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Electrophysiological effects of a cannabinoid on neural activity in the globus pallidus

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Abstract

The globus pallidus contains a dense distribution of cannabinoid receptors and appears to be a site of action of cannabinoids in the production of catalepsy. Single unit electrophysiology was used to explore the role of cannabinoid receptors in the globus pallidus of the rat. Intravenous injections of the potent and selective synthetic cannabinoid (*R*)-(+)-[2,3-dihydro-5-methyl-3-[(4-morpholinyl)methyl]-pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl](1-napthalenyl) methanone (WIN 55,212-2; up to 0.5 mg/kg, i.v.) inhibited the spontaneous firing of neurons in the globus pallidus. In a second set of experiments, WIN 55,212-2 antagonized the inhibition of pallidal firing produced by electrical stimulation of the striatum. The pharmacological specificity of the effects of WIN 55,212-2 on basal and evoked activity in the globus pallidus was demonstrated by the lack of effect of the inactive enantiomer WIN 55,212-3. These results indicate that cannabinoids may produce functionally opposite effects on spontaneous and evoked activity in the globus pallidus: a decrease in spontaneous firing and a decrease in the inhibition of firing produced by the striatopallidal projection.

Keywords: Basal ganglia; Cannabinoid; Globus pallidus; Cannabinoid receptor; Motor system; Marijuana; Tetrahydrocannabinol; WIN 55,212-2; Aminoalkylindole; Anandamide

1. Introduction

The discovery and cloning of the cannabinoid receptor (Howlett et al., 1987; Devane et al., 1988; Matsuda et al., 1990) and the identification of anandamide, a naturally occurring ligand for the cannabinoid receptor (Devane et al., 1992), established the existence of an endogenous cannabinoid neurotransmitter system. Cannabinoid receptors are densely distributed in the basal ganglia and the cerebellum, regions closely associated with the regulation and coordination of motor activity (Herkenham et al., 1991a). As the distribution would suggest, cannabinoids profoundly affect motor activity (Abood and Martin, 1992). Low doses increase motor activity, while higher doses inhibit motor activity and produce catalepsy (Garriott et al., 1967; Grunfeld and Edery, 1969; Holtzman et al., 1969). These motor effects of cannabinoids have also been observed following administration of anandamide (Crawley et al., 1993; Fride and Mechoulam, 1993; Wickens and Pertwee, 1993; Smith et al., 1994; Romero et al., 1995).

Recent reports have described the effects of cannabinoids in the basal ganglia. One site where cannabinoids appear to affect basal ganglia outflow is the substantia nigra pars reticulata. In this region the synthetic cannabinoid (*R*)-(+)-[2,3-dihydro-5-methyl-3-[(4-morpholinyl)-methyl]pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl](1-napthalenyl)methanone (WIN 55,212-2) reversed the inhibition of spontaneous firing produced by striatal stimulation. Furthermore, the compound produced a modest increase in the spontaneous firing of substantia nigra pars reticulata neurons (Miller and Walker, 1995). Behavioral studies also revealed significant actions of cannabinoids in the substantia nigra pars reticulata. Microinjection of cannabinoids into the substantia nigra pars reticulata attenuated both the contralateral circling induced by coadministration of a dopamine D_1 receptor agonist and the ipsilateral circling induced by coadministration of a dopamine D_2 receptor agonist (Sañudo-Peña et al., 1995). These findings are in

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general agreement with the observations of Anderson et al. (1995), who examined the effects of intraperitoneal (i.p.) administration of the synthetic cannabinoid receptor agonists WIN 55,212-2 and CP 55,940 in rats with 6-hydroxydopamine lesions of the substantia nigra. They found that the cannabinoids attenuated the contralateral turning behavior produced by i.p. administration of a dopamine D_1 receptor agonist but not that produced by a dopamine D_2 receptor agonist. Taken together, these findings suggest that cannabinoid receptors modulate outflow of information from the basal ganglia.

Another area of the basal ganglia that appears to be important in the motor effects of cannabinoids is the globus pallidus. Microinjection of Δ^9-tetrahydrocannabinol into the posterior medial region of the globus pallidus resulted in mild but significant catalepsy, and this effect was potentiated by the benzodiazepine chlordiazepoxide (Pertwee and Wickens, 1991). Likewise, pallidal injections of cannabinoids potentiated the cataleptic effect of muscimol in rats (Wickens and Pertwee, 1993). These findings suggest that the pallidum may mediate the cataleptic effects of cannabinoids, but the cellular basis for these actions is unknown.

Cannabinoid receptors in the globus pallidus are located primarily on striatopallidal terminals (Herkenham et al., 1991b) and may thus regulate striatopallidal neurotransmission. Therefore, it was of interest to examine whether a cannabinoid would modulate the inhibitory effects of striatal stimulation in the globus pallidus. In the present experiments, we examined the effects of WIN 55,212-2 on spontaneous and evoked activity in the globus pallidus using extracellular single neuron recording in rats.

2. Materials and methods

2.1. Drugs and chemicals

WIN 55,212-2 was purchased from Research Biochemicals International (Natick, MA, USA); WIN 55,212-3 was a gift from Sterling-Winthrop. WIN 55,212-2 and WIN 55,212-3 were suspended in an ethanol-alkamuls (emulphor)-saline solution (1 : 1 : 18). Test tubes and syringes were siliconized with Sigmacote (Sigma-Aldrich, St. Louis, MO, USA) in order to prevent the drugs from adhering to the surfaces.

2.2. Animals and surgical preparation

Male Sprague-Dawley albino rats ($n = 35$, 250–350 g) were anesthetized with a 25% solution of urethane in normal saline (1.25 g/kg, i.p.). The rat's body temperature was maintained at 37°C throughout the experiment. A craniotomy was performed at coordinates of 0.8–1.2 mm posterior to bregma and 2.5–3.5 mm lateral to the midline (derived from Paxinos and Watson, 1986).

2.3. Electrophysiological recordings

Single barrel glass electrodes were prepared from 2.0 mm omega dotstock (Glass Co. of America, Millville, NJ, USA) using a Narashige PE2 puller, and the tips were broken back under a microscope to 1–2 μm. The electrode was lowered into the brain using a Kopf hydraulic microdrive. Amplified action potentials were passed through low and high pass filters into a window comparator that produced a logic pulse for each action potential which was passed to a computer. Electrical signals were monitored on an audio amplifier and displayed on an oscilloscope.

Pallidal neurons were identified by their short duration action potentials (< 1 ms), a firing rate of 10–70 Hz (Bergstrom et al., 1984) and a depth of 5–7 mm below the brain surface. Following each experiment, fast green dye was ejected from the recording electrode tip as an anion by iontophoresis (5–30 μA, 20 min). Animals were sacrificed and perfused with 10% formalin. Brains were frozen, sectioned at 40 μm and stained with neutral red, and all recording sites were verified microscopically.

2.4. Effect of WIN 55,212-2 on spontaneous firing rate

Cumulative doses of WIN 55,212-2 (0.0625–0.5 mg/kg, i.v.), WIN 55,212-3 (0.0625–0.5 mg/kg, i.v.) or vehicle were injected into the lateral tail vein following a 3–5 min baseline. The mean firing rates were determined for the last minute of the baseline period and for at least 30 s following each injection.

2.5. Striatal stimulation studies

A second set of experiments was carried out in order to determine whether WIN 55,212-2 would modify the inhibitory effect of striatal stimulation on neural firing in the globus pallidus. The striatum was electrically stimulated while activity was recorded in the globus pallidus. Stimulating electrodes were constructed from stainless steel insect pins (No. 00; 0.25 mm diameter) insulated with Epoxylite, except for 0.5 mm exposed at the tip. A stimulating electrode and a grounding electrode, separated by 0.2 mm, were lowered 1.5 mm into the striatum (1.0 mm anterior to bregma and 1.8 and 3.8 mm lateral to the midline). Trains (500 ms) of 300–500 μA square pulses (300 μs duration, 45 Hz) were delivered to the striatum at 20 s intervals using a Grass (Quincy, MA, USA) model S-88 stimulator and constant current photoisolation unit.

A computer recorded the time of occurrence (to 0.1 ms accuracy) of each action potential for a prestimulation period of 1 s, sent a signal to the stimulator which produced the train of pulses, and continued to record the time of occurrence of each action potential for a post-stimulation period of 2.5 s. Striatal stimulation produced a brief inhibition of neural activity in the globus pallidus. In

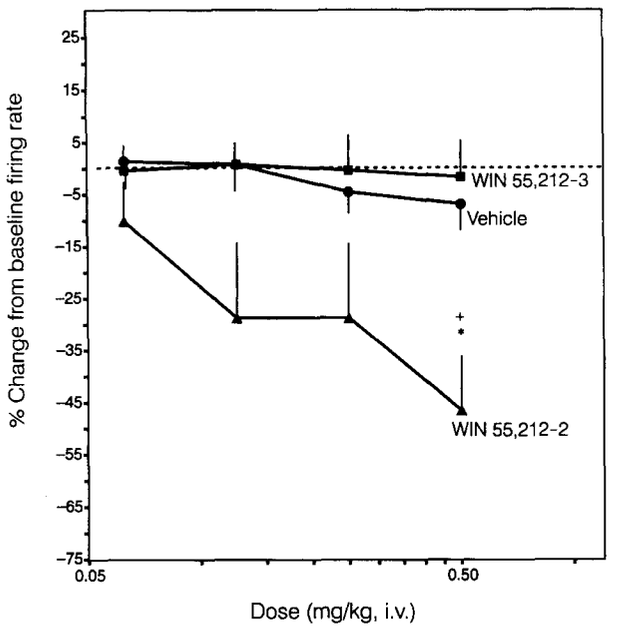

Fig. 1. Effect of WIN 55,212-2 (cumulative doses of 0.0625–0.5 mg/kg, i.v.) on the spontaneous firing rate of neurons in the globus pallidus. WIN 55,212-2 produced a dose-dependent decrease in the spontaneous firing rate (dashed line) of neurons in the globus pallidus ($n = 18$, $P < 0.05$; * significantly different from vehicle; + significantly different from the inactive enantiomer, WIN 55,212-3).

some cells, striatal stimulation did not have an effect, presumably due to the location of the stimulating electrodes; in such cases, a different cell was selected. Following a baseline period during which 10 stimulations were delivered, either WIN 55,212-2, WIN 55,212-3, or vehicle was injected intravenously (cumulative doses of 0.0625, 0.125, 0.25 and 0.5 mg/kg). Five stimulation trials were carried out following each injection. At the end of each experiment, a direct current (300–500 μA) was passed through the stimulating and grounding electrodes for 20 s to mark their locations within the brain. Recording and histological techniques were performed as described above.

2.6. Data analyses

Experiments that examined spontaneous firing were analyzed by calculating the mean firing rate during the baseline period and following each drug or vehicle dose. Rates were expressed as the percentage changes from baseline firing rate and were subjected to a repeated measures analysis of variance (ANOVA; BMDP Statistical Software, Los Angeles, CA, USA). Data are expressed in terms of cumulative doses.

Striatal stimulation experiments were analyzed by calculating the mean firing rate at each dose during the 100 ms period following the termination of striatal stimulation. Mean prestimulation firing rates were also determined for each drug or vehicle dose. Values were expressed as percent of prestimulation firing rate at each dose, because WIN 55,212-2 decreased prestimulation firing rate. Drug effects were analyzed by means of a two-way repeated measures ANOVA.

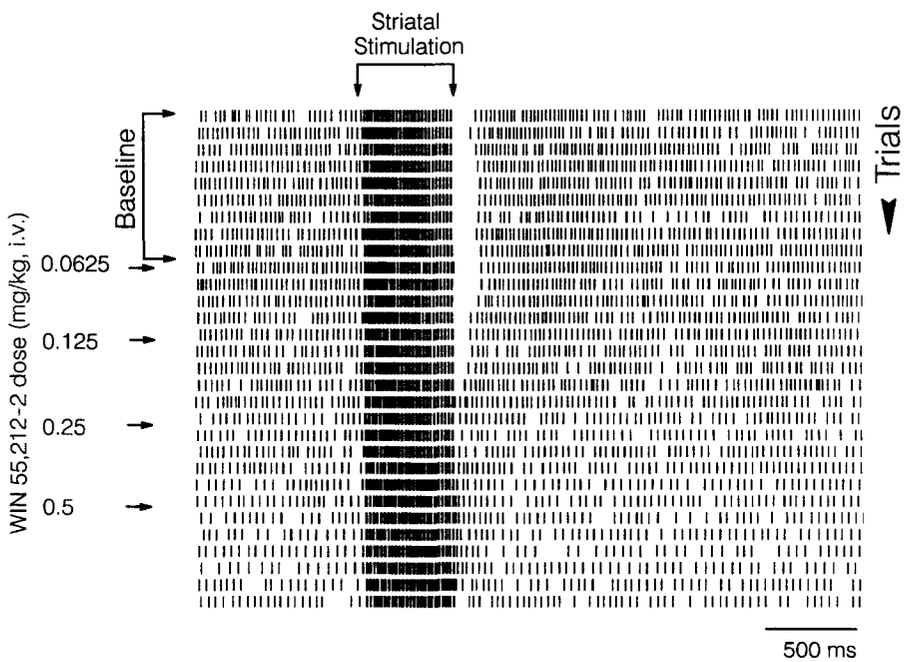

Fig. 2. Raster plot showing the effect of WIN 55,212-2 on the inhibition of a globus pallidus neuron evoked by electrical stimulation of the striatum. Each tick mark represents the time of occurrence of a single action potential. Each row represents one stimulation trial. Striatal stimulation produced a brief inhibition of activity in the globus pallidus which was most pronounced during the first 100 ms following stimulation. WIN 55,212-2 injections began following the 10th trial (cumulative doses of 0.0625–0.5 mg/kg) and were repeated every fifth trial. Note the reversal of inhibition following injection of WIN 55,212-2.

In order to eliminate the possibility of spurious significant P estimates that can occur in the repeated factor analysis of variance when the assumption of homogeneity of variance and covariance is violated, the conservative Greenhouse-Geisser correction was applied to degrees of freedom for repeated factors whenever the violation of sphericity test was significant. Post-hoc analyses were performed using t-tests with the Bonferroni adjustment to maintain experiment-wise an error rate of $P < 0.05$.

A correlation coefficient was calculated and evaluated for significance in order to determine whether the effect of 0.5 mg/kg WIN 55,212-2 on spontaneous (prestimulation) activity of cells in the globus pallidus correlated significantly with the effect of the cannabinoid on evoked activity.

3. Results

3.1. Effects of systemically administered WIN 55,212-2 on spontaneous firing of globus pallidus neurons

Intravenous injection of up to 0.5 mg/kg WIN 55,212-2 produced a decrease in the spontaneous firing rate of neurons in the globus pallidus: Fig. 1, $n = 18$; $F(4,30) = 3.29$; $P < 0.05$. Post-hoc analysis revealed a significant drug-induced decrease relative to the inactive enantiomer and vehicle at 0.5 mg/kg ($P < 0.05$). At this dose WIN 55,212-2 produced a $47 \pm 10\%$ decrease from baseline firing in the globus pallidus.

3.2. Effects of WIN 55,212-2 (i.v.) on striatal stimulation-evoked inhibition of firing of globus pallidus neurons

As reported by others (Levine et al., 1974; Napier et al., 1983), striatal stimulation produced a brief (approximately 100 ms) inhibition of the firing of neurons in the globus pallidus. Under pre-drug (or pre-vehicle) conditions, striatal stimulation inhibited the firing of globus pallidus neurons by a mean ($\pm$S.E.M.) of $75 \pm 2\%$ for all cells combined. The initial prestimulation firing rates for the three groups were not significantly different (30.6 ± 5.0 Hz), and there was no statistically significant difference between inactive enantiomer and vehicle controls.

The cannabinoid receptor agonist WIN 55,212-2 dose dependently attenuated the stimulation-evoked inhibition: Figs. 2 and 3, $n = 17$; $F(4,18) = 3.36$; $P < 0.05$. Post-hoc analysis revealed that this effect was significant at the dose of 0.5 mg/kg (compared to vehicle) and at the doses of 0.25 and 0.5 mg/kg (compared to WIN 55,212-3). Reversal was complete in 5 of the 6 cells tested with WIN 55,212-2.

In 5 of 18 neurons, the inhibition produced by striatal stimulation was followed by a brief excitation which subsided before the beginning of the next trial (mean $= 25 \pm 5\%$ increase from baseline, occurring 450–600 ms following striatal stimulation). Two of the neurons that showed this effect were treated with the cannabinoid receptor agonist. In these cells the increase in firing was not

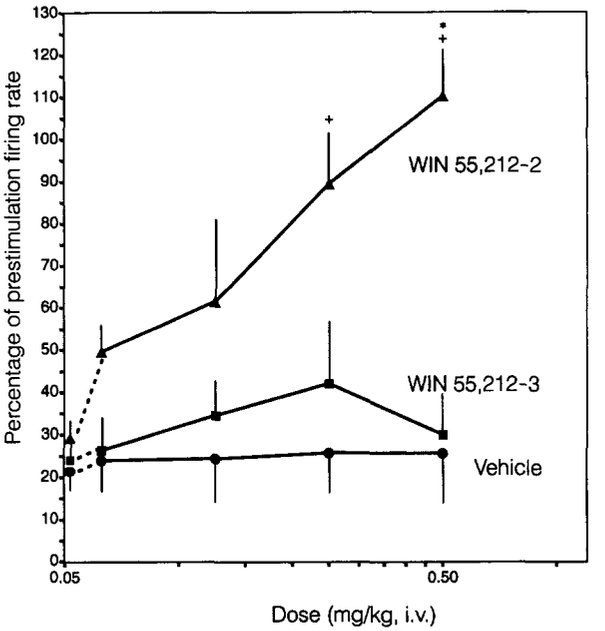

Fig. 3. Effect of WIN 55,212-2 on striatal stimulation-evoked inhibition in the globus pallidus. WIN 55,212-2 dose dependently reversed the stimulation-evoked inhibition in the globus pallidus ($n = 17$, $P < 0.05$; * significantly different from vehicle; + significantly different from WIN 55,212-3). The leftmost points on the graph (connected with dashed lines) represent the baseline firing rate.

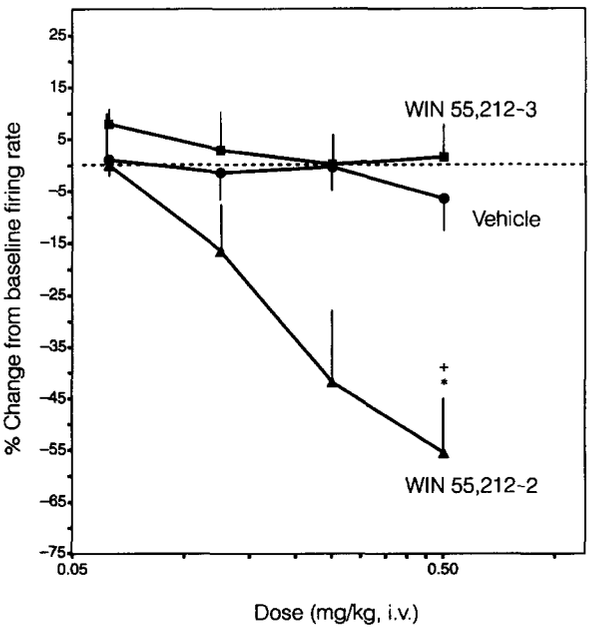

Fig. 4. Effect of WIN 55,212-2 on prestimulation rates in the globus pallidus. Cellular activity of neurons in the globus pallidus was recorded before and after striatal stimulation. WIN 55,212-2 produced a dose-dependent decrease in prestimulation firing rates. This was interpreted as a decrease in the spontaneous activity of neurons in the globus pallidus ($n = 12$, $P < 0.05$; * significantly different from vehicle; + significantly different from WIN 55,212-3).

observed following administration of the two highest doses of the drug (Fig. 2).

WIN 55,212-2 produced a dose-dependent decrease in prestimulation firing rate, confirming the decrease in the spontaneous activity of globus pallidus neurons reported above: Fig. 4, $n = 17$, $F(3,19) = 3.46$. Post-hoc analysis revealed that this effect was significant at 0.5 mg/kg compared to either WIN 55,212-3 or vehicle. At this dose, WIN 55,212-2 produced a $55 \pm 10\%$ decrease from prestimulation firing rate.

Effects of the maximal dose of WIN 55,212-2 on spontaneous (prestimulation) firing rate and on evoked activity were not significantly correlated ($r = -0.056$; $P > 0.05$).

4. Discussion

The main finding from these experiments was that WIN 55,212-2 produced functionally opposite effects on spontaneous and evoked activity in the globus pallidus. WIN 55,212-2 inhibited spontaneous firing in the globus pallidus. On the other hand, the drug reversed striatal stimulation-evoked inhibition, an effect that resulted in a net increase of neural activity in the globus pallidus. These effects of WIN 55,212-2 on neural activity in the globus pallidus were most likely due to the compound's interaction with cannabinoid receptors, since they were not observed following administration of the inactive enantiomer, WIN 55,212-3.

Studies with γ-aminobutyric acid (GABA) receptor agonists suggest that an inhibition of activity in the globus pallidus leads to a decrease in motor activity and to catalepsy. Microinjection of muscimol into the posterior region of the globus pallidus in the rat reduces spontaneous motor activity and inhibits amphetamine-induced hyperactivity; microinjection of muscimol into the anterior region of the globus pallidus produces catalepsy followed by hyperactivity (Ossowska et al., 1984). Long-lasting catalepsy has been observed in the rat following microinjection of baclofen or muscimol into the ventromedial globus pallidus, suggesting the involvement of $GABA_A$ and $GABA_B$ receptors (Scheel-Krüger, 1986). Since GABAergic compounds inhibit neural activity in the globus pallidus (Waszczak et al., 1981) and produce catalepsy when microinjected into this region, and since similar effects are obtained with cannabinoids (Pertwee and Wickens, 1991; Wickens and Pertwee, 1993), it is reasonable to speculate that cannabinoids produce catalepsy by inhibiting the activity of neurons in the globus pallidus.

Direct or indirect mechanisms could account for the effect of WIN 55,212-2 on evoked firing in the globus pallidus. The reversal of striatal stimulation-evoked inhibition in the globus pallidus might be due to an inhibition of GABA or enkephalin release from striatopallidal neurons, since these neurotransmitters are involved in striatopallidal transmission (Huffman and Felpel, 1981; Napier et al., 1983; Nakanishi et al., 1985). Cannabinoid receptors on striatal cell bodies might regulate striatopallidal release by hyperpolarizing striatal neurons, perhaps by enhancing K^+ A-currents (Deadwyler et al., 1993).

Alternatively, cannabinoid receptors on striatopallidal terminals may regulate the release of GABA and/or enkephalins from the striatum into the globus pallidus. One mechanism through which cannabinoids might affect receptors on striatopallidal terminals is through regulation of the c-AMP second messenger system. Cannabinoids have been shown to inhibit adenylate cyclase through a G-protein-coupled receptor (Howlett et al., 1987; Bidaut-Russell et al., 1990). Cannabinoids might also affect the presynaptically located receptors in the globus pallidus through the inhibition of N-type Ca^{2+} channels (Mackie and Hille, 1992.). All three of these mechanisms would be expected to result in a decrease of neurotransmitter release (Klein and Kandel, 1980; Dooley et al., 1987; Hescheler et al., 1987; Miller, 1987).

There are several possible mechanisms through which cannabinoids might inhibit spontaneous activity in the globus pallidus. For example, this could occur through enhancement of voltage-sensitive K^+ A-currents (Deadwyler et al., 1993), as noted above. However, it is unlikely that cannabinoids act on receptors that are intrinsic to globus pallidus neurons, since the globus pallidus does not contain detectable levels of cannabinoid receptor mRNA (Mailleux and Vanderhaeghen, 1992). Alternatively, cannabinoids may inhibit neural activity in the globus pallidus by decreasing the release of excitatory amino acids from the subthalamic nucleus into pallidal neurons. Since the subthalamic input to the globus pallidus is tonically active, this mechanisms could account for the tonic inhibition of spontaneous activation of pallidal neurons by the cannabinoid.

The experiments on spontaneous and evoked firing were performed separately. However, inhibition of spontaneous prestimulation firing was observed in the experiments that examined stimulation evoked-firing. This indicates that inhibition of spontaneous firing and the reduction of inhibitory effect of striatal stimulation does indeed occur in the same neurons. Since the striatum exerts phasic rather than tonic inhibition of activity in the globus pallidus (Kimura et al., 1990), a mechanism that inhibits neurotransmitter release from striatopallidal terminals might only produce a modest increase in the spontaneous firing rate of pallidal neurons. This modest increase could then be overcome by a separate mechanism which profoundly inhibits the spontaneous firing of pallidal neurons. The lack of a significant correlation between the effect of the cannabinoid spontaneous vs. evoked firing is consistent with the possibility of multiple independent actions of the cannabinoid on different inputs to the pallidum.

Pathology of the globus pallidus contributes to Huntington's disease and certain other motor disorders. In the

monkey, microinjection of bicuculline into the lateral segment of the globus pallidus produces chorea and myoclonus (Crossman et al., 1988), suggesting that disruption of the striatopallidal pathway might be an important contributing factor to the motor abnormalities observed in Huntington's disease. It is interesting that patients with Huntington's disease display a preferential loss of cannabinoid receptors in the lateral globus pallidus (homologous to the rat globus pallidus) as compared to the medial globus pallidus (homologous to the rat entopeduncular nucleus) and that this differential loss increases with the severity of the disease. This finding suggests the lateral globus pallidus is particularly affected in Huntington's disease (Richfield and Herkenham, 1994). A better understanding of the role of cannabinoid receptors in the basal ganglia might lead to new pharmacotherapies for Huntington's disease or other motor disorders that involve the basal ganglia.

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