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Acute monoaminergic depletion in the rat potentiates the excitatory effect of the subthalamic nucleus in the substantia nigra pars reticulata but not in the pallidal complex

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Summary. Recent neurochemical evidence suggests that chemical or electrial stimulation of the subthalamic nucleus (STH) increases dopamine release in the substantia nigra (SN) with a subsequent decrease in the striatum. In a previous paper, we reported that bicuculline-induced activation of the STH increases neuronal activity in the substantia nigra pars reticulata (SNpr) and in the pallidal complex. In order to investigate the role played by the dopaminergic system in the observed activation, the neuronal responses of subthalamic nucleus target structures were studied in amine depleted rats following subthalamic stimulation. Amine depletion was accomplished by pretreating the rats with reserpine (2 mg/kg; S.C.) and with alpha-methyl-para-tyrosine (α-mpt; 50 mg/kg; I.P.).Following this treatment, dopamine levels were reduced by 94% in the striatum as measured by HPLC. Amine depletion significantly increased the spontaneous activity of subthalamic cells by 53%. In the SNpr, no significant changes in the spontaneous neuronal activity were observed, but the excitatory responses to bicuculline-induced stimulation of the STH were potentiated as compared to non-treated animals. In the pallidial complex (GP-EP), no potentiation was found. The data suggest that the spontaneous pattern of discharge of the STH is probably under monoaminergic control. They also suggest a reciprocal interaction between dopamine and glutamatergic afferent terminals from the STH within the SNpr, but not in the pallidal complex.

Keywords: In vivo electrophysiology, extracellular recordings, bicuculline, reserpine, alpha-methyl-para-tyrosine, dopamine depletion.

Introduction

The subthalamic nucleus (STH) is a subcortical structure within the "basal ganglia". Lesions of this structure in man are characterized by involuntary large

amplitude movements of the extremities known as hemiballism. The STH has two major afferent systems. One is excitatory arising from the cerebral sensorimotor cortex (Kitai and Deniau, 1981; Rouzaire-Dubois and Scarnati, 1985), and the other is inhibitory and GABAergic (Rouzaire-Dubois et al., 1980) originating from the globus pallidus (GP). The STH efferents project to the substantia nigra (SN), the globus pallidus, and to the entopeduncular nucleus (EP) from branched output neurons (Deniau et al., 1978; Hammond et al., 1983; Van Der Kooy and Hattori, 1980). An increasing body of evidence suggests that the STH efferents are excitatory in nature. In this sense, immunohistochemical studies confirm data on excitatory transmission by showing that the STH contains glutamatergic neurons (Albin et al., 1989; Parent et al., 1989). Electrophysiological experiments, in vitro, have also demonstrated that electrical stimulation of the rat STH can induce excitatory responses in the SN (Kitai and Kita, 1987), EP (Nakanishi et al., 1988), and GP (Kitai and Kita, 1987). Moreover, our in vivo experiments using bicuculline-induced activation of the STH, provide further support for these results by showing increased unit activity in the projection structures (Robledo and Feger, 1990).

The subthalamic nucleus as well as its afferent nuclei can also be modulated by the ascending dopaminergic nigrostriatal system. Anatomical data has shown the presence of dopaminergic varicose terminals in the STH (Brown et al., 1979; Meibach and Katzman, 1979). In addition, neurochemical studies have demonstrated the existence of D 1 and D 2 dopaminergic receptors at the level of the STH (Brown et al., 1979; Martres et al., 1985) as well as in the pallidal complex (Besson et al., 1988; Richfield et al., 1987). The STH has also been shown to react to the microiontophoresis of DA (Campbell et al., 1985; Mintz et al., 1986 a). In turn, some evidence exists showing that the STH can influence dopaminergic activity. In this sense, experiments using push-pull cannulae techniques have revealed that chemical or electrical stimulation of the STH increases dopamine release in the SN, followed by a decrease in the striatum (Mintz et al., 1986 b).

The consequences of DA release in the SN after subthalamic stimulation would be to increase the spontaneous activity of non-dopaminergic cells in the substantia nigra pars reticulata (SNpr) (Mathews and German, 1986; Ruffieux and Schultz, 1981; Waszczak and Walters, 1983). In the same manner, the subsequent reduction of DA release in the striatum may influence neuronal activity in the pallidal complex. Therefore, it was of interest to investigate whether dopamine played a role in the excitatory responses observed in the projection structures after subthalamic activation. The present study compared the responses of the subthalamic afferent nuclei (GP, EP, and SNpr) to bicuculline-induced activation of the STH in monoamine depleted animals to those obtained in control rats studied in these same conditions in a previous experiment (Robledo and Feger, 1990).

Material and methods

Forty nine male Wistar rats weighing between 280 and 320 gr were pretreated with reserpine (2 mg/kg; s.c.) seventeen hours before recording, and with alpha-methyl-para-tyrosine (α-mpt, 50 mg/kg; i.p.), four hours before the experiment. Ten other rats were pretreated only with α-mpt (250 mg/kg; i.p.) four hours prior to extracellular recording in the substantia nigra pars reticulata. Forty seven non-treated rats from a previous experiment (Robledo and Feger, 1990) were used as control animals in this study. All rats were anesthetized with ketamine (100 mg/kg; i.p., supplemented as needed), and fixed to a stereotaxic frame in a horizontal position with the incisor bar 3 mm below the interaural line. Body temperature was maintained at 38 °C by a thermostatically controlled heating device. Extracellular unit activity was recorded using single glass micropipettes (impedance = 10 MΩ) filled with 1% pontamine sky blue in 1 M NaCl. Two cells were recorded per animal, one in each hemisphere. Spike frequency was amplified, counted by a rate meter every 10 seconds, and plotted on a paper chart. The effect of pretreatment on spontaneous neuronal activity was determined by averaging spike frequency for two periods of 200 seconds. After microinjection of bicuculline, counts were performed every five minutes until a plateau was reached. Cells were recorded from the following nuclei: STH (A: 5.0 L: 2.4 H: 8.0), SN (A: 3.0 L: 2.0 H: 8.0), EP (A: 6.0 L: 3.0 H: 8.0), and GP (A: 7.6–8.0 L: 3.0–3.8 H: 5.0–5.7) (Paxinos and Watson, 1986). Bicuculline methiodide (Sigma; 0.39 mM in 0.2 µl) was injected into the STH by means of a stainless steel cannula (30 gauge in diameter) connected to a microsyringe driven by an infusion pump (Precidor). The injection rate was of 0.1 µl in 30 seconds. Bicuculline was dissolved in 0.5% eosine-saline solution in order to visualize the injection site and to estimate the diffusion. At the end of the experiment rats were sacrificed, and the brains were removed, frozen and cut into 50 µ sections. Histological verifications of recording and injection sites were performed in cresyl violet colored slices. The effects of pretreatment (reserpine and α-mpt) on the pattern of spontaneous discharge were analyzed qualitatively in the EP and GP. Five minute spike trains were analyzed in cells of non-treated and depleted rats using a Neurolog system. This system counts the intervals of time elapsed between two spikes and orders them from the smallest to the largest. Finally, it constructs an interspike interval histogram which can be viewed on an oscilloscope. For cells with similar distributions of interspike intervals, the maximum and minimum intervals (milliseconds) were averaged. Biochemical assays of DA content in the striatum were carried out in five rats treated with reserpine and α-mpt, and compared to five control rats. After quick decapitation, three slices 0.5 mm thick were cut at the level of the neostriatum using a cryostat. Four punches 1 mm in diameter were performed in each slice, 2 per hemisphere. The punches were homogenized and centrifuged with 200 µl of extraction liquid plus 40 µl of DBA. The supernatant was dosed for dopamine and its metabolites by HPLC with coulometric detection (Kilpatrik et al., 1986). The protein content of the pellet was analyzed according to the Lowry method (Lowry et al., 1961). Statistical analysis was performed using a t-test for paired comparisons.

Results

Treatment with reserpine and α-mpt resulted in a 94% reduction in the level of dopamine in the striatum as compared to non-treated controls.

In the subthalamic nucleus of rats treated with reserpine and α-mpt, spontaneous neuronal activity was significantly ($p < 0.04$) increased by 53%. In control rats (i.e. rats which are not treated with reserpine or α-mpt), the mean spike discharge was of 15.0 ± 2.0 sp/sec; $n = 10$, mean of treated animals $= 23.0 \pm 3.0$ sp/sec; $n = 11$. A microinjection of bicuculline (0.39 mM) in the

STH significantly ($p < 0.001$) increased the neuronal activity of subthalamic cells ($n = 11$) in treated animals by 196% as compared to the baseline rate. However, the increased level of spike discharge (mean = 68.0 ± 7.0 sp/sec) was not significantly different from that observed in non-treated animals (mean = 70.0 ± 6.0 sp/sec; $n = 9$, see Fig. 1 A).

In the substantia nigra pars reticulata, no changes were observed in the spontaneous neuronal activity of animals treated with reserpine and α-mpt (mean = 31.0 ± 4.0 sp/sec; $n = 8$), or in those treated with α-mpt alone (mean = 30.5 ± 3.4 sp/sec; $n = 10$; data not shown) as compared to non-treated controls (mean = 32.0 ± 1.0 sp/sec; $n = 20$). A microinjection of bicuculline in the STH of animals treated with reserpine and α-mpt significantly increased baseline activity to a mean of 99.0 ± 6.0 sp/sec ($p < 0.001$) in eight out of nine cells tested, one cell showed a decrease in firing rate. This mean increase in neuronal discharge observed in treated animals with respect to baseline rate (217%) was significantly greater than in non-treated control animals (activity after bicuculline = 55.0 ± 4.0 sp/sec, 69% increase, $p < 0.001$; $n = 20$; Fig. 1 B). In animals treated with α-mpt alone, bicuculline injections in the STH produced a mean increase of 171% in the firing rate of seven cells tested with respect to baseline (data not shown) which was significantly greater than the increase observed in non-treated control animals ($p < 0.003$). The neuronal activity of one cell was inhibited by 61%. This potentiation of the excitatory effect exerted by the STH, observed in animals treated with α-mpt alone was not significantly different from that observed in animals treated with both reserpine and α-mpt.

In the EP of non-treated control animals, 8 cells tested had a mean discharge of 15.6 ± 3.1 sp/sec. Five out of eight of these cells were found to discharge with a continuous pattern characterized by an interspike interval distribution ranging from 8 to 56 ms (Fig. 2 A). In animals treated with reserpine and α-mpt, the mean spontaneous discharge rate was not significantly different from non-treated controls (21.0 ± 5.0 sp/sec; $n = 15$). However, the pattern of discharge of nine of these cells was modified to become characterized by bursting activity with an interspike interval displaced to the left ranging from 3 to 60 ms (Fig. 2 B). A microinjection of bicuculline in the STH of treated animals significantly ($p < 0.01$) increased the spontaneous neuronal activity of the EP by 96% with respect to baseline levels (mean = 40.1 ± 8.2 sp/sec; $n = 15$; Fig. 1 C). This increase however was not significantly different from the increase observed in non-treated controls (97%; mean = 30.7 ± 4.0; $n = 8$).

In the globus pallidus of non-treated control animals the mean spontaneous neuronal activity was found to be of 32.4 ± 5.4 sp/sec ($n = 9$). In animals treated with reserpine and α-mpt, the mean spontaneous discharge rate was of 26.6 ± 5.3 sp/sec ($n = 15$), and not significantly different from non-treated controls (Fig. 1 D). In control animals six out of nine cells showed a pattern of discharge characterized by bursting activity with an interspike interval distribution ranging from 2 to 45 ms (Fig. 2 C). In treated animals, GP cells presented a large interspike interval distribution ranging from 4 to 100 ms, and bursting

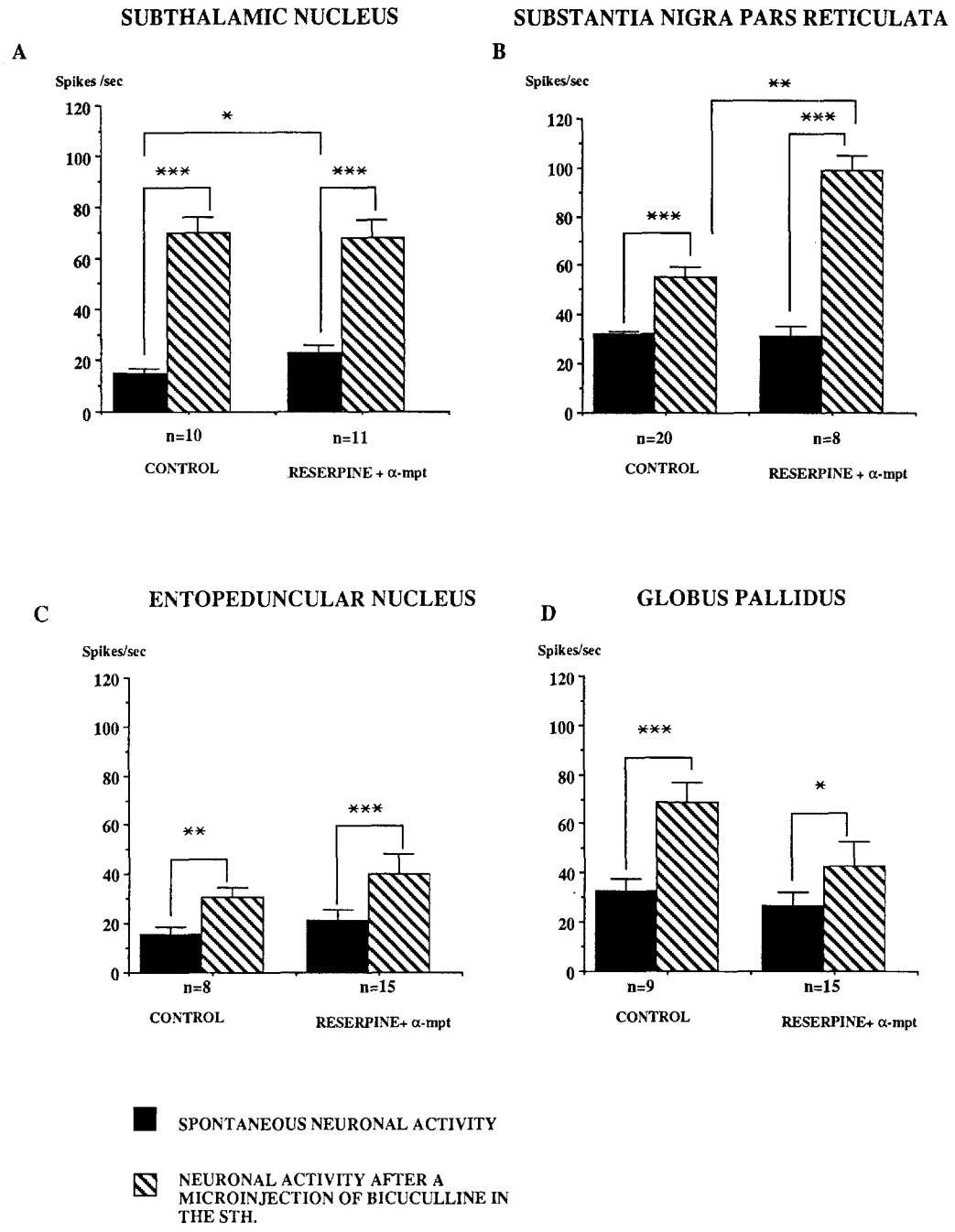

Fig. 1. Effects of an acute monoaminergic depletion (animals treated with reserpine and alpha-methyl-para-tyrosine) on the spontaneous firing rate and on the excitatory response induced by an injection of bicuculline (0.39 mM) into the subthalamic nucleus of cells recorded in the subthalamic nucleus (**A**), the substantia nigra pars reticulata (**B**), the entopeduncular nucleus (**C**), and the globus pallidus (**D**), *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$ (paired t-test)

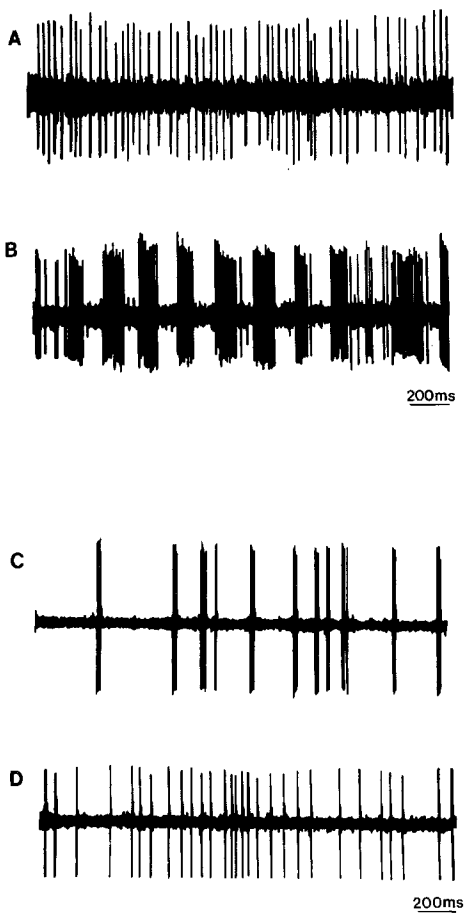

Fig. 2. Neuronal firing pattern of cells recorded in control animals in the entopeduncular nucleus (**A**) and in the globus pallidus (**C**). **B** and **D** show the firing patterns of cells recorded in animals treated with reserpine and alpha-methyl-para-tyrosine in the entopeduncular nucleus and globus pallidus respectively

activity completely disappears (Fig. 2 D). A microinjection of bicuculline increased the discharge rate in non-treated controls by 112% as compared to baseline rates. In treated animals a microinjection of bicuculline in the STH also significantly increased ($p < 0.05$) the discharge rate by 60% as compared to baseline rates (mean = 42.6 ± 10.1 sp/sec; n = 15; three cells were inhibited following the injection of bicuculline in the STH). However, no significant difference was found with respect to the STH-induced activation between treated and non-treated animals (Fig. 1 D).

Discussion

In animals treated with reserpine and α-mpt significant changes were found in the spontaneous neuronal activity of cells recorded in several basal ganglia stuctures, and in their responses to bicuculline-induced stimulation of the STH

as compared to non-treated control animals studied in these same conditions in a previous experiment (Robledo and Feger, 1990). An increase in the spontaneous activity of cells located in the subthalamic nucleus was observed. In the substantia nigra pars reticulata on the other hand, no significant changes in the spontaneous discharge rate were found following amine depletion, but excitatory responses to bicuculline injections were potentiated. In contrast, the pallidal complex displayed no potentiation of bicuculline-induced activation.

In the present study bicuculline was used to activate subthalamic neurons in amine depleted rats, the increases observed in the subthalamic projection structures may have been due to diffusion of this substance to the recorded areas. However, the small volume and concentrations used favors a limited extent of this diffusion (see Robledo and Feger, 1990).

The present study shows that subthalamic neuronal activity is increased following acute amine depletion in the rat. Similar results have recently been found in the monkey rendered parkinsonian by MPTP injection (Bergman et al., 1990). This effect is probably mediated via the striato-pallido-subthalamic pathway. The striatum controls the GP through an inhibitory projection (Nakanishi et al., 1985), and the globus pallidus in turn, inhibits the STH through a GABAergic pathway (Fonnum et al.,1978; Rouzaire-Dubois et al., 1980). Presumably, the absence of DA in the striatum produces an increase in inhibitory activity in the striato-pallidal pathway (Pan et al., 1985; Segovia et al., 1986), and thus disinhibition of the STH. Moreover, iontophoresed dopamine can increase neuronal activity of pallidal cells (Bergstrom and Walters, 1984; Nakanishi et al., 1985). Therefore, treatment with reserpine and α-mpt would probaly reduce pallidal inhibitory input to the STH. In the monkey, dopaminergic depletion induced by treatment with the neurotoxin MPTP produces decreased pallidal activity (Miller and De Long, 1987). Furthermore, our results also show that the proportion of pallidal cells having lower discharge rates increases in treated rats. Thus, reduced activity in the GP either by increased striatal input or decreased dopaminergic activity, would result in disinhibition of the subthalamic nucleus. A direct effect of dopamine deleption in the STH itself is difficult to interpret because of the contradicting data on the respone of STH cells to applied dopamine. One study shows mainly inhibitory (46%), but some excitatory (15%) responses to iontophoresed dopamine (Campbell et al., 1985). However, in another electrophysiological study only excitatory responses were obtained (Mintz et al., 1986 a).

In the substantia nigra pars reticulata, the spontaneous activity of non-dopaminergic cells was not changed in animals treated with reserpine and α-mpt. Dopamine however, has been shown to increase the firing rate of nigral neurons directly, or by attenuating GABA inhibition (Waszczak and Walters, 1983, 1986). Therefore, after dopaminergic depletion we expected a reduction in the spontaneous activity of these cells. Our results showing no change were rather surprising since they suggest that dopamine spontaneously released from dendrites of dopaminergic neurons (Cheramy et al., 1981) may not tonically

influence the activity of reticulata cells. It might be argued that the absence of the expected effect may be due to the depletion of serotonin which is also produced by reserpine. However, this is unlikely since in animals treated with α-mpt alone, which produces primarily catecholamine depletion, similar results were obtained. It is possible that in the amine depleted animals the absence of dopamine did in fact reduce nigral activity, but this reduction was counterbalanced by indirect influences coming to the substantia nigra from the striatum, the GP, or the subthalamic nucleus all of which are profoundly influenced by the dopaminergic system. Our results show that excitatory subthalamic activity increases under conditions of amine depletion, and therefore might compensate for the lack of excitatory dopaminergic input.

Treatment with reserpine and α-mpt as well as with α-mpt alone potentiated the excitatory effect of the STH on pars reticulata neurons. The fact that both treatments induced the same effect suggests that serotonin depletion may not play a role in the potentiation observed. Norepinephrine (NE) levels, are also presumably reduced after treatment with α-mpt. Therefore, it might be argued that the potentiation of the excitatory effect exerted by the STH on pars reticulata nigral cells is due to the NE depletion. Indeed, this neurotransmitter is present in massive quantities in the SN (Dray et al., 1976). In another neuronal system, the hippocampus, it has been demonstrated that NE produces an increase in the response of a pyramidal cell to an excitatory stimulation. This effect is related to the accommodation of action potentials resulting from a decrease in the calcium-dependent hyperpolarization produced by the outflow of potassium (Madison and Nicholl, 1982). If a similar phenomenon occurs in the SN, we would have expected a smaller response to the stimulation of the STH following NE depletion than in normal conditions, and not a potentiation as we actually observed. Therefore, the major neurotransmitter involved in the potentiation of subthalamic excitatory activity in the SNpr in amine depleted animals is probably dopamine. Moreover, this potentiation of the subthalamic excitatory effect suggests that in normal conditions, dopamine probably interacts with the neurotransmitter released by subthalamic efferents.

Recently, it has been shown that the STH exerts an excitatory action in its projection structures possibly through the neurotransmitter glutamate (Albin et al., 1989; Parent et al., 1989). Further, we have demonstrated that the glutamatergic antagonist kynurinic acid blocks the excitatory response of pars reticulata nigral cells to the bicuculline-induced stimulation of the STH (Robledo and Feger, 1990). Very few data exist on dopamine-glutamate interactions in the SNpr. Mintz et al. (1986) have shown that electrical or chemical stimulation of the STH produces an increase in the release of dopamine in the SN. Another study reported that in certain cases, the iontophoretic application of DA in the SNpr reduces the excitatory responses induced by glutamic acid (Waszczak and Walters, 1983). In the striatum however, glutamate released following stimulation of the corticostriatal pathway has been found to facilitate the release of DA in vivo. Conversely, DA has been shown to exert an inhibitory influence

on the release of ^{3}H-glutamate (Nieoullon et al., 1983). Moreover, recent studies in vivo and in vitro, suggest that DA acts to inhibit the reuptake of glutamate, and this inhibition is dependent on the activity of the corticostriatal neurons (Kerkerian et al., 1989). These same authors show that on the other hand, dopaminergic antagonists haloperidol, or α-mpt the catecholamine synthesis inhibitor, do not modify the basal level of glutamate uptake, but potentiate the excitatory response of striatal cells to cortical stimulation. To our knowledge, there is no direct anatomical evidence for glutamate-dopamine interactions in the striatum nor in the SN. However, neurophysiological data point to a potential for these interactions in the SN (Kornhuber et al., 1984; Cheramy et al., 1981). Our results in the SNpr may be interpreted as being caused by indirect compensatory mechanisms, but it is also very likely that they are caused by a dopaminergic modulation of glutamatergic transmission, in a similar manner to that observed in the striatum.

Monoaminergic depletion was found to induce important changes in the spontaneous pattern of discharge of pallidal cells. In the globus pallidus bursting activity disappeared whereas in the entopeduncular nucleus bursting increased. Similar results were obtainend by Miller and De Long (1987) in monkeys rendered parkinsonian by injections of the neurotoxin MPTP. These authors show that the activity of the medial pallidal segment (homologue of the EP in the rat) was augmented and bursting activity increased. In another study with monkeys lesioned at the level of the medial forebrain bundle, the neurons in the medial segment of the GP were found to discharge continually in bursts, during movement, rest and sleep. In contrast, neurons in the lateral segment displayed some bursting, but noncontinuously (Filion, 1979). In our study, treatment with reserpine and α-mpt produced a 94% reduction in the level of striatal DA. Therefore, acute dopaminergic depletion in the rat as well as chronic depletion in the monkey produced similar changes in the pattern of discharge in the two pallidal complex nuclei. The mechanisms by which dopamine controls the specific firing patterns of these cells are not yet understood, however these results are interesting since they show that the rat may provide a good model for continuing neuropharmacological and electrophysiological experiments designed to clarify the mechanisms controlling the firing pattern of the pallidal complex which may help to develop new strategies in the treatment of parkinsonism.

The present study shows that stimulation of the STH in amine depleted rats still induces excitatory responses in the SNpr and in the pallidal complex. These results were obtained in rats anesthetized with ketamine which has been shown to be a noncompetitive NMDA-receptor antagonist (see Yamamura et al., 1990 for review). Thus, we cannot exclude the possibility that some of the responses recorded after stimulation of the presumed glutamatergic subthalamic pathway might have been affected by this treatment.

In conclusion, our study suggests that the excitatory effect of the STH on its projection structures is not mediated through the monoaminergic system,

but that it is rather a direct effect. However, a reduction of the brain catecholamine content potentiates the excitatory effect of the STH in the pars reticulata. A great deal of attention has been given to the STH in the past few years because of its key involvement in movement disorders (hemiballism-chorea-parkinsonism). Nevertheless, little is known about transmitter interactions between the STH and its target structures. Our results suggest a possible reciprocal interaction between DA and STH glutamatergic afferent terminals within the SNpr, but not in the pallidal complex. Further research along these lines will help to elucidate how the dopaminergic modulation of the subthalamic excitatory action at the level of the SNpr is involved in the control of movement.

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