Any perturbations within the basal ganglia system lead to movement disorders [1]. The striatum, receiving its main input from the cerebral cortex, is the first relay of this system, and its medium-sized spiny neurons give rise to the output pathways. Two subpopulations of these efferent GABAergic neurons have been identified. The neurons projecting to the globus pallidus, striatopallidal, express enkephalin and mostly the dopamine D2 receptor, whereas the neurons projecting to the substantia nigra pars reticulata, striatonigral, express substance P, dynorphin, and the dopamine D1 receptor [2]. These two subpopulations give rise to different loops, acting respectively as an inhibitory and an excitatory pathway to the thalamus [1]. In addition, two classes of interneurons mostly represent the remaining striatal neurons: the cholinergic and the somatostatin-expressing neurons.

The dopaminergic nigrostriatal pathway influences these two striatal subpopulations differentially. Reduction of dopamine input into the striatum decreases substance P expression in striatonigral neurons, whereas it increases enkephalin expression in the striatopallidal subpopulation [2]. Moreover, these actions of dopamine are differentially mediated by dopamine D1 and D2 receptors [2], the former being mainly expressed in striatonigral neurons and the latter mainly in striatopallidal neurons [2]. It has been proposed that hyperkinetic states such as Huntington’s disease or hemiballism, and hypokinetic states such as parkinsonism, all result from disequilibria between these two striatal subpopulations and/or the specific pathways originating from them [1].

The expression of adenosine A2a receptor is selectively detected in the striatum [3–8]. Moreover, this receptor is mainly expressed by striatopallidal neurons that also express enkephalin and the dopamine D2 receptor [4,6,8]. Conversely, it is not expressed by the striatonigral neurons expressing substance P and the dopamine D1 receptor, by the cholinergic interneurons, nor by the somatostatin-expressing interneurons [4,6,8,9]. These neuroanatomical data constitute the substratum for involvement(s) of this receptor in the basal ganglia physiology because the adenosine analogues have been recognized as strong depressors of the locomotor activity, most probably by acting at this striatal A2 receptor [10–12]. Moreover, interactions with the dopamine D2 receptor
occur in controlling this behavior [11–13] and $A_2a/D_2$ receptor interactions have been also observed in the rat striatum at either the membrane level [14,15] or in the regulation of the GABA release [15–17].

Adenosine receptors are also involved in the regulation of gene expression in the rat striatum, and this effect is also subject to interactions between adenosinergic and dopaminergic systems. The present chapter will summarize these recent data.

**Regulation of Gene Expression in the Dopamine-Depleted Striatum**

In the case of dopamine depletion in the striatum, such as encountered in Parkinson's disease, enkephalin expression is increased while substance P expression is decreased [2]. In that condition D$_2$ agonist selectively normalizes expression of enkephalin and D$_1$ agonist selectively normalizes expression of substance P [2]. In the control of adenylyl cyclase activity and locomotor activity, $A_2a$ and D$_2$ receptors have opposite effects. It was therefore hypothesized that blockade of this $A_2a$ receptor, selectively expressed by the striatopallidal neurons, would have the same effect as activation of the D$_2$ receptor.

To test this hypothesis, rats unilaterally depleted of dopamine in the right side subsequently received chronic saline or caffeine treatments [6]. As expected, in saline-treated animals expression of enkephalin and substance P were increased (Figs. 9-1A, 9-4B) and decreased (Figs. 9-1C, 9-4B), respectively, in the dopamine-depleted striatum. In this dopamine-depleted striatum, caffeine treatment decreased and therefore tended to normalize the level of enkephalin expression (Figs. 9-1B, 9-4C), without any effect on the decreased level of substance P (Figs. 9-1D, 9-4C) [6]. This validates the hypothesis because, indeed, this action of caffeine is totally similar to that observed for a D$_2$ agonist [2]. In hypokinetic disorders such as Parkinson's disease, all treatments that reduced the hyperactivity of the loop arising from the striatopallidal neurons completely resolve the parkinsonian syndrome. This includes D$_2$ agonist administration and lesion of the subthalamic nucleus [18]. Therefore, selective adenosine $A_2a$ antagonists, which also decrease the hyperactivity of this loop in dopamine-depleted rats, should widen the therapeutic arsenal of Parkinson's disease and other syndromes characterized by parkinsonism. Moreover, the opposite effects of $A_2a$ and D$_2$ agonists on the same neuronal target, suggest that, like D$_2$ antagonists, selective $A_2a$ agonists could be useful in the treatment of schizophrenia.

**Regulation of Gene Expression in the Intact Striatum**

From the previous series of experiments, it also appeared that, unexpectedly, the same caffeine treatment regulates differentially the expression of substance P and enkephalin in the normal striatum (left side) (Fig. 9-1B, 9-1D) [6]. Indeed, in the normal striatum caffeine increased and decreased the expression of enkephalin and that of substance P, respectively (Figs. 9-1B, 9-1D, 9-4D) [6]. These effects were significantly reversed by concomitant treatment with 5'-N-carboxyamidoadenosine (NECA) but not by concomitant treatment with N$^6$-cyclohexyladenosine (CHA) [6], suggesting that caffeine at least partially acts at an $A_2$ receptor. This caffeine-induced modifications of gene expression are identical to that observed in the case of dopamine depletion (see Fig. 9-1 and compare Fig. 9-4B and 9-4D).

Moreover, the same chronic caffeine treatment also induces the expression of neurotensin and cholecystokinin mRNAs (Figs. 9-2, 9-3) in different subsectors of the striatum, the subcallosal region (Fig. 9-2), and the dorso- and ventro-lateral quadrants (Fig. 9-3), respectively [19]. Once again, these peculiar patterns of expression are very similar to those observed in the case of dopamine depletion [20,21].