REVIEW

Pharmacological Studies on the Interrelation between the Dopaminergic, GABAergic and Opioid Peptidergic Systems in the Central Nervous System of the Rat

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Abstract—To elucidate the functional connections between dopaminergic, GABAergic and opioid peptidergic systems in rats, electrophysiological, behavioral, neurochemical and histological investigations have been undertaken, focusing on the changes in drug sensitivity in the central nervous system (CNS). Changes in sensitivity in the CNS can be induced by denervation, chronic administration of antagonists or agonists, and by the inhibition of the axoplasmic transport system. It is conceivable that the changes in sensitivity of the CNS to transmitters may be related to the etiology of mental illnesses such as schizophrenia and mania and may be related to the symptoms of Parkinson’s disease. Investigation of changes in sensitivity of the CNS to transmitters or drugs may provide the key for elucidating the biological nature of mental illness.

1. The nigrostriatal dopamine (DA) system: The major DA projection to the striatum originates in the ipsilateral substantia nigra zona compacta (SNC). As shown in Fig. 1, DA cells have autoreceptors on the cell body or nerve terminal. When DA is released from the dendrites of DA cells, the DA may act on the autoreceptors and also act on non-DA cells which are located in the substantia nigra zona reticulata (SNR). It has been reported that spontaneous firing rates of dopaminergic neurons are regulated, at least in part, by DA autoreceptors (1). Prolonged amphetamine abuse can elicit a schizophrenic-like psychosis in humans, which is often indistinguishable from paranoid schizophrenia (2). Amphetamine, a drug which has been known to release DA from synaptic vesicles and to inhibit the high affinity DA reuptake, has dramatic effects on DA neurons in the SNC. It is well-known that stereotyped behavior or locomototional behavior is enhanced after long-term treatment with amphetamine (3–5). Therefore, we have proposed that DA autoreceptors may play a key role in the amphetamine psychosis in humans or in the sensitization in animals following chronic amphetamine treatment (6–10). In fact, since the amphetamine-induced inhibition of activity of the DA cells in the SNC is mediated, at least in part, by a local release of DA from dendritic terminals or recurrent axon collaterals, following long-term treatment with amphetamine, DA neurons in the SNC are less sensitive to a challenge injection of apomorphine, a DA agonist. The reduced sensitivity of DA autoreceptors produces a decrease in the self-inhibition of DA neurons; an increase in DA activity produces a corresponding increase in DA transmission at postsynaptic sites; an increase in DA activity produces the subsensitivity of postsynaptic DA receptors in the striatum. Although postsynaptic sites

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may be subsensitive, a corresponding increase in DA release can counteract this effect and produce the sensitization. Moreover, recent experimental evidence suggests that various amphetamine-induced actions may be involved in the changes in the release of ascorbic acid in the striatum (11-15).

On the other hand, chronic administration of neuroleptics, DA antagonists, has been shown to produce a supersensitivity to DA receptor agonists after these drugs are withdrawn (16-19). In these animals, DA receptor binding in the striatum is increased (20), and there is a corresponding increase in the behavioral response to DA agonists (21, 22). Furthermore, it has been reported that the up-regulation of dopamine receptors in rat striatum after denervation and receptor blockade is additive (23, 24). Development of supersensitivity may be caused by the loss of the transmitter, the blockade of neurotransmission and/or by removing the influence of some neurofactor: e.g., trophic factor, which might be released independently of, or in conjunction with, the transmitter. Denervation-like supersensitivity can be caused by the blocking of axoplasmic transport in the peripheral organs. When colchicine, a drug which has been shown to suppress axoplasmic transport, is directly applied to a nerve, axoplasmic transport is blocked, with a resultant denervation-like supersensitivity of skeletal (25, 26) and smooth muscle (27-29). Recently, we demonstrated that methamphetamine produces contralateral circling behavior in rats micro-injected with colchicine into the SNC (30). Since DA levels in the striatum ipsilateral to the injection side were reduced to 44% of that on the intact side, methamphetamine can release the DA in the striatum on both sides. However, animals rotated away from the injection side, indicating that postsynaptic
DA receptors in the ipsilateral striatum appear to be supersensitive to the released DA. From these results, we have suggested that colchicine may produce a variety of changes in the postsynaptic DA receptors by interrupting the influence of some neurotrophic factor (e.g., trophic factor) via an inhibitory action of the fast axonal transport system, as it is known to do in peripheral adrenergic nerve fibers (31) and in the central nervous system (32). Furthermore, methamphetamine-induced contralateral circling behavior in colchicine-treated rats was significantly increased by chronic treatment with haloperidol, indicating that development of supersensitivity following colchicine and chronic haloperidol involves different regulatory processes of postsynaptic supersensitivity. Of particular interest in this connection is the observation that in animals with bilateral injections of 6-hydroxydopamine (6-OHDA) into the nucleus accumbens and chronic haloperidol administration, there is a greater increase in the density of \(^{3}H\)-spiperone-binding sites than there is with either treatment alone, and the affinity constant is not altered (23).

2. The striatonigral GABAergic system: An accumulating body of evidence suggests that the striatonigral pathways play an important role in not only feedback regulation of DA neurons in the SNC but also in maintaining rotational behavior. It has been well documented that apomorphine produces contralateral circling behavior in rats unilaterally denervated with 6-OHDA (33), and the contralateral rotation caused by apomorphine is converted into ipsilateral turning following kainic acid lesions of the substantia nigra (34). Herrera-Marschitz and Ungerstedt (34) suggest that this conversion of apomorphine-induced contralateral rotation into ipsilateral circling is mainly dependent upon striatonigral pathways on the intact side. Consistent with this hypothesis, we have reported that microinjection of GABA into the SNR produces contralateral circling which is not affected by 6-OHDA lesions of the ipsilateral striatum but is decreased by electrolylesions of the nucleus ventromedialis thalami or the nucleus parafascicularis thalami (35). These results indicate that the striato-nigral-thalamic system may play an important role in the apomorphine-induced contralateral circling behavior. Thus, GABA unilaterally microinjected into the SNR activated the striato-nigral thalamic system as shown in Fig. 2, and the unilaterally activated system may be responsible for the circling behavior. In fact, it has been reported that rats with unilateral striatal kainic acid lesions exhibit ipsilateral rotational responses to challenge injection of peripherally administered apomorphine (36-38). This response may be due to the ipsilateral destruction of a striatal efferent system (striatonigral GABAergic system) and the subsequent predominant action of apomorphine or methamphetamine on the intact contralateral striatum. It is likely, therefore, that peripherally administered apomorphine or methamphetamine may activate the striato-nigral thalamic system in rats with unilateral lesions of the striatum by kainic acid, and thus, ipsilateral circling may be induced by the drug. In fact, it has been found that systemic administration of apomorphine stimulates the turnover of GABA in the substantia nigra (39). Anatomical examinations have shown that 30-50% of the cells in the striatum project into the SN

![Fig. 2. Proposed synaptic connections for the DA agonist-induced circling behavior. Note that the striatum may play an important role in the initiation of circling behavior and that the thalamus has a critical role in mediating the connections of the striatum to the motor cortex.](image-url)
approximately 90% of the afferent input of the SN arises from cells located in the striatum (42–44); and most striatonigral afferents synapse preferentially in the zona reticulata (42, 44, 45). Recently, I have investigated the circling behavior induced by DA agonists after microinjection of colchicine into the unilateral striatum, to determine the functional role of the striatonigral system in the circling behavior of rats and to examine the mode of action of colchicine in more detail (46). Surprisingly, intracaudate injection of colchicine caused atrophy of the caudate nucleus. Both apomorphine and methamphetamine produce ipsilateral circling behavior in rats microinjected with colchicine into the unilateral striatum, a result which indicates that damage to the ipsilateral striatonigral pathway may occur in such cases. Since intracaudate injection of colchicine not only damages the dopaminergic neurons but also causes atrophy of the striatum with loss of neuronal perikarya, it is tempting to speculate that treatment with colchicine may be used to generate a model of senile atrophy or degenerative atrophy in these animals. With respect to the detailed mechanism of the degenerative action of colchicine, further investigations are required. In particular, the atrophy in the brain induced by intracerebral injection of colchicine suggests that efforts should be made to elucidate the mechanism of the degenerative action of colchicine before full support can be given to its use as a model system for the evaluation of possible pharmacotherapy in the case of senile atrophy.

It has been reported that long-term treatment with neuroleptics, chlorpromazine or haloperidol decreases the turnover rate of GABA in the SN (47) and produces a marked increase in the binding of GABA to receptors in the SN (48). These effects of neuroleptics on non-dopaminergic (GABAergic) neurotransmission are considered to be secondary to the blockade of DA receptors produced by haloperidol. SNR neurons receive a GABAergic input from the striatum (49) and are very sensitive to inhibition by GABA or muscimol (50). It is likely, therefore, that long-term treatment with neuroleptics may result in reduced synaptic activity of GABAergic neurons which leads, subsequently, to a compensatory increase in the number of receptors for GABA in the SNR. By contrast, long-term treatment of animals with DA receptor agonists may activate the striatonigral GABAergic pathway. In fact, peripherally administered apomorphine stimulates the turnover rate of GABA in the SN (39). Furthermore, it has been reported that apomorphine inhibits not only DA cell firing but also the firing rate of SNR neurons (51). The inhibitory action of apomorphine on SNR neurons is blocked by transection of the striatonigral pathway (51), indicating that the inhibitory action of apomorphine on SNR neurons may involve the striatonigral system. We have recently demonstrated that long-term treatment with methamphetamine significantly decreases the sensitivity of SNR neurons to challenge i.v. injections of muscimol or to iontophoretic application of GABA (52). These results suggest that long-term treatment with methamphetamine may activate chronically the striatonigral GABAergic neurons and, thereby, cause the decreased sensitivity to GABA or a GABA agonist.

As mentioned above, it is well documented that the striatonigral pathways play a role in not only maintaining rotational behavior but also in the feedback regulation of DA neurons in the SNC. Several studies suggest that SNR and SNC neurons display reciprocal firing patterns both spontaneous ones and in response to certain drugs (50, 53). SNR neurons are known to receive a GABAergic input from the striatum and to relay this information either directly or via interneurons to the SNC neurons (49, 50, 53). SNR neurons are more sensitive to inhibition by GABA than are DA cells (50, 53). Furthermore, preferential inhibition of SNR neurons by low doses of peripherally administered GABA agonist disinhibits DA cells and, thus, increases DA cell activity (50, 53). For example, GABA applied iontophoretically into the SNR increases the spontaneous firing of SNC DA cells probably due to disinhibition (50); and intranigral muscimol, a GABA agonist, stimulates DA release in the striatum (54). We also have investigated DA
release in the striatum after microinjection of GABA into the SNR by using in vivo voltammetry (55). We have been especially interested in determining how DA release ipsilateral to the injection side is altered by the long-term treatment with haloperidol. We have shown clearly that the microinjection of GABA into the SNR significantly and dose dependently enhanced the DA and/or DOPAC peak. When GABA is given to animals treated chronically with haloperidol, no increase at all is observed in DA and/or DOPAC (55). From these results, one possible explanation concerning the dose-dependent increased DA release in the striatum after infusion of GABA into the SNR may be expressed by the following sequence of events. SNR neurons are inhibited by microinjection of GABA; the decreased activity of SNR neurons induces disinhibition of DA neurons; the increased activity of DA neurons induces a marked release of DA in the striatum ipsilateral to the injection side, thereby resulting in the enhanced height of the DA and/or DOPAC peak. On the other hand, the increased release of DA in the striatum by microinjection of GABA into the SNR is reduced by chronic treatment with haloperidol. Recently, it has been reported that long-term treatment with neuroleptics decreases the number of spontaneously active DA neurons in the rat SNC (56) and ventral tegmental area (57). DA cells inactivated by neuroleptics could be induced to fire by iontophoretic application of GABA (56) but not glutamic acid, suggesting that they were in a state of tonic depolarization inactivation (56, 57). The proposed process of depolarization inactivation suggests that neuroleptics cause continuous excitation (or disinhibition) of DA cells, which causes them to exceed their maximal firing rate; eventually, this inactivates the spike-generating mechanism of the cell and so the resting membrane potential raised above the threshold level (56, 57). This mechanism of depolarization inactivation may explain why an increased release of DA in the striatum after an infusion of GABA into the SNR is reduced by chronic treatment with neuroleptics.

As mentioned above, when DA is released from the dendrites of DA cells, the DA may act not only on the autoreceptors but also on the non-DA cells which locate in the SNR. Wszczak and Walters (58) have reported that iontophoretically applied DA markedly attenuates the inhibition of SNR neurons by applied GABA. Recently, they extended their findings by providing evidence that the modulatory effect of DA is significantly enhanced in rats which received 6-OHDA lesions of the nigrostriatal DA neurons (59). Therefore, one may predict that release of DA from the dendrites of DA cells normally plays a physiological role in modifying SNR response to GABA. If all SNR neurons control the activity of DA neurons in the SNC via an inhibitory process, the following sequence of events is predicted after the microinjection of apomorphine into the SNR. Microinjection of apomorphine into the SNR interrupts the neurotransmission of the striatonigral GABAergic pathway by attenuating SNR response to GABA; the decreased response of SNR neurons to GABA produces hyperactivity of SNR neurons; the increased activity of SNR neurons may send many more inhibitory impulses to DA neurons in the SNC; and the inhibitory impulses may cause hypoactivity of the nigrostriatal DA pathway. However, I found a marked increase in the DA and/or DOPAC peak in the striatum by microinjection of apomorphine into the ipsilateral SNR (60). It is conceivable, therefore, that all SNR neurons are not homogenous in their response to apomorphine. From this unexpected finding, it is tempting to speculate that novel types of interneurons between the SNC and the SNR may occur. Further understanding of the mechanisms which underly these changes in the DA and/or DOPAC peak in the striatum may shed new light on the neuronal systems and on the processes which mediate the behavioral alterations produced by microinjection of apomorphine into the SNR.

3. The mesolimbic DA system: There is a functional and anatomical interrelationship between the endogenous opioid peptidergic and dopaminergic systems. In fact, it has been reported that the opioid peptidergic system is nerve-terminated on the dopamin-
ergic nerve terminals as shown in Fig. 3 (61). Both systemic and iontophoretic application of opiates markedly enhances neuronal activity of DA in the ventral tegmental area (VTA) (62). On the other hand, morphine as well as β-endorphin has shown the ability to modulate DA release in both in vitro and in vivo studies (63). Therefore, one may predict that the opioid system controls the activity of dopaminergic neurons in the mesolimbic and mesocortical areas via either an excitatory or an inhibitory process. It has been reported that stress elevates mesolimbic and mesocortical DA turnover but not nigrostriatal DA turnover (64, 65). The mesolimbic and mesocortical areas receive DA projections from the VTA, and there are considerable data suggesting that DA is necessary for the maintenance of intracranial self-stimulation (ICSS). We have found that significantly decreased response rates to ICSS are observed by an electric footshock stress when the electrodes are situated in the VTA, and the effect is completely antagonized by treatment with naloxone or methamphetamine (66). From our findings, it is suggested that endogenous opioid peptides may be released in the mesolimbic or mesocortical area in response to footshock stress. The released opioid peptides, which bind to opiate receptors located on dopaminergic nerve endings, may divert intraneuronal DA to non-functional metabolism as suggested by Kuschinsky and Hornykiewicz (67), and they may block transmission in the mesolimbic or mesocortical DA pathways. This decreased transmission may mediate the decreased response rates to ICSS. This version of events can explain why both naloxone and methamphetamine antagonize the decreased response rates to ICSS caused by footshock stress. These results suggest that opioid peptidergic neurons, which terminate at dopaminergic nerve terminals, may play an important role in regulation of DA release when animals are subjected to stress.

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