The cortico-basal ganglia-thalamocortical circuit with synaptic plasticity. II. Mechanism of synergistic modulation of thalamic activity via the direct and indirect pathways through the basal ganglia

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Abstract

A possible mechanism underlying the modulatory role of dopamine, adenosine and acetylcholine in the modification of corticostriatal synapses, subsequent changes in signal transduction through the 'direct' and 'indirect' pathways in the basal ganglia and variations in thalamic and neocortical cell activity is proposed. According to this mechanism, simultaneous activation of dopamine D_1/D_2 receptors as well as inactivation of adenosine A_1/A_{2A} receptors or muscarinic M_4/M_1 receptors on striatonigral/striatopallidal inhibitory cells can promote the induction of long-term potentiation/depression in the efficacy of excitatory cortical inputs to these cells. Subsequently augmented inhibition of the activity of inhibitory neurons of the output nuclei of the basal ganglia through the 'direct' pathway together with reduced disinhibition of these nuclei through the 'indirect' pathway synergistically increase thalamic and neocortical cell firing. The proposed mechanism can underlie such well known effects as 'excitatory' and 'inhibitory' influence of dopamine on striatonigral and striatopallidal cells, respectively; the opposite action of dopamine and adenosine on these cells; antiparkinsonic effects of dopamine receptor agonists and adenosine or acetylcholine muscarinic receptor antagonists. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

1. Introduction

The numerous movement disorders are explained by functional model of the cortico-basal ganglia-thalamocortical motor loop (DeLong, 1990). In humans, lesions at the basal ganglia levels lead to hypokinetic and hyperkinetic dys-

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functions attributive to Parkinson's and Huntington's disease. Diverse changes in signal transduction through the basal ganglia can be caused by modifications in the efficacy of cortical inputs to the striatum, the entry structure of the basal ganglia. Plasticity of excitatory corticostriatal inputs, such as long-term potentiation and depression (LTP, LTD), involves convergent actions of glutamate, dopamine, adenosine and acetylcholine (Calabresi et al., 1992, 1998, 1999a). However, mechanism underlying different changes in signal transduction through the basal ganglia, produced by modulatory neurotransmitters, remains unclear. The aim of this work has been to analyze the feasible mechanisms of variations of neuronal activity in the cortico-basal ganglia-thalamocortical loop, triggered by modification of corticostriatal synapses. Earlier suggested modification rules (Silkis, 2001) were used for this analysis. According to these rules, an activation of dopamine D_1 and D_2, or adenosine A_{2A} and A_1, or muscarinic M_1 and M_4 receptors on striatal cells promotes the induction of LTP and LTD, respectively. Based on these rules we expected that modulatory neurotransmitters variously modify the neuronal interactions in the 'direct' and 'indirect' pathways through the basal ganglia, since different receptor types are expressed on striatal cells, originative these pathways.

2. Functional organization of the cortico-basal ganglia-thalamocortical 'motor' circuit

The main features and character of operation of the cortico-basal ganglia-thalamocortical 'motor' loop are widely described (Alexander and Crutcher, 1990; DeLong, 1990; Parent and Hazrati, 1995a,b). Signals initiated in the precentral motor areas activate the inhibitory spiny cells in the putamen. This part of the striatum is one of the 'input' structures of the basal ganglia. Striatal cells inhibit 'output' neurons of the basal ganglia which are possess in the motor portion of the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr). This pathway is known as 'direct' (Fig. 1). Another group

of striatal cells inhibits the external segment of the globus pallidus (GPe) which inhibits excitatory cells of the subthalamic nucleus (STN) and inhibitory cells of GPi. This pathway is known as 'indirect' (Fig. 1). One segment of STN is reciprocally connected with GPe, while another projects to the output basal ganglia cells (Parent and Hazrati, 1995b). Possibly, the striatum more effectively reduce the activity of GPe than GPi, since striatal terminals form 85 and 31% of all inhibitory contacts on the soma of GPe and GPi cells, respectively (Shink and Smith, 1995). GPe, which makes 47% of contacts on the soma of GPi cells (Shink and Smith, 1995) can strongly inhibit GPi. Cells of GPi/SNr inhibit the ventrolateral thalamus, which activates the precentral motor areas. Thalamic cells excite those spiny striatal neurons, that influence thalamic activity through GP/SNr (Funaki et al., 1998; Parent and Hazrati, 1995a). Terminals from ventrolateral nucleus
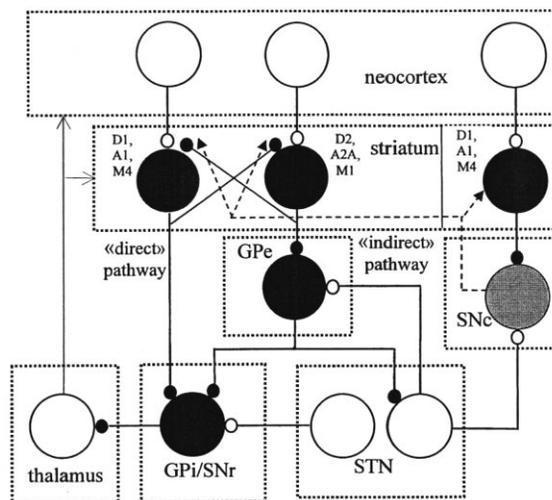

Fig. 1. The scheme of excitatory and inhibitory connections in the cortico-basal ganglia-thalamocortical loop. GPi and GPe, internal and external segments of the globus pallidus, respectively; SNr and SNc, substantia nigra pars reticulata and compacta, respectively; STN, subthalamic nucleus; D_1 and D_2, receptors sensitive to dopamine; A_1 and A_{2A}, receptors sensitive to adenosine; M_1 and M_4, muscarinic receptors sensitive to acetylcholine. Large white, black and gray circles, excitatory, inhibitory and dopaminergic cells, respectively. Small white and black circles, excitatory and inhibitory synapses, respectively.

make synaptic contacts with cortical neurons, projecting to the striatum (Zin-Ka-leu et al., 1998). Thus, the thalamo-cortico-striatal loop is formed by monosynaptic connections. Striatonigral/striatopallidal cells, which are located in the matrix, express dopamine D_1/D_2 receptors (Loschmann et al., 1997). Neurons of striosomes, projecting to the dopaminergic cells of substantia nigra pars compacta (SNc) contain D_1 receptors that are colocolized with muscarinic M_4 receptors (Harrison et al., 1996). Adenosine A_1 (A_{2A}) receptors are specifically expressed on striatonigral (striatopallidal) cells, where they are colocolized with D_1 (D_2) receptors (Ferre et al., 1997; Fuxe et al., 1998; Svenningsson et al., 1999). Muscarinic M_1 receptors are more often located on striatopallidal cells, while coexpression of D_1, and M_4 receptors on striatonigral neurons has been demonstrated (Wang and McGinty, 1996). Thus, the sign of modification (LTP or LTD) of synapses on spiny neurons giving rise to the direct and a indirect pathways through the basal ganglia, depends on the activating $D_1/A_1/M_4$ and $D_2/A_{2A}/M_1$ receptors, respectively (Fig. 1). It is clear that in the absence of dopamine, adenosine and acetylcholine the cortex disinhibits the thalamus through the direct pathway, while the indirect pathway is inhibitory (Fig. 1). Any persistent impact of modulatory neurotransmitters on the efficacy of corticostriatal synapses can lead to a shift in the balance between neural interactions in the direct and indirect pathways and subsequent variations in the thalamic and cortical functioning.

3. Synergistic changes in the basal ganglia-thalamic transmission due to the opposite modification of cortical inputs to striatonigral and striatopallidal cells

According to earlier suggested modification rules (Silkis, 2001), an activation of dopamine D_1 (D_2) receptors leads to LTP (LTD) of excitatory cortical inputs to striatonigral (striatopallidal) cells and augmenting (lowering) GABA release into GPi/SNr (GPe). Actually, precisely this type of influence of D_1, and D_2 receptors on GABA

release by striatonigral and striatopallidal cells has been obtained (Hossain and Weiner, 1995; Ferre et al., 1996a; Harsing and Zigmond, 1997; Hooper et al., 1997; Wooten, 1997). It has also been shown that these changes lead to variations in neuronal activity in the direct and indirect pathways. We assume that the proposed role of dopamine in LTP and LTD induction can underlie 'excitatory' and 'inhibitory' effect of dopamine on striatal cells, projecting into the GPi/SNr and GPe, respectively (DeLong, 1990). If an activation of A_1 (A_{2A}) receptors promotes LTD (LTP) in striatonigral (striatopallidal) cells (Silkis, 2001), then GABA release into GPi/SNr (GPe) can be reduced (strengthened) by adenosine. Indeed, A_1 receptor activation antagonistically influenced GABAergic striatal input to the entopeduncular nucleus, the homologue of the non primates GPi (Ferre et al., 1996a). In contrast, an agonist of A_{2A} receptors caused an augmentation of GABA release into the GPe (Corsi et al., 1999). This means that the sign of modification of each synapse depends on the difference between parameters of current and prior activation (Silkis, 1998). Apparently for this reason, both depression and potentiation of activity of SNr neurons have been observed after an injection of a selective D_1, receptor agonist as well as D_2 receptor agonist (Akkal et al., 1996).

In spite of suggested modification rules (Silkis, 2001) it seems paradoxical that the coactivation of D_1 and D_2 receptors resulted in striatal LTD (Calabresi et al., 1992). We assume that this effect is the sequence of reciprocal inhibition between striatal neurons (Fig. 1) that occurs through both $GABA_A$ and $GABA_B$ receptors (Shi and Rayport, 1994). Therefore, the efficacy of inhibitory connections can be modified (Silkis, 1998, 2000). An inducing LTP (LTD) in striatonigral (striatopallidal) cell caused by activation of D_1 (D_2) receptors, can lead to the rising (lowering) the inhibitory influence on striatopallidal (striatonigral) cell. This should promote a decrease (enlargement) in postsynaptic Ca^{2+} and cAMP concentration and intensifying LTD (LTP) of excitatory cortical input simultaneously with LTP (LTD) of inhibitory input to a striatopallidal (striatonigral) cell. Indeed, LTD in striatopallidal cells, caused by D_2

receptor activation, has been strengthened by D_1 receptor agonists (Ruskin et al., 1998). We assume that reciprocal inhibitory connections can also enhance the opposite modification of cortical inputs to striatonigral and striatopallidal cell through the net interactions between A_1 and A_{2A} receptors, A_1 and D_2 receptors, A_{2A} and D_1 receptors. Actually, it had been shown, that the effect caused by D_1 receptor agonist has been strongly potentiated by inactivation of A_{2A} receptors (Fenu et al., 1997; Le-Moine et al., 1997). Interaction between A_{2A} and D_1 receptors produced by transneuronal interactions has been obtained in behavioral experiments too (Ferre et al., 1997). Modifiable inhibitory reciprocal connections could be adjunct to the models of recurrent networks with Hebbian learning such as the model for cortical and brainstem premotor circuits (Hua et al., 1999).

The presence (absence) of dopamine in the striatum can intensify (reduce) an inhibition of GPi/SNr as directly, by striatonigral cells in consequence of LTP (LTD) in cortical inputs, as indirectly by GPe neurons, which become more weakly (strongly) inhibited by striatopallidal cells due to LTD (LTP) of their cortical inputs (Fig. 2a). Thus, the synergistic decrease in the activity of output inhibitory neurons of the basal ganglia could be caused by dopamine. A change in GPi/SNr activity caused by additional dopamine (deficit of dopamine) in the striatum must lead to a disinhibition (inhibition) of the thalamic and neocortical cell activity. Indeed, an increase and decrease in the amount of dopamine in the striatum resulted in strengthening and weakening thalamo-cortical inputs, respectively (Rodriguez and Gonzales-Hernandez, 1999). The presence (absence) of adenosine in the striatum must lead to the opposite effects due to the promotion of LTD (LTP) on striatonigral cells and LTP (LTD) on striatopallidal cells (Fig. 2b). Since dopamine (adenosine) induced modification of corticostriatal synapses synergistically influence the activity of output GPi/SNr cells, a conjunctive activation of D_1 and D_2 (A_{2A} and A_1) receptors should cause more strong effects than those produced by activation of one type of receptors. Actually, the selective agonist of D_1 or D_2 receptors produced
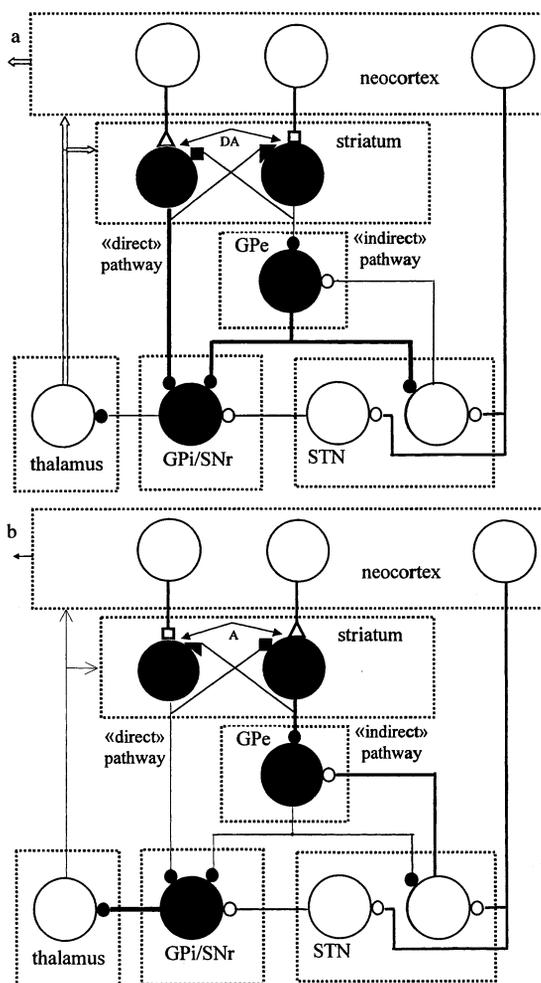

Fig. 2. Changes of synaptic transmission in the 'direct' and 'indirect' pathways through the basal ganglia in consequence of dopamine (a) and adenosine (b) induced modification of corticostriatal synapses. Small triangles and squares, potentiated and depressed synapses, respectively. Other designations are as in Fig. 1.

changes in firing rate of 23% or 17% of SNr neurons, respectively, while joint activation of both receptors resulted in changes of 70% of cells (Murer et al., 1997).

According to suggested modification rules, dopamine and adenosine oppositely influence the efficacy of cortical inputs to striatonigral (striatopallidal) cells due to coexpression of D_1 and A_1 (D_2 and A_{2A}) receptors. So, one can expect that a

blockage of adenosine receptors together with activation of dopamine receptors on both striatonigral and striatopallidal cells will more strongly enhance the activity of the thalamus and neocortex. The same must be true for the joint activation of dopamine receptors and blockade of muscarinic receptors. This is because M_1–D_2 receptors and M_4–D_1 receptors are coexpressed on striatopallidal and striatonigral cells, respectively. In line with modification rules (Silkis, 2001), dopamine and muscarine oppositely influence the efficacy of a cortical input to a striatopallidal as well as to a striatonigral neuron, since an activation of M_1 and M_4 receptors can promote the induction of LTP and LTD in these cells. Actually, acetylcholine oppositely affects striatopallidal and striatonigral cells (Harrison et al., 1996; Wang and McGinty 1997).

Due to presence of excitatory thalamic afferents in the striatum (Fig. 1), an increase of thalamic activity can facilitate the firing rate of striatal cells. Additional excitation can promote LTP on striatonigral. cells, but impede LTD on striatopallidal neurons. The last effect must reduce thalamic and striatal activation. Thus, the excitation in the thalamo-basal ganglia-thalamic loop can be limited. On the other hand, LTD induction on striatopallidal cells, subsequent disinhibition of GPe neurons and augmented inhibition of STN cells can in turn decrease the excitation of GPe neurons (Fig. 2). Therefore, this local circuit can reduce inhibitory action of GPe not only on STN, but also on GPi/SNr, and thus decrease the disinhibitory effect of dopamine on the thalamus through the indirect pathway. An activation of D_1 receptors on spiny cells of striosomes and LTP induction must increase the inhibition of dopaminergic cells in SNc (Fig. 1) and cause a decrease of dopamine release in the striatum. The deficit of dopamine must impair corticostriatal LTP and decrease the inhibition of SNc. These effects can prevent the variation of dopamine concentration through a large range.

The tendency to bursting discharges and oscillations has been found in corticostriatal and thalamic cells (Magnin et al. 2000; Plenz and Aertsen 1996). Such synchronization must promote the modification of synapses in the striatum as well as in the whole basal-ganglia-thalamocortical net, since it provides the fulfillment of the Hebbian rule (coincidence in the activity of pre- and postsynaptic neurons).

We have postulated that only receptors activated by transmitter are modifiable (Silkis, 1998, 2000b). This postulate, which provides the fulfillment of the Hebbian rule and input specificity of LTP/LTD, is experimentally supported in different structures, including the basal ganglia (Calabresi et al., 1999b; Harsing and Zigmond, 1997; Matuszewich and Yamamoto, 1999). So, dopamine and others neuromodulators, which are diffusely released into the striatum after arriving of excitatory signals from one or several cortical areas, can modulate the efficacy of those corticostriatal synapses that have been simultaneously activated by others cortical areas. This effect may lead to the selection of signals and their 'correction' depending on other ones. Such mechanism may underlie the one of the most important functions of the basal ganglia — the integration of information from different neocortical areas.

4. Correlation between effects emerging from proposed mechanism, and available data related to motor disorders and treatment of Parkinson's and Huntington's disease

The motor disorders at Parkinson's disease are thought to be a sequence of the deficit of dopamine, modification of cortical inputs to striatal cells and decrease of inhibition of output neurons of the basal ganglia (Gibb, 1997; Chase et al., 1998). Subsequent enlargement of the activity of output neurons causes inhibition of thalamic and cortical neurons and akinesia or rigidity. Huntington's disease is also associated with an activation of dopamine-sensitive receptors on striatal neurons and consequent changes of signal transduction in the cortico-basal ganglia-thalamocortical loop (Lawrence et al., 1998). It is believed, that the coexisting of hypo- and hyperkinetic disorders of locomotions at Huntington's disease can be a consequence of changes in the direct and indirect pathways (Berardelli et al., 1999). At Huntington's disease the number of spiny neurons with D_1

receptors in caudate nucleus of the striatum increases (Augood et al., 1997). From the point of view of suggested mechanism, such fact should rise the probability of LTP induction on striatonigral cells and subsequent intensifying of a motor activity (hyperkinesia) through the direct pathway. It is known, that endogenous dopamine activates D_2 receptors and does not activate D_1, receptors (Harsing and Zigmond, 1997). We assume that LTD in striatopallidal cells, caused by D_2 receptor activation, may promote a basic lowering thalamic inhibition through the indirect pathway.

It follows from proposed mechanism, that the blockade of adenosine and/or acetylcholine sensitive receptors on striatal cells can facilitate LTP/LTD induced by dopamine and thus reinforce disinhibition of thalamic and cortical activity. Actually, a treatment of Parkinson's disease by antagonists of adenosine and/or muscarinic receptors enhances the therapeutic effects caused by dopamine alone. Systemic administration of A_1 receptor antagonist essentially potentiated a motor activity caused by D_1 receptor agonist (Popoli et al., 1996), while A_{2A} receptor antagonist, caffeine, enhanced effects induced by D_2 receptor agonist (Pollack and Fink, 1995). In the caudate nucleus A_{2A} receptors are activated by endogenous adenosine. The model suggests that the preventing this activation can be useful in the treatment of hypokinesia. Indeed, the blockade of A_{2A} receptors strengthened motor responses (Fuxe et al., 1998; Svenningsson et al., 1999), especially for animal with a low level of dopamine (Hauber et al., 1998), and caused a strong augmentation of a motor activity at small doses of L-dopa (Fenu et al., 1997). Moreover, A_{2A} receptor antagonists administered alone produced antiparkinsonian effects that reached the level of efficacy of L-dopa but was less likely to elicit dyskinesias (Grondin et al., 1999).

As concern the antiparkinsonic effect of muscarinic receptor antagonists, on the one hand, there are some proofs that it is linked to an excitatory action of cholinergic interneurons on those striatal cells that contain enkephalin (Alexander and Crutcher, 1990). These cells giving rise to the indirect pathway. On the other hand, it has

been shown, that antiparkinsonic effect is related to a blockage of those muscarinic receptors (M_4 or M_2 that inhibit the activation of adenylate cyclase, caused by D_1 receptor activation (Olianas and Onali, 1996). These receptors allow controlling the activity of striatal neurons originative the direct pathway. According to the current view, antagonistic interactions between A_{2A} and D_2 receptors as well as interactions between A_1 and D_1 receptors in the basal ganglia could underlie a depressive influence of agonists of adenosine receptors on motor activity (Ferre et al., 1996b). It follows from suggested mechanism that effects obtained on the macrolevel, are based on the opposite influence of adenosine and dopamine on cAMP concentration and protein kinase A activity in both striatonigral and striatopallidal neurons. Antagonistic interactions between D_1 and M_4 receptors or D_2 and M_1 receptors could be also based on the opposite influence of dopamine and acetylcholine on the activity of protein kinases in striatal spiny cells.

Single-unit registration from GPe, GPi, STN and thalamus had shown that the oscillatory properties of individual cells, combined with the dynamic properties of the cortico-basal ganglia-thalamocortical network, are responsible for the parkinsonian symptoms (Magnin et al. 2000). The frequency of oscillations in the neuronal network depends on the parameters of inhibitory transmission between its elements. Therefore, the shift in the dynamic properties of the net, specific to Parkinson's or Huntington's disease, can be artificially corrected by diverse neurotransmitters, which modulate the strength of inhibitory connections in the basal ganglia.

5. Conclusion

According to the suggested modification rules for striatal synaptic plasticity, conjunctive activation (inactivation) of dopamine D_1 receptors and inactivation (activation) of adenosine A_1 or muscarinic M_4 receptors on striatonigral neurons together with an activation (inactivation) of D_2 receptors and inactivation (activation) of A_{2A} or M_1 receptors on striatopallidal neurons can pro-

mote LTP and LTD (LTD and LTP) of cortical inputs to striatonigral and striatopallidal cells, respectively. Subsequent simultaneous changes in signal transductions via the direct and indirect pathways through the basal ganglia can lead to a synergistic decrease (increase) in the activity of inhibitory neurons of the output nuclei of the basal ganglia and cause an essential disinhibition (inhibition) of thalamic and neocortical cell activity. The proposed mechanism makes it possible to explain intensifying of a motor activity observed after joint administration of agonists of dopamine receptors and antagonists of adenosine and/or acetylcholine muscarinic receptors.

Acknowledgements

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