia), storage (four out of four reports) and transporter binding (29 out of 29 reports). Taken together, in vivo imaging methods can be employed for the diagnosis of idiopathic and early-onset Parkinson's disease as well as "Parkinson plus" syndromes and Huntington's disease. Moreover, differentiation is feasible between, firstly, Parkinson's disease and the "Parkinson plus" syndromes multiple system atrophy and progressive supranuclear palsy, secondly, multiple system atrophy/progressive supranuclear palsy and the other "Parkinson plus" syndromes dementia with Lewy bodies and corticobasal degeneration, and, thirdly, Alzheimer's disease and other forms of dementia.

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1. Introduction

The chemical synapse consists of the presynaptic terminal and the postsynaptic membrane. Between the pre- and the postsynaptic cells lies the synaptic cleft, which is about 20 nm wide, and allows rapid increases or decreases of neurotransmitter concentrations. The presynaptic terminal contains the neurotransmitter molecules, which, upon synthesis, are taken up into membrane-bound storage vesicles by vesicular membrane transporters (e.g. vesicular monoamine transporter type 2 [VMAT2], vesicular acetylcholine transporter [VAChT]). Neurotransmitter release is triggered by the arrival of an action potential, which produces an influx of calcium ions through voltage-dependent calcium-selective ion channels. The calcium influx elicits a biochemical cascade leading to the fusion of synaptic vesicles with the presynaptic membrane, and to the exocytosis of the neurotransmitter into the synaptic cleft. There, the neurotransmitter can bind to the ionotropic or metabotropic receptors on the postsynaptic membrane. Ionotropic receptors are ion channels, which open upon neurotransmitter binding, and thus permit ions to flow into or out of the cell. Direct synaptic transmission through ionotropic receptors is fast, and takes only several milliseconds. In contrast, indirect signal transduction via metabotropic receptors usually involves the activation of G proteins and intracellular second messenger systems, which, in turn, target potassium and calcium channels. Responses mediated by metabotropic receptors may last seconds, minutes or hours. Indirect synaptic transmission provides a mechanism for signal amplification, since many ion channels can be activated by one G-protein-coupled receptor.

Whether a synapse acts in an excitatory or in an inhibitory mode, depends on the type of ion channel conducting the postsynaptic current, which, in turn, is a function of the type of receptor and of the neurotransmitter employed at the synapse. At excitatory synapses, positively charged ions enter the postsynaptic cell and induce a depolarisation of the neuron, whereas at inhibitory synapses, a flow of negatively charged ions leads to neuronal hyperpolarisation. In the mammalian central nervous system, the main excitatory neurotransmitter is glutamate, while γ-amino butyric acid (GABA) and glycine are the major inhibitory neurotransmitters. Other important neurotransmitters are dopamine (DA), acetylcholine (ACh), serotonin (5-HT), histamine and endogenous opiates.