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Synaptic plasticity in the basal ganglia: A similar code for physiological and pathological conditions

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Abstract

It is widely accepted that the complexity and adaptability of neuronal communication, which is necessary for integrative and higher functions of the brain, is amply represented by plastic changes occurring at synaptic level. Therefore, long-term modifications of synaptic efficacy between neurons have been considered the cellular basis of learning and memory. Accordingly, there is a plethora of experimental evidence supporting this contention. Indeed, synaptic modifications in the hippocampus, the cerebral and cerebellar cortices regulate composite neuronal functions such those related to cognition, awareness, memory storage, and motion.

In recent years, the concept that enduring changes of excitatory glutamatergic synaptic potentials [long-term potentiation (LTP) and long-term depression (LTD)] are not limited to the hippocampus and cortices but occur also in other brain areas has emerged. For instance, plasticity at different excitatory pathways has been clearly demonstrated in the basal ganglia.

Here we present an overview of the experimental data regarding synaptic plasticity in the basal ganglia and highlight how results reported in the literature are often contradictory, especially when compared to those obtained in the hippocampal area. In trying to propose possible explanations to some of these contradictions, we present a holistic approach that re-interprets the basal ganglia synaptic plasticity in terms of expression of physiological and pathological phenomena and therapeutic effects of drugs.
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Keywords: Addiction; Basal ganglia; Dopamine; Electrophysiology; Glutamate; Huntington's disease; Ischemia; Long-term potentiation; Long-term depression; Parkinson's disease; Schizophrenia

Contents

Abbreviations: 3-NP, 3-nitropropionic acid; AMPA, α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate; cAMP, cyclic adenosine monophosphate; CB_1, cannabinoid 1 receptor subtype; Cdk5, cyclin-dependent kinase 5; D_1, dopamine D_1 receptor subtype; D_2, dopamine D_2 receptor subtype; DA, dopamine; DBS, deep brain stimulation; ERK, extracellular signal-regulated kinase; HD, Huntington's disease; HFS, high-frequency stimulation; L-DOPA, levodopa; LFS, low-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; EPSP, excitatory postsynaptic potential; GABA, γ-aminobutyric acid; $GABA_{A/B}$, ionotropic/metabotropic GABA receptor subtype; GluR1/2, glutamate receptor subunits; M_1, muscarinic 1 receptor subtype; $mGluR_{1/5}$, group I metabotropic glutamate receptor; $mGluR_{2/3}$, group II metabotropic glutamate receptor; MS, medium spiny neuron; NAc, nucleus accumbens; nAchR, nicotinic acetylcholine receptor; NMDA, *N*-methyl-D-aspartic acid; NR2B, *N*-methyl-D-aspartate receptor subunit; PSD-95, postsynaptic density 95; SN, substantia nigra; PD, Parkinson's disease; PKA, protein kinase A; SOD, superoxide dismutase; STN, subthalamic nucleus; TANs, tonically active neurons; THC, tetrahydrocannabinol; VTA, ventral tegmental area.

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1. Introduction

The basal ganglia are classically subdivided into a ventral pars, represented mainly by the nucleus accumbens (NAc) (ventral striatum), and the ventral tegmental area (VTA), and a dorsal pars, comprising the dorsal striatum (striatum), and the substantia nigra (*pars compacta* and *pars reticulata*).

It has been speculated that the ventral pars of the basal ganglia is primarily involved in psychic functions, while the dorsal pars plays a major role in motor functions. However, this schematic view may suffer from oversimplification, as it does not consider that either psychic or motor activities are due to overlapping functions, which are endowed in both ventral and dorsal structures (Everitt et al., 2001; Gerdeman et al., 2003; Percheron et al., 1994; Samejima et al., 2005).

Interestingly, while the extensive inputs to the basal ganglia are excitatory, the outputs are inhibitory (Bolam et al., 2000; Gerfen and Wilson, 1996). In particular, the excitatory inputs originating from the cortex and the thalamus innervate principal cells in the NAc and dorsal striatum, the GABAergic medium spiny (MS) neurons. MS neurons then project through the direct pathway to the internal division of the globus pallidus/substantia nigra *pars reticulata*. The inhibitory efferents of these nuclei mainly terminate in the thalamus, which in turn projects to the cortex and the striatum. There are also intrinsic neuronal loops within basal ganglia. One of these (the indirect pathway), controlled by the striatum via the striato-pallidal pathway, originates in the external pallidum and inhibits the subthalamic nucleus (STN), whose glutamatergic neurons project to the internal pallidum and the substantia nigra (SN). Another intrinsic loop is represented by the mesoaccumbens (ventral anterior) and the nigro-striatal (dorsal posterior) dopaminergic systems, which exert a modulatory role on neuronal activity in the ventral and dorsal striatum (Albin et al., 1989).

LTP and LTD have been reported at glutamatergic synapses of the cortico-striatal and cortico-accumbal pathways and at glutamatergic afferents to the ventral midbrain and the subthalamus. It is believed that these long-term modifications in the efficacy of the excitatory signals contribute to optimization, shaping and maintenance of basal ganglia functions. Indeed, animal models of basal ganglia dysfunctions highlighted specific alterations in LTP and/or LTD expression at glutamatergic afferents.

Although there is a common agreement on the ability of glutamatergic synapses in the basal ganglia to undergo enduring changes in their efficacy, several discrepancies may be encountered when looking at the specific forms of synaptic plasticity expressed, especially in the ventral and dorsal striatum. Thus LTP, as opposed to LTD, or even no change in synaptic efficacy, has been described in theoretically similar experimental conditions.

Here we propose that the plastic synaptic changes induced in the basal ganglia could be either bidirectional or less delineated in terms of polarity. Consequently, not only the plastic modification in excitatory postsynaptic potential (EPSP) amplitude but also the long-term maintenance of an unmodified synaptic message could represent key codes for controlling either movement, habit changes, volition, pleasure, therapeutic effects of medications, or addiction, movement/psychic disorders and ischemic damage.

2. Plastic changes in the ventral pars of the basal ganglia

2.1. Nucleus accumbens

Both LTP and LTD of synaptic transmission have been induced in the nucleus accumbens (NAc), by a high-frequency electrical stimulation (HFS) of the excitatory cortical inputs, when associated to a depolarization of the MS neurons that resembles the up state observed *in vivo* (Vergara et al., 2003; Wilson, 1993). Alternatively, a stimulating protocol to induce LTD consists in 10–13 Hz stimulation applied for several minutes, possibly in the presence of $GABA_A$ receptor

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