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Roles of μ-Opioid Receptors in GABAergic Synaptic Transmission in the Striosome and Matrix Compartments of the Striatum

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Abstract The striatum is divided into two compartments, the striosomes and extrastriosomal matrix, which differ in several cytochemical markers, input–output connections, and time of neurogenesis. Since it is thought that limbic, reward-related information and executive aspects of behavioral information may be differentially processed in the striosomes and matrix, respectively, intercompartmental communication should be of critical importance to proper functioning of the basal ganglia-thalamocortical circuits. Cholinergic interneurons are in a suitable position for this communication since they are preferentially located in the striosome-matrix boundaries and are known to elicit a conditioned pause response during sensorimotor learning. Recently, μ-opioid receptor (MOR) activation was found to presynaptically suppress the amplitude of GABAergic inhibitory postsynaptic currents in striosomal cells but not in matrix cells. Disinhibition of cells in the striosomes is further enhanced by inactivation of the protein kinase C cascade. We discuss in this review the possibility that MOR activation in the striosomes affects the activity of cholinergic interneurons and thus leads to changes in synaptic efficacy in the striatum.

Keywords Basal ganglia · Striatum · Dopamine islands · μ-opioid receptor · Striosomes/patches · γ-aminobutyric acid (GABA)

Introduction

The basal ganglia functions as one of the key stations of the cortico-basal ganglia-thalamo-cortical loop circuits and plays important roles in motor control, reinforcement learning, and drug addiction [1, 2]. The striatum is a major input stage of the basal ganglia and consists of a heterogeneous mosaic of neurochemically distinct, interdigitating compartments known as striosomes (or patches) and the extrastriosomal matrix, each with its unique input–output connections and neurotransmitters, neuromodulators, and associated receptors [3, 4]. Striosomes project mostly to dopaminergic neurons of the substantia nigra pars compacta (SNc) and receive input from prelimbic, infralimbic, orbitofrontal, and anterior cingulate cortex [5–10]. Neurons in the striosomes are rich in μ-opioid receptors (MORs), D1 dopamine receptors, substance P, dynorphin, and enkephalin [3, 11]. In contrast, the matrix gives rise to two distinct, parallel pathways termed 'direct' striatonigral and 'indirect' striatopallidal pathways and receives inputs mainly from somatosensory and associational areas of the cerebral cortex [3, 5]. Cells in the matrix more abundantly express acetylcholinesterase (AChE), calbindin-D28K, D2 dopamine receptors, and somatostatin [3, 11]. These anatomical features suggest that striosomes and matrix play different roles in the processing of cortical inputs. Indeed, during resting and neutral behavioral states, the highest metabolic activity in the striatum was observed in the matrix compartment rather than in the striosomes [12]. In contrast, electrical stimulation through electrodes in contact with striosomes but not matrix led to rapid acquisition and maintenance of bar-pressing behaviors associated with reward [13]. It is therefore currently believed that reward-related, limbic-based forebrain circuits are centered in the striosomes, while sensorimotor and associative circuits are present in the matrix. Compared with the rapid progress in anatomical understanding of the striosome and matrix compartments, physiological studies have long been hampered by difficulty with selective identification of one compartment or the other due to the small size and patchy distribution of the striosomes. Recently, we found that brain

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slice preparations obtained from a transgenic mouse expressing green fluorescent protein (GFP) under the control of tyrosine hydroxylase (TH) gene promoter (TH-GFP mouse) were helpful in selective identification of each of the compartments and exhibited compartment-specific modulation of GABAergic synaptic transmission by MOR, which is selectively localized in the striosomes [14]. Then, how do the MOR in the striosomes influence the activity of the striatum? Cholinergic interneurons are in a suitable position in this context for this intercompartmental communication since they are preferentially located in the striosome-matrix boundaries, have MORs in the striosomes and are known to elicit a conditioned pause response during sensorimotor learning. In this review, we summarize our recent work and future issues to be addressed with physiological techniques and discuss the roles of MOR in intercompartmental communication and the roles of the striosomes in neuropsychiatric disorders.

MORs in the Striosome Compartment

The striatum is one of the nuclei of the central nervous system in which endogenous opioids and their receptors (μ, δ and κ) are abundantly expressed [15]. It was first determined with autoradiography using radiolabeled opioid ligands that opioid receptors (MORs) were distributed in a patchy fashion in the striatum [16], and subsequently demonstrated that the patches corresponded to acetylcholinesterase (AChE)-poor striosomes [4, 17, 18]. MOR mRNA and peptide are expressed in the striosomal medium-sized (MS) projection neurons from the early postnatal period to adulthood [19–22]. There are two possible ligands for MOR in the striosomes, endomorphins and enkephalin. Endomorphins (endomorphin-1 and endomorphin-2) are the most potent endogenous ligands for MOR in the brain, though it is still too early to conclude that they are the transmitters that striosomal cells receive, since perikarya expressing endomorphin-like immunoreactivity are found elsewhere in the brain without any connections with the striosomes [7, 23, 24]. MOR is also activated by endogenous enkephalin released from the MS projection neurons of the "indirect" striatopallidal pathway. Consistent with this, the distribution of MORs matched that of enkephalin in the striosomes well [25, 26].

Electron microscopic analysis further demonstrated that in striosomes, MOR was expressed on extrasynaptic plasma membranes of dendritic shafts and spines and on synaptic vesicles and plasma membranes in axon terminals [27]. Injection of an anterograde tracer into prefrontal cortex revealed that axon terminals derived from neurons in deep layer V and layer VI of the prefrontal cortex, 14% of which contained MORs, formed asymmetric, excitatory synapses with MOR-labeled and MOR-unlabeled spines [9]. In turn, 10% of all MOR-labeled axon terminals formed asymmetric excitatory synapses with MOR-labeled or MOR-unlabeled spines. On the other hand, Leu^5-enkephalin, which is known to be localized on indirect MS GABAergic neurons, exhibited co-localization with MOR and was contained within axon terminals presynaptic to MOR-labeled dendrites [9, 27, 28]. These findings suggest that MOR plays a critical role in postsynaptic and presynaptic modulation of corticostriatal excitatory as well as GABAergic inhibitory synaptic transmission.

Physiologically, opioid modulation itself was tested previously by Jiang and North [29] and Barral et al. [30] using rat brain slices, who demonstrated that in the MS cells corticostriatal excitatory postsynaptic potentials (EPSPs) were presynaptically inhibited by μ and δ-selective opioids, whereas inhibitory synaptic potentials (IPSPs) were decreased by δ-selective opioids alone, and that hyperpolarization was observed in only a small subpopulation of cells with administration of δ-selective opioids [29, 30]. These studies, however, did not address the issue of differences in the roles of the striosome and matrix compartments, so that the data obtained in their studies were mostly of matrix origin.

Striosomes Identified as "Dopamine Islands"

In the developing striatum in the rat, the neurons born at embryonic day 12 (E12) form patchy islands as later-born neurons (at E18–E21) migrate out into the neostriatum [31, 32]. The patchy islands are concurrently innervated by the nigrostriatal dopamine neurons and form TH-positive patches called "dopamine islands". It was found that the dopamine islands corresponded to the AChE-poor and MOR-enriched striosomes/patches, whereas the later-born neurons formed the matrix compartment [17, 26]. The dopamine islands, which are initially demarcated clearly from the surrounding matrix, gradually become blurred and disappear as a second wave of dopamine innervation to the later-born matrix cells progresses during the first postnatal week and is completed after postnatal day 16 (P16). It was recently demonstrated that differentiation of striosomal cells is critical for normal development of striatal architecture [33]. The presence of ephrin-A1 and/or ephrin-A4 in the developing striosomes results in the exclusion of matrix neurons and their developing dendrites from these regions [34]. Striosomal MS neurons express mRNA and protein of glial cell line-derived neurotrophic factor (GDNF), which protects and restores dopaminergic neurons. In early postnatal stages, GDNF protein is preferentially observed in the striosomal regions, suggesting anterograde and/or retrograde transport of GDNF [35, 36]. Study of *reeler*

mutant mice also demonstrated that embryonic striosomal cells supply the ventral mesencephalon with Reelin, which plays a role in positioning of the nigral dopaminergic neurons [37]. Striosomes thus develop concomitantly with the arrival of dopaminergic afferents from the substantia nigra [38–41]. Disruption of striosome-matrix organization by knockout of the transcription factor *Ctip2* (also known as *Bcl11b*) correspondingly resulted in abnormal dopaminergic innervation [33]. In the TH-GFP mouse, GFP is successfully expressed in more than 94% of dopaminergic neurons in the SNc [42]. The dopamine islands can be easily identified as bright GFP-positive areas under a fluorescence microscope until approximately postnatal day 35 (P35), probably because turnover of GFP lags behind the disappearance of the dopamine islands. The GFP-positive bright areas were immunohistochemically confirmed to correspond to MOR-immunoreactive striosomes and to contain no TH-positive cell bodies and instead nigrostriatal TH-positive fibers (Fig. 1).

Inhibition of EPSCs by μ-Opioids in the Striatum

As reported previously by Jiang and North [29], we found that application of the selective MOR agonist [D-Ala^2-*N*-Me-Phe^4, Gly-ol^5]-enkephalin (DAMGO) suppressed corticostriatal EPSCs by at most 10% (Fig. 2). This unexpectedly weak response is consistent with a report

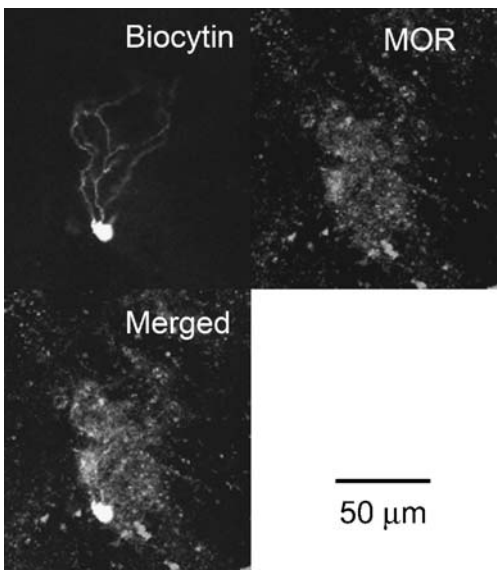

Fig. 1 Confinement of dendritic arborizations of a medium spiny projection neuron within the striosome compartment. Immunostaining images of a medium spiny (MS) projection cell recorded (*Biocytin*) and a striosome compartment (*MOR*, bright signals). The dendrites are confined within the striosome where the cell body is located (*Merged*). Patch-clamp recordings were made from cells in a striatal slice preparation obtained from a transgenic mouse (TH-GFP mouse). After recordings, the slice was immunostained for biocytin and MOR

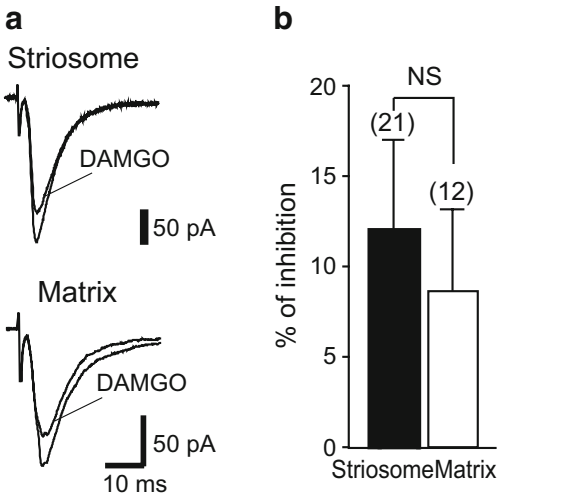

Fig. 2 EPSCs are suppressed via MORs in both striosome and matrix compartments. **a** EPSCs were recorded from a striosomal MS cell (holding potential=−80 mV) in the presence of bicuculline (10 μM). To stimulate the corticostriatal inputs, a bipolar electrode was placed in the white matter close to the cells recorded. Bath application of DAMGO (1 μM), an MOR agonist, decreased EPSCs in both striosome and matrix MS cells. The EPSCs slowly recovered after washout of the drug. **b** Inhibition of EPSCs by DAMGO in striosomal cells was not significantly different from that in matrix cells. NS: not significant. Numbers of cells recorded are indicated in *parentheses*—Modified from [14]

indicating that only 14% of prefrontal corticostriatal axons and axon terminals were immunoreactive for MOR [9]. Moreover, this inhibition was also observed in the matrix compartment. This agrees well with a recent developmental study using in situ hybridization histochemistry that showed that MOR mRNA expression in the matrix compartment was as strong as that in the striosomes at the time of birth, but declined rapidly to low levels and persisted until P22, the final timepoint examined, whereas MOR mRNA was fairly well-preserved in the striosomes [22]. MOR mRNA, which is mildly expressed in the cortex and heavily in the thalamus, may be transported to glutamatergic terminals in the striatum [15, 19]. Thus, a subset of excitatory inputs is subject to focal control by striatal MS projection neurons of the indirect pathway that contain and release enkephalin.

Presynaptic Inhibition of IPSCs by μ-Opioids in the Striosomes

The effects of MOR on striosomal circuits are poorly understood. Targeting the striosome cells of the TH-GFP mouse under fluorescent microscopy, we obtained for the first time evidence that in the striosomes DAMGO suppressed GABAergic IPSCs by about 20% but exhibited no such suppression in the matrix (Fig. 3). This MOR-mediated suppression of GABAergic IPSCs in the strio-

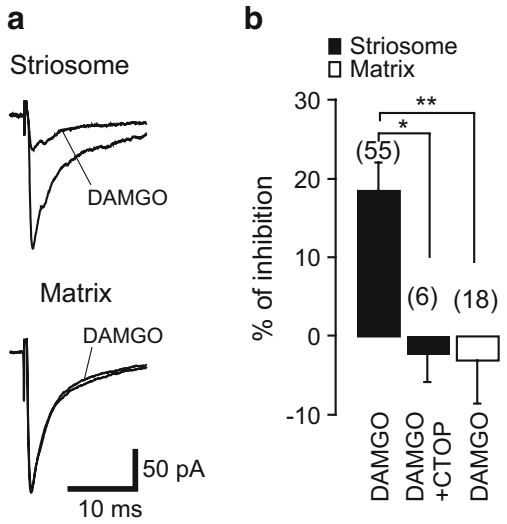

Fig. 3 IPSCs are inhibited by DAMGO only in the striosome compartment. **a.** Amplitudes of IPSCs recorded from striosomal MS cells (holding potential=−80 mV) were measured in the presence of CNQX (10 μM) and APV (25 μM). Bath-applied DAMGO (1 μM) decreased the amplitude of IPSC in the striosome (up), but not in the matrix (down). To evoke GABAergic IPSCs, a glass stimulating electrode was placed in the vicinity of the cells. **b** The suppression by DAMGO of the amplitude of IPSCs was statistically significant in striosomal cells (closed bars) but not in matrix cells (open bar; **:$p<$ 0.01), and was completely blocked by the MOR antagonist CTOP (filled bars; *: $p<0.05$). Numbers of cells recorded are indicated in parentheses—modified from [14]

somes was proved to be presynaptic. Negative presynaptic modulation of GABAergic inhibitory transmission takes place only in the striosome compartment.

The most likely candidate for the source of the MOR-sensitive GABAergic inputs is axon collaterals of other neighboring MS cells [43–45]. MORs are localized predominantly in dendrites and dendritic spines, and to a lesser degree in perikarya and axon terminals in the striosomes [27]. MS projection neurons give off axon collaterals that form symmetrical GABAergic synapses with other spiny neurons [46, 47]. Although mutual inhibition had previously been considered to be physiologically absent or non-functional in the striatum [48, 49], recent paired whole-cell recording experiments demonstrated monosynaptic IPSPs/IPSCs between MS projection neurons in striatal slices and organotypic slice cultures [43–45]. The large population of MS projection neurons in the striatum (90–95%) thus suggests that modulation of local inhibitory connections plays an important role in processing of cortical inputs [50]. Another likely candidate for the source of the GABAergic inputs is MOR-bearing recurrent collaterals from neurons of the external segment of the pallidum (GPe). This is unlikely, however, since no MOR modulation was found in the matrix in our study, while it is known that these collaterals innervate both compartments [51]. The involvement of several types of GABAergic interneurons such as parvalbumin-containing fast-spiking (FS) interneurons and somatostatin (neuropeptide Y, nitric oxide synthase)-containing low-threshold spike (LTS) interneurons in this inhibitory modulation of IPSPs should be examined in the future.

Reciprocal Regulation of μ-Opioid Modulation by PKA and PKC: What and How?

Opioid receptors belong to the G-protein-coupled receptor (GPCR) superfamily and are known to be negatively coupled to adenylate cyclase through Gi/Go proteins. A decrease in the level of intracellular cAMP and the resultant protein kinase A (PKA) inhibition eventually open K^+ channels and/or close voltage-dependent calcium channels, leading to pre- and postsynaptic inhibition [52–55]. In fact, presynaptic inhibition of corticostriatal excitatory inputs by MOR activation was demonstrated to be mediated by K^+ channel modulation in the rat striatum [30]. Likewise, we found that MOR activation inhibited GABA release mainly through activation of 4-AP-sensitive K^+ channels by suppression of the adenylate cyclase pathway in the striosomes [14]. On the other hand, involvement of the arachidonic acid cascade in the presynaptic modulation of IPSCs by MOR appeared unlikely in the striatum, although it has been reported in the periaqueductal gray and central amygdala [56, 57]. More interestingly, however, we unexpectedly found that chelerythrine, an inhibitor of protein kinase C (PKC), significantly enhanced the effect of DAMGO (20% to 35%), whereas chelerythrine itself did not alter the baseline amplitude of GABAergic IPSCs [58]. These observations suggest that decrease in PKC and PKA may synergistically regulate the effects of MOR [59, 60]. Neurotransmitters known to positively couple with PKC signaling pathways include substance P (SP; from direct pathway MS cells), acetylcholine (from cholinergic interneurons), and glutamate (from cortico- and thalamostriatal pathways) in the striatum. Whether some of these transmitters indeed counterbalance the effects of MOR on IPSCs is an interesting issue to be addressed [61, 62].

Roles of Cholinergic Interneurons in Intercompartmental Communication

Intracellular staining with biocytin showed that although there is a subset of MS cells that extend their dendrites across the boundaries, the dendrites of MS cells in the striosome and matrix compartments are confined mostly to their compartment of origin, and that they avoid crossing the striosome-matrix boundaries (Fig. 1) [63, 64]. Axonal arbors of the cells in the striosome compartments are also extended widely within the compartments they belong to,

but finally cross over compartmental boundaries and innervate output nuclei of the basal ganglia [65]. Interestingly, enkephalin immunoreactivity is densely observed in the periphery of the human striosomes, the so-called "annular compartment" [66, 67]. Such annular-like heterogeneity of the striosomes has also been observed in the form of preferential distribution of other neurotransmitters and receptors, such as SP and SP receptors (SPRs), choline acetyltransferase (ChAT), neuropeptide Y, neurotensin, and limbic system-associated protein (LAMP), suggesting that intercompartmental communication may occur on the border between the striosomes and the matrix [68–72]. Key players for this may be interneurons in the striatum. GABAergic FS interneurons are present in both the striosome and matrix compartments, and their axons and dendrites arborize without apparent regard to the boundaries between compartments. They are also electrotonically coupled with each other through gap junctions and mediate strong feedforward inhibition to MS cells [73]. Giant aspiny cholinergic interneurons and GABAergic LTS neurons were mostly found to have dendrites that extend across compartmental boundaries and axons that innervate the surrounding matrix, suggesting that they might act as mediators between striosomes and matrix [66, 68, 74–77]. Among these interneurons, cholinergic interneurons are particularly interesting because they are more numerous in the periphery of the striosomes and have been intensively studied so far [66], while the role of the other two types of interneurons in the intercompartmental communication has been largely unknown.

Compared with rapid transmitters such as glutamate and GABA, SP and enkephalin are neuropeptides whose effects last for tens to hundreds milliseconds [78]. It is known that SP-containing boutons make synapses on the SPR-expressing dendrites of cholinergic interneurons [79–81]. Thus, SP released from MS neurons of the striatonigral direct pathway strongly depolarizes cholinergic interneurons [78]. Each spike elicited by cholinergic interneurons was found to evoke acetylcholine release, which may faithfully excite target GABA interneurons located in the matrix via activation of nicotinic receptors, leading to instantaneous inhibitory regulation of matrix MS projection neurons [82]. On the other hand, enkephalin released by striatopallidal indirect MS neurons in the striosomes may activate MOR, which would presynaptically suppress the release of SP and GABA from the striatonigral direct MS neurons in the matrix [78, 83]. Enkephalin also hyperpolarizes cholinergic interneurons by activation of DOR on them and stops the release of acetylcholine [29]. In addition, because suppression of acetylcholine release does not induce firing of GABA interneurons via nicotinic receptors, MS cells in the matrix would be relieved of GABAergic inhibition. In this fashion, direct and indirect pathway MS cells in the striosomes may reciprocally regulate the activities of the matrix MS cells by switching acetylcholine release on and off, respectively (Fig. 4) [84–88]. As noted above, inactivation of the PKC pathway may eventually enhance inhibitory modulation by MORs of GABAergic IPSPs and thus significantly decrease IPSP amplitude in the striosomal MS neurons [14, 29]. This PKC cascade can be switched on by SP, acetylcholine, and glutamate in the striatum. Whether and how those transmitters are involved in the presynaptic modulation of IPSPs in the striosomes is a matter to be explored.

It was recently reported that MOR was expressed in a subset of cholinergic neurons located in striosome-enriched dorsal striatum (the limbic/prefrontal territory) but not in matrix-enriched dorsal striatum (the sensorimotor territory). Curiously, MOR expression in cholinergic interneurons was far more prominent in the afternoon (80%) than in the morning (32%), so that MOR-mediated synaptosomal release of acetylcholine was higher in the afternoon than in the morning [89]. Endogenous SP thus facilitates acetylcholine release in the morning, while in the afternoon, when MOR expression is high, blockade of MOR is required to observe facilitatory effects of SP on acetylcholine release [90]. The functional role of this diurnal

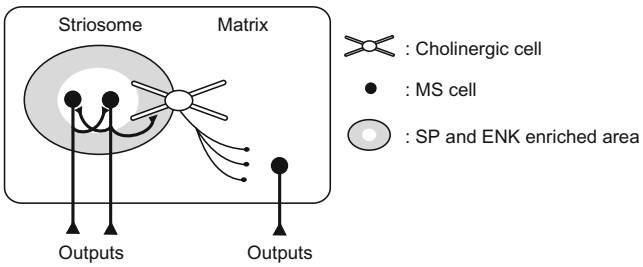

Fig. 4 A schematic diagram showing functional relationships between striosomal MS cells and cholinergic interneurons. Striatal MS cells send collaterals to neighboring MS cells as well as cholinergic cells. Cholinergic interneurons are preferentially located on the striosome-matrix borders, where substance P (*SP*) and enkephalin (*ENK*) are enriched. The collaterals arising from striatonigral MS cells release GABA, which mediates fast inhibitory transmission, and SP, which slowly but strongly excites cholinergic cells [78]. In turn, cholinergic cells innervate the matrix and release acetylcholine (ACh) [134]. Inactivation of MORs fails to inhibit GABAergic inputs and thus decreases the activity of MS cells. In contrast, activation of MORs by endogenous and/or exogenous ligands suppresses GABAergic inputs and relieves MS cells from reciprocal GABAergic inhibition. Output from the striosomes should therefore increase if MOR activation takes place only in the striatum. In addition to MOR activation, repetitive firing of MS cells results in a profound increase in SP, which excites cholinergic cells and then increases the release of ACh. During sensorimotor learning, a barrage of excitatory inputs from the cerebral cortex and thalamus as well as a burst of dopaminergic inputs cooperatively induce a TAN pause response, which further amplifies the release of dopamine only in the target areas of the cholinergic interneurons [97, 98]. Very low levels of acetylcholine and high concentrations of dopamine induce LTD in the matrix MS cells [103]. MOR activation in the striosomes by cortical inputs may thus induce plastic changes in the matrix output

variation of MOR expression in the striosome-enriched dorsal striatum is unclear at present. However, it is reasonable to suggest that MOR regulation of cholinergic transmission, which occurs only in the striosome compartments, might have a significant impact on information processing in basal ganglia-thalamocortical circuits.

Striosomes and TAN Pause Response

Since cholinergic interneurons can fire tonically without any excitatory drive, they are called tonically active neurons (TANs) in vivo [91, 92]. In primates, TANs were also found to be enriched in the striosome-matrix borders [74]. It is known that TANs in the primate striatum acquire a conditioned response termed the 'TAN pause response' during sensorimotor learning [93]. This TAN pause response is made up of an initial, brief spike discharge followed by a long pause of firing which is terminated by a rebound discharge of spikes. Because TANs fire tonically as a result of intrinsic membrane properties, cessation of tonic firing should be of importance during sensorimotor learning. Simultaneous recordings from both TANs and midbrain dopamine neurons of primates revealed that dopamine neurons increased their firing frequency robustly in response to a conditioning stimulus and at the same time TANs exhibited a pause response [94]. It was recently demonstrated that blockade or desensitization of nicotinic receptors amplifies dopamine release during phasic but not tonic firing activity of dopamine neurons [95, 96]. Because TAN does not release acetylcholine during the pause response, simultaneously occurring phasic activity of dopamine neurons should result in a dramatic increase in dopamine release only in the striatal regions where the TAN pause response occurs [97]. In fact, dopamine appears to be necessary for the initiation and development of the TAN pause response. The TAN pause response does not occur when dopamine neurons are depleted by the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [98]. It is likely that dopamine D1-like (probably D5) receptor-dependent long-term potentiation in the tonically active cholinergic interneurons underlies the initial activating phase and the ensuing pause or after hyperpolarization phase of the TAN pause response [99, 100]. The larger the amplitude of the EPSP, the longer the duration of the pause [100]. In addition, the pause is prolonged and maintained by suppression of both hyperpolarization activated channels (Ih or HCN) and voltage-dependent sodium channels via activation of dopamine D2 receptors [101, 102]. Remarkably, it was recently found that suppression of acetylcholine release by D2 receptors in the cholinergic interneurons potentially favors the induction of long-term depression (LTD) in the MS cells of, probably, the matrix, in the following two fashions. First, suppression of cholinergic spikes significantly increases corticostriatal EPSPs in MS cells [84]. This is made possible by suppression of presynaptic inhibition of glutamate release from the corticostriatal terminals by muscarinic receptor activation. Second, this suppression decreases the activity of M1 muscarinic receptors located on spines near the corticostriatal glutamatergic synapses in the MS cells, triggering a cascade of events including calcium influx and production of endocannabinoids in response to synaptic depolarization and leading to presynaptic activation of CB-1 receptors, and then LTD in MS cells [103].

Returning to the MOR in striosomes, at the time of goal-directed behavior, striosomes receive a barrage of reward-related limbic information from caudal orbitofrontal and anterior cingulate cortical areas [5, 6, 104]. Corticostriatal inputs excite both direct and indirect striosomal MS cells. Indirect MS cells release enkephalin that presynaptically dampens GABAergic inhibition via MOR activation of MS cells and cholinergic interneurons in the striosome compartments. Enkephalin from indirect MS cells and SP from direct MS cells hyperpolarize and depolarize the cholinergic interneurons, respectively, though regardless of which transmitter they receive, a barrage of thalamostriatal and corticostriatal excitatory inputs dominate and excite cholinergic interneurons, which, with a concomitant increase in dopamine release in the striatum, trigger the TAN pause response and LTD in matrix MS cells. As a result of this, disinhibition of MS cell activity in the striosomes may inhibit dopamine neurons in the SNc and terminate the series of events associated with goal-directed behavior.

Emerging Roles of the Striosome Compartments in Neuropsychiatric Disorders

Lastly, we move on to the roles of the striosomes. One approach to determining them is to record activities of the striosome compartment during ongoing behavior. With this approach, it has been shown that the striosomes may be involved in reward-related behavior, whereas the matrix may be engaged in resting and neutral sensorimotor-related behavior [12, 13]. Another approach is to deduce the physiological functions from the behavioral changes induced by selective inactivation or activation of the striosomes. Three kinds of neuropsychiatric disorders are worth mentioning here. The reader is referred to several other recent reviews on other disorders which might be related to the striosomes and dysfunction of cholinergic interneurons, such as Parkinson's disease, progressive

supranuclear palsy, Tourette syndrome, and obsessive–compulsive disorder [105–108].

Huntington's Disease and X-linked Recessive Dystonia Parkinsonism

What happens when the striosomes are selectively inactivated can be deduced from two pieces of clinical evidence. The first concerns Huntington's disease, a neurodegenerative disease caused by an autosomal dominant mutation of the *huntingtin* (IT15) gene. This mutation causes an expanded trinucleotide (CAG)-repeat in IT15, which results in massive cell death in the striatum and cortex [109]. Tippett et al. [110] recently found on postmortem examination that there were three patterns of striatal abnormality in Huntington's disease patients: loss of striosomes, loss of matrix, and mixed cases. They compared the compartmental patterns of striatal abnormality and the patterns of mood and motor symptoms exhibited by patients at clinical onset and clinical end-stage, and found that Huntington's disease patients with predominantly striosomal defects exhibited mood disturbances and a milder course of disease. Mood dysfunction here included symptoms of depression, anxiety, irritability, and compulsive behavior. Second, X-linked recessive dystonia parkinsonism (XDP; DYT3), which is endemic in Panay island of the Philippines, is characterized by a clinical onset with dystonia, followed by parkinsonism [111, 112]. The dystonia of XDP is predominant in the first 10 to 15 years of illness but is gradually replaced by parkinsonism in the later years of life. Economic difficulties and accompanying psychiatric symptoms frequently drive patients to despair and suicide. Goto et al. carried out postmortem analysis of the striatum obtained from male Filipino XDP patients who committed suicide and manifested dystonia, and found that the striosomes exhibited severe degeneration, while the matrix was relatively spared [113–115]. Because neurons in the striosomes are thought to innervate and inhibit nigrostriatal dopaminergic neurons via $GABA_A$ receptor activation, neuronal loss in the striosomes in the dystonia stage of XDP should release dopamine neurons from GABAergic inhibition and induce a hyperdopaminergic state in the matrix. Dopamine overflow should eventually lead to inactivation of the output nuclei of the basal ganglia through increased and decreased activities of direct and indirect pathways, respectively, and then overactivation of the thalamocortical pathways, which may induce a hyperkinetic state or dystonia. In the subsequent parkinsonian stage, despite an excess of dopamine influx, loss of dopaminoceptive neurons in both compartments of the striatum should lead to a net activation of the output nuclei, and produce the parkinsonian state. In this XDP model, the striosome compartment should play an important role in regulation of the activity of dopamine neurons. However, the mood dysfunction associated with the neuronal loss in the striosomes in the dystonia stage has not been described in detail in the literature.

Drug Addiction

Another example of selective striosomal activation can be found in drug addiction. It was reported by Canales and Graybiel [116] that in the rat, acute treatment of psychomotor stimulants such as cocaine and amphetamine produced a striosome-enhanced pattern of expression of the immediate early gene product Fos, and that after chronic treatment, the striosome predominance of the gene expression was further enhanced by an increase in the Fos-positive neurons in the striosomes and a decrease in Fos-positive matrix cells. Moreover, the ratio between the density of Fos-positive neurons in the striosomes and that of Fos-positive neurons in the matrix was strongly correlated with the severity of motor stereotypy in both acute and chronic treatments [116]. This phenomenon requires concurrent activation of dopamine D1- and D2-class receptors [117]. A strong correlation between striosome-predominant gene expression and stimulant-induced stereotypy was found in the monkey, as well, and intense expression of Fos proteins in the dorsal part of the striatum, especially in the putamen, was also noted in the monkey [118]. Preferential induction of Fos proteins in the striosomes after amphetamine challenge in amphetamine-pretreated animals was further replicated by Vanderschuren et al. in the rat and by Glickstein and Schmauss in the mouse [119, 120]. Interestingly, in both of these studies the authors argued against the suggestion that enhanced striosomal activation is a predictor of motor stereotypy in general. In the former study, whereas stereotypic behaviors became more intense with increasing doses (0, 0.5, 1.0, 2.5, 5.0 mg/kg) of amphetamine, the preferential cellular activation of the striosomes were observed only after 5.0 mg/kg amphetamine was administered. Also, 1.0 mg/kg amphetamine challenge of amphetamine (2.5 mg/kg)-pretreated rats evoked no stereotyped activity and instead a sensitized psychomotor response despite the preferential cellular activation of the striosomes, so that the striosome predominance was rather associated with amphetamine sensitization than the severity of motor stereotypies. However, the fact that acute administration of psychostimulants as well as combinations of dopamine D1 and D2 agonists produced the preferential activation of striosomes indicates that sensitization may not be directly linked to the striosome predominance. In addition, the dose of amphetamine in this study was different from the report by Canales and Graybiel [116] in which 5.0 mg/kg of amphetamine

was used throughout in both acute and chronic experiments. In the latter study of Glickstein and Schmauss [120], strong stereotypy was observed in the dopamine D2 receptor knockout mouse and D2/D3 receptor double knockout mouse, though no preferential activation of striosomes was found in these animals. The reason for this discrepancy in findings is unclear. Assessment of motor behavior may have differed in certain aspects between the studies, or the developmental changes in neuronal circuitry in the mutant striatum may underlie the differential expression of c-Fos in the striatum. In fact, targeted ablation of striatal cholinergic and nitric oxide synthase (NOS)/somatostatin-containing GABA interneurons with a neurotoxin altered rotational responses to dopamine receptor agonist challenge and blurred the striosome-predominant pattern of expression of c-Fos, but did not prevent the induction of behavioral stereotypy [121]. These observations suggest the following. First, although the striosome predominance of early gene activation is indeed involved in motor repetitiveness, local circuit neurons play a significant role in expression of the predominant striosome activation induced by psychostimulant treatment. Second, there must be multiple redundant pathways for expression of motor stereotypy. Third, striosomes are more sensitive to psychostimulants than matrix and repeated use of psychostimulant drugs can induce preferential activation of the striosomes and persistent suppression of the matrix in the striatum. How these neuronal adaptations affect electrophysiological properties of striosomal and matrix neurons and lead to motor stereotypies remains to be determined [1].

Numerous studies have found that blockade of opioid receptors attenuated psychostimulant-induced behavioral sensitization [122–131]. It was also shown that concurrent intrastriatal injection of morphine enhanced the behavioral responses induced by single intraperitoneal injection of low-dose *d*-amphetamine, and yielded motor stereotypy normally associated with high doses of *d*-amphetamine [132]. Is it the case, then, that MORs in the striosomes play a role in the psychostimulant-induced neuronal adaptations described thus far? Although not straightforward, the answer appears to be yes. Recently, Horner and Keefe [133] showed that in the rostral striosomes alone, prior blockade of MORs attenuates the expression of preprodynorphin mRNA induced by the single exposure but not chronic exposure of dopaminergic stimulants, whereas psychostimulant-induced *zif/268* messenger RNA expression in the striosome and matrix compartments was attenuated equally throughout the dorsal striatum. In contrast, MOR blockade had no effect on psychostimulant-induced increase in *c-fos* expression [133]. Although the basis of these findings is not yet clear, it seems reasonable to conclude that MOR activation plays different roles in psychostimulant-induced immediate early gene mRNA expression in the striosome and matrix compartments of the dorsal striatum.

Concluding Remarks

Of the several molecular compounds differentially expressed in the striosome and matrix compartments, μ-opioid receptor (MOR) was the first found to exhibit preferential distribution in the striosomes [16]. Despite several lines of anatomical evidence suggesting functional roles for the striosomes, little is known concerning the physiological significance of the MOR or how MOR activation affects the physiological properties of cells in the local neural circuits of the striatum. We recently found that striosomal MS cells are electrophysiologically similar to matrix cells, while the cellular development of the striosomes appears to be relatively protracted even though they are generated earlier, indicating the uniqueness of the striosomes [14]. Moreover, MOR activation in the striosomes was found to presynaptically decrease the amplitude of GABAergic IPSCs in MS cells of striosomes but not the matrix. This presynaptic inhibition of IPSCs by MOR activation was further augmented by prior blockade of PKC-dependent pathways, which may result from muscarinic receptor inactivation. It is thus possible that cessation of acetylcholine release from cholinergic interneurons, i.e., TANs in the primate striatum, favors inhibitory regulation by MORs of IPSCs in striosomal cells. MOR activation in the striosomes might thus free both MS cells and cholinergic cells within the striosomes from GABAergic inhibition, and favor the ensuing plastic changes in the striatum. Likewise, chronic intake of psychostimulants may induce overactivation of prefrontal dopaminoceptive neurons and their synaptic target, striosomal neurons, which thereby compensate for drug-induced excessive dopamine overflow [116, 118]. Conversely, the degeneration of striosomal cells observed in one type of Huntington's disease and the dystonia stage of XDP may robustly increase dopamine influx to the striatum, with development of choreic and/or dystonic movements [110, 115]. Therefore, endogenous and exogenous opioids may, via disinhibition of striosomes by MOR activation, have profound effects on the activities of the output neurons of the striatum, and eventually alter basal ganglia output. Use of physiological approaches to testing of these hypotheses has only just begun. Clarification of the circuitry of goal-directed behaviors should contribute to the development of drug strategies for insidious neuropsychiatric disorders such as Huntington's disease, dystonia, obsessive-compulsive spectrum disorders, and Parkinson's disease.

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