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DOPAMINE AGONISTS INCREASE PALLIDAL UNIT ACTIVITY: ATTENUATION BY AGONIST PRETREATMENT AND ANESTHESIA

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Intravenous administration of a single bolus dose of 1 μmol/kg of the dopamine agonists, pergolide and lisuride, caused marked increases in the unit activity of globus pallidus neurons in awake, paralyzed, locally anesthesized and artificially respired rats. These agonist effects were similar to those observed after administration of 1 μmol/kg apomorphine to awake, paralyzed rats; in rats anesthetized with chloral hydrate, however, responses to apomorphine were markedly attenuated. Subsequent administration of haloperidol reversed the effects of pergolide and pretreatment with haloperidol blocked the effects of lisuride. LSD (1 μmol/kg i.v.) did not effectively stimulate pallidal neuronal activity, suggesting that the ability to stimulate pallidal firing rates correlates better with dopamine, as opposed to serotonin, agonist potency. The ability of a non-excitatory dose of apomorphine to attenuate responses of pallidal neurons to a normally excitatory 1 μmol/kg dose of this agonist administered subsequently, was reconfirmed. Pretreatment with this 'priming' dose of apomorphine also attenuated the rate increases produced by d-amphetamine (8.7 μmol/kg) and enhanced the rate inhibitory effects of haloperidol. The 'priming' effect appears related to the dopamimetic effects of apomorphine; a non-excitatory dose of a second dopamine agonist, lisuride (0.07 μmol/kg i.v.), similarly blocked the effect of excitatory doses of lisuride (1 μmol/kg i.v.) on pallidal activity

Single unit recording Chloral hydrate anesthesia Apomorphine Ergot derivatives Globus pallidus

1. Introduction

Research over the past several years has suggested that there are many sites at which dopamine agonists can act in the basal ganglia to affect information processing in this region. Dopamine neurons projecting to the striatum are thought to contain, on their cell bodies and terminal regions, dopamine autoreceptors which are preferentially sensitive to low doses of dopamine agonists (Kehr et al., 1972; Skirboll et al., 1979). Dopamine receptors of various types are also located on striatal neurons (Kebabian and Calne, 1979; Klemm et al., 1979) and on terminals of neurons projecting into the striatum (Schwarcz et al., 1978). Moreover, binding studies have demonstrated the presence of dopamine binding sites in the globus pallidus (Burt et al., 1976; Fields et al., 1977), an area which has a sparse but widespread dopaminergic innervation (Lindvall and Björklund, 1979).

Since the globus pallidus receives a major projection from the striatum as well as a direct dopaminergic input, pallidal cells are in a position to be affected, either directly or indirectly, by the actions of dopamine agonists at all these dopamine receptor sites. Thus, investigation of the effects of dopamine agonists on the spontaneous activity of globus pallidus neurons should provide information about how the effects mediated by stimulation of these different dopamine receptors

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summate (Bergstrom and Walters, 1981; Bergstrom et al., 1982a, b). Single unit recording studies have demonstrated that systemic administration of the dopamine agonist apomorphine, in doses adequate to stimulate postsynaptic dopamine receptors, produces marked increases in the activity of spontaneously firing neurons in the globus pallidus of gallamine paralyzed, artificially respired and locally anesthetized rats (Bergstrom et al., 1982a). It was hypothesized that smaller doses of apomorphine might cause changes in the opposite direction from those of larger doses, since preferential stimulation of the more sensitive dopamine autoreceptors should lead to inhibition of dopamine release and a net decrease in postsynaptic dopamine receptor stimulation. However, smaller amounts of apomorphine produced no significant changes in pallidal activity (Bergstrom et al., 1982a). On the other hand, these small doses of apomorphine did exert an interesting effect; they significantly attenuated the response of the pallidal cells to subsequent injections of larger doses of apomorphine (Bergstrom et al., 1982b).

The present investigation explores further these actions of apomorphine and tries to determine whether similar changes in pallidal activity can be produced by other dopamine agonists. The responses of pallidal neurons to systemic administration of two ergot dopamine agonists, lisuride and pergolide, have been examined. LSD, an ergot derivative which is a weaker dopamine agonist, but, like lisuride, is a potent serotonin agonist, was also examined. The effects of apomorphine pretreatment on pallidal responses to d-amphetamine and haloperidol are explored as is the ability of small doses of the agonist lisuride to alter subsequent responsiveness of pallidal cells. Finally, we have investigated how general anesthesia affects the changes in activity induced by dopamine agonist administration.

2. Materials and methods

Male, Sprague-Dawley rats (250–350 g) were used for single unit recordings of globus pallidus neurons. Animals were either anesthetized with 400 mg/kg chloral hydrate i.p. and given additional injections of chloral hydrate as needed through a tail vein throughout the experiment or paralyzed with gallamine, locally anesthetized and artificially respired. For the paralyzed rat preparation, all surgical procedures were carried out under halothane anesthesia. All incision sites and pressure points were thoroughly infiltrated with the local anesthetic, mepivacaine HCl. Gallamine triethiodide (16 mg/kg) was injected via a tail vein. Animals were respired on room air at a rate adjusted to maintain an expired CO_2 of 3.5-4.2% as measured by a CO_2 analyzer. Additional injections of gallamine were administered routinely throughout the experiment. Eyedrops of a tetrahydrozoline HCl solution were applied intermittently to prevent discomfort due to corneal drying. Body temperature was monitored and maintained at 36–38°C with an electric heating pad.

Extracellular, single unit recordings were conducted according to standard techniques. A 3 mm burr hole was drilled through the skull 2.6 mm lateral to lambda and 7.3 mm anterior to the lambdoid suture for recording in the globus pallidus. An electrode was passed through the hole to the appropriate level with a hydraulic microdrive (Bergstrom and Walters, 1981). Electrode potentials were passed through a high input-impedance amplifier and monitored on an oscilloscope and audiomonitor. Extracellular action potentials were isolated to a signal-to-noise ratio of 3 : 1 or more. Integrated firing rates were recorded by a rate-meter and displayed as histogram plots of the number of extracellular action potentials counted in successive 10 s intervals on a strip chart recorder.

Single barrel recording electrodes were pulled from 2.0 mm glass capillary tubing (1.0 mm, I.D., Corning Glass Works, Corning, NY) which contains several strands of fiber glass. After being pulled, the micropipettes were filled with a 1% Pontamine Sky Blue (GURR, High Wycombe, Bucks, United Kingdom) in 2 M NaCl and the tips broken back to a diameter of approximately 1–2 μm. The electrodes used in these studies had impedances between 3.6 and 6.0 MΩ (measured at 135 Hz).

Spontaneously active pallidal cells with extracellular, biphasic action potentials of short duration (mean, 0.78 ± 0.04 ms) in the frequency

range of 10-70 spikes/s were investigated. Pallidal cells displaying either constant firing patterns, irregular firing patterns, or bursting discharge patterns were included in this study. The recording site, which was marked by passing a 15 nA current through the electrode for about 15 min, was identified by locating the Pontamine Sky Blue deposit after the brain was fixed, sectioned, mounted and stained.

Following the location of an appropriately firing neuron, a 5 min period of baseline activity was recorded before drugs were administered intravenously through a lateral tail vein. In all experiments only one cell per animal was studied. Where the data are expressed as the percentage of baseline control, this percentage was determined by comparing the firing rates averaged over a 5 min baseline period with the rates observed at specific time intervals after the drug was administered (typically, at the intervals where maximum rate effects were evident). This procedure allowed for comparison of group data despite individual neuronal differences with respect to baseline firing rates. The 'n's' reported indicate the number of cells (i.e., the number of animals) studied. The data are expressed as the mean $\pm$ the standard error of the mean. Differences between the treatment groups were analyzed using the Student's t-test with a criterion of significance of $P < 0.05$.

The following drugs were used in these studies: d-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO), apomorphine hydrochloride (Merck & Co., Inc., Rahway, NJ), chloral hydrate (Sigma Chemical Co., St. Louis, MO), gallamine triethiodide (American Cyanamid Co., Pearl River, NY), haloperidol (McNeil Laboratories, Fort Washington, PA), lisuride hydrogen maleate (Schering AG, Berlin), (+)-lysergic acid diethylamide (+)-tartrate (LSD) (National Institute of Drug Abuse) and pergolide mesylate (Eli Lilly & Co., Indianapolis, IN). Doses of drugs are given in terms of the weight of their salts and were injected in volumes of 0.1-0.2 ml per animal. Pergolide mesylate was dissolved in a 30% ethanol-distilled water solution and warmed.

3. Results

3.1. Dopamine agonist effects

As shown previously (Bergstrom et al., 1982b), 0.32 mg/kg apomorphine (1 μmol/kg) when administered as a single bolus i.v. injection, caused marked increases in pallidal activity in gallamine-paralyzed, locally anesthetized and artificially respired rats (fig. 1A). Maximum effects, which were obtained in the 3-5 min interval following injection, averaged $119 \pm 11\%$ above predrug control baseline ($n = 12$). To determine whether this ability to stimulate pallidal cell firing rates is a property shared by other types of dopamine agonists, the effects of pergolide, lisuride and LSD on pallidal activity were compared with those of apomorphine in paralyzed, locally anesthetized and artificially respired rats.

When a 0.43 mg/kg dose of pergolide (1 μmol/kg) was administered systemically as a single bolus injection, consistent increases in pallidal firing rates were observed (fig. 1B). The rate-increasing effects of pergolide were typically seen 60-180 s after injection of the drug into the lateral tail vein, reached a maximum within 3-6 min and averaged $95 \pm 15\%$ above control baseline rates ($n = 12$). Thirty min after injection, pallidal firing rates were still maximally elevated ($n = 5$). Vehicle injections of a 30% ethanol solution (0.15-0.20 ml) did not produce alterations in baseline firing rates ($n = 10$). This effect of pergolide on pallidal firing rates was reversed by subsequent administration (15-30 min later) of haloperidol (0.1-0.4 mg/kg i.v.) in 7 of the 7 cells tested.

Intravenous administration of a single bolus injection of a 0.48 mg/kg dose of lisuride (1 μmol/kg) also significantly increased the firing rates of pallidal neurons (fig. 1D). The rate-increasing effects of lisuride were typically observed 30-120 s after injection into the lateral tail vein, reached a maximum within 2-5 min, averaged $93 \pm 24\%$ above control baseline rate ($n = 10$) and were maximally maintained throughout the 30 min of post-injection recording time ($n = 7$). However, haloperidol, administered i.v. in doses up to 1.6 to 3.2 mg/kg, did not cause effective reversals of the rate-increasing effects of lisuride ($n = 7$) when it

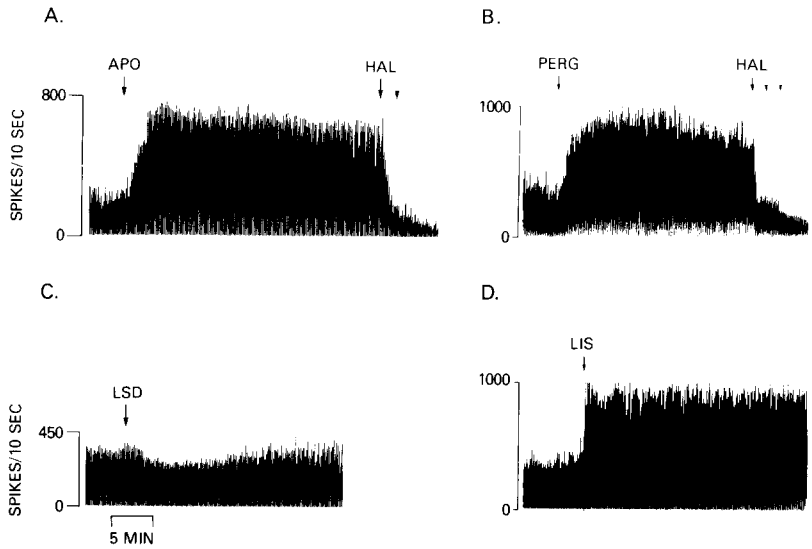

Fig. 1. Effects of intravenous administration of apomorphine and 3 dopamine ergot agonists upon the single unit activity of spontaneously firing pallidal neurons in paralyzed, locally anesthetized and artificially respired rats. (A) An intravenous bolus injection of 0.32 mg/kg apomorphine (APO) increased the firing rate of this neuron; subsequent administration of haloperidol (HAL) (repeated i.v. doses of 0.2 mg/kg) reversed the increase in pallidal firing. (B) Recording shows response of a pallidal neuron to an intravenous bolus injection of 0.43 mg/kg pergolide (PERG). Subsequent administration of haloperidol (HAL) (repeated i.v. doses of 0.2 mg/kg) reversed the increase in pallidal firing. (C) This cell displayed no significant rate change in response to an intravenous bolus injection of 0.45 mg/kg d-lysergic acid diethylamine (LSD). (D) The ratemeter recording presented above demonstrates the effect of an intravenous bolus injection of 0.48 mg/kg lisuride (LIS). Subsequent administration of haloperidol did not cause significant and consistent reversals of the rate effects of lisuride (data not shown).

was administered according to the same dose and time schedule which had been effective in reversing apomorphine's and pergolide's effects. On the other hand, when animals were pretreated with haloperidol (0.4 mg/kg i.v.), subsequent administration of lisuride (0.48 mg/kg i.v.) did not produce significant rate-increasing effects ($n = 8$). Over the 20 min time period following the administration of haloperidol and lisuride, the firing rate of 1 cell increased 28%, the rate of 1 cell did not change and the rates of 6 cells decreased by an average of $39 \pm 7\%$; the overall average change in firing rate was a decrease of $24 \pm 11\%$.

To explore the role of serotonin receptor stimulation in ergot-induced activation of pallidal firing rates, the effects of LSD were determined. In the globus pallidus, a 1 μmol/kg dose of LSD, administered i.v., produced variable effects on neuronal firing rates of the 11 units investigated (fig. 1C). The firing rates of 2 units increased ($> 20\%$), rates of 2 units decreased ($> 20\%$) and rates of the remaining 7 units did not show notable changes ($< 20\%$); the average increase in firing for the 11 units was $6 \pm 15\%$, a statistically non-significant change.

3.2. 'Priming' dose effects

The response of pallidal neurons to apomorphine has been shown to be affected by prior exposure of the animal to dopamine agonist (Bergstrom et al., 1982b). To investigate this further, experiments were performed to determine whether apomorphine could alter pallidal responses to other drugs which stimulate or block dopamine receptors.

In confirmation of previous studies (Bergstrom and Walters, 1981) d-amphetamine (3.2 mg/kg i.v.) significantly increased pallidal activity (fig. 2A). The average increase in firing rate for the 8 neurons tested was $114 \pm 27\%$ above baseline control rate. However, diminished responses to d-

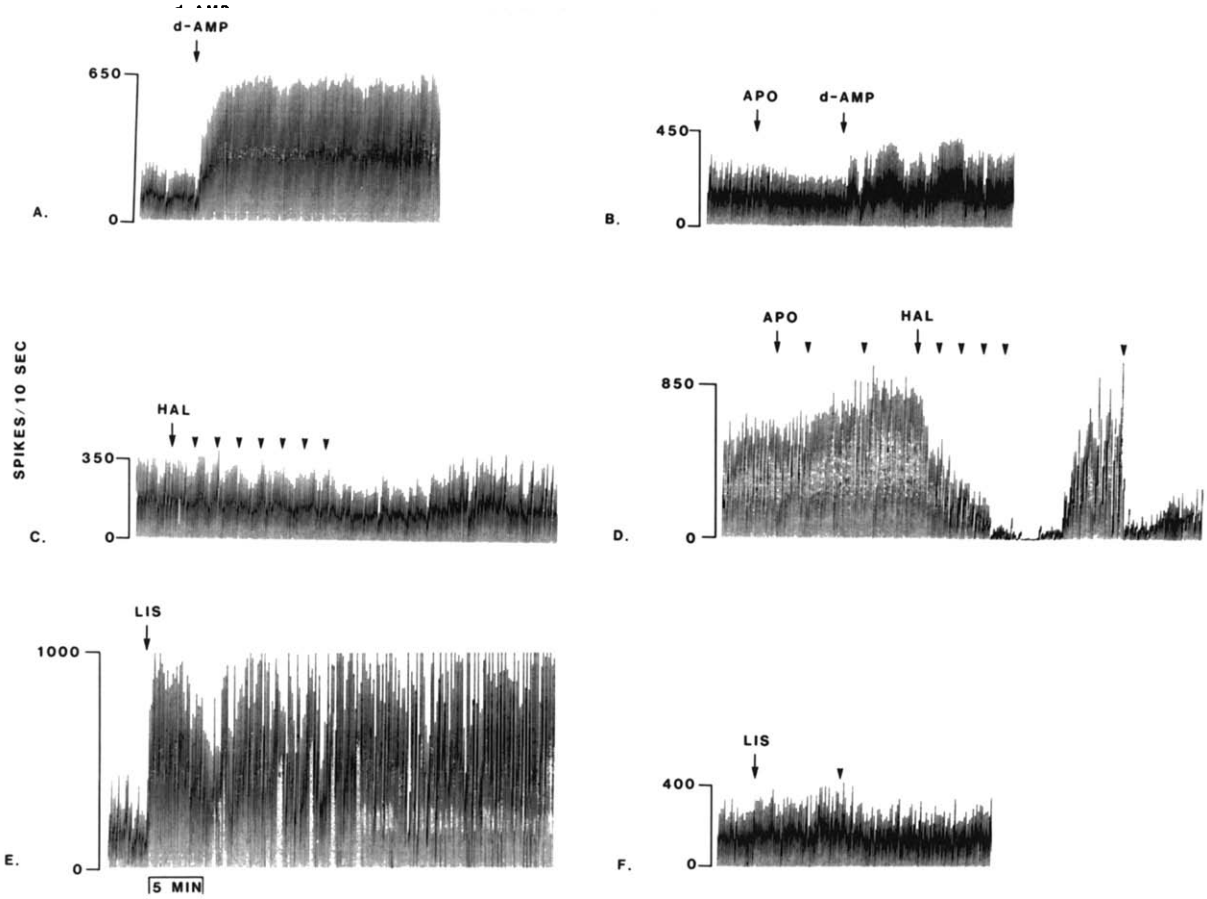

Fig. 2. Effects of 'priming' dose pretreatment with a dopamine agonist on pallidal responsiveness to subsequent administration of d-amphetamine (d-AMP), haloperidol (HAL) and lisuride (LIS). Animals were paralyzed with gallamine, locally anesthetized and artificially respired. (A) In the example depicted here, a single bolus injection of 3.2 mg/kg d-amphetamine (d-AMP) produced a marked increase in firing of this pallidal neuron which lasted throughout the recording time of 21 min. (B) This neuron showed a significantly attenuated responses to d-amphetamine (d-AMP) when a non-excitatory 'priming' dose of apomorphine (APO) (20 μg/kg) was given 8 min before the administration of an excitatory dose of 3.2 mg/kg d-AMP. The firing rate did not increase after 20 μg/kg apomorphine and showed small and inconsistent changes after 3.2 mg/kg d-AMP as compared to the neuron depicted in (A). (C) Here, haloperidol was administered in exponentially increasing doses at 2-min intervals, so that each dose doubled the previous cumulative dose (0.025, 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6 mg/kg; cumulative dose, 3.2 mg/kg). Only a slight decrease in firing rate was observed. (D) Potentiated responses to haloperidol (HAL) were observed when haloperidol, in exponentially increasing doses, was given 5 min after the administration of apomorphine (APO) (administered in a divided dose regimen of 5, 35, 280 μg/kg, 3-5 min apart). A significant, although somewhat transitory, inhibition in firing was observed. Rapid recovery was reversed by administration of more haloperidol. (E) A single bolus injection of 0.48 mg/kg lisuride (LIS) produced an increase in firing of this pallidal neuron which lasted throughout the recording time of 37 min. (F) A non-excitatory 'priming' dose of lisuride (30 μg/kg) was given 8 min before the administration of an excitatory dose of 0.48 mg/kg lisuride. The firing rate of this unit did not change markedly from baseline rate after the administration of either the 'priming' or the normally excitatory dose of lisuride.

amphetamine were observed when 3.2 mg/kg d-amphetamine was given i.v. 8 min after a non-excitatory 'priming' dose of apomorphine (20 μg/kg i.v.) (fig. 2B) but not when control saline injections ($n = 6$) were given. The average increase in firing for the 11 units tested with apomorphine and d-amphetamine was $40 \pm 18\%$ above baseline control rate. Thus, small 'priming' non-excitatory doses of apomorphine significantly attenuate the effects of normally excitatory doses of both

apomorphine and d-amphetamine on pallidal activity.

The ability of apomorphine to alter the effects of the dopamine antagonist, haloperidol, on pallidal activity was also investigated. As previously observed (Bergstrom et al., 1982a) haloperidol, administered alone, in increasing doses so that each dose doubled the previous cumulative dose (0.025, 0.025, 0.05, 0.1, 0.2, 0.4, 0.8, 1.6 mg/kg; total dose, 3.2 mg/kg i.v.), caused a 21 ± 7% decrease in neuronal firing rates (n = 9) (fig. 2C and 3). In contrast, haloperidol produced a considerably greater inhibitory effect on pallidal activity when it was administered after the animals had been treated with apomorphine. In this study, a total of 0.32 mg/kg of apomorphine was administered i.v. in 3 doses (5, 35, 280 μg/kg i.v., 3-5 min apart). This divided dose schedule, like the 'priming' dose pretreatment, resulted in an attenuated (39 ± 19%) increase in pallidal firing rates, as compared to the effects of a single dose of 0.32 mg/kg apomorphine. Subsequent administration of haloperidol, given 5 min after the last dose of apomorphine, caused a significantly greater degree of inhibition than that seen with haloperidol alone (fig. 2D and 3). Fourteen of 15 cells showed a 90-100% decrease in firing rate below that recorded during the predrug baseline control period. One cell (not included in the data averaged for fig. 3) showed no decrease below baseline with haloperidol. In cases where the cells were held for a period after haloperidol administration, however, the marked degree of inhibition induced by haloperidol was often transitory. Cells began to recover fairly rapidly although they often could be subsequently inhibited to very low firing rates by additional injections of haloperidol. Inhibitions of this nature were not observed when haloperidol was administered alone as described above.

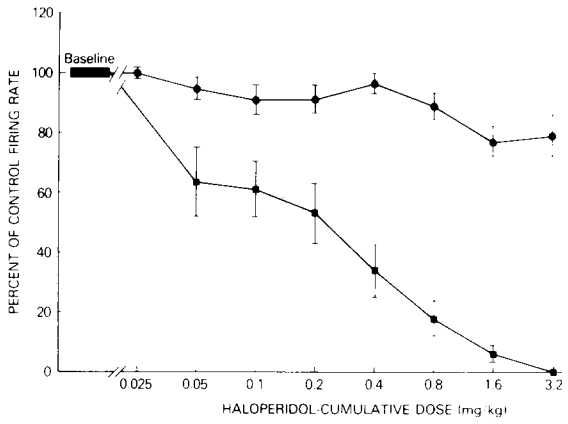

Fig. 3. Cumulative dose-response curves of the effects of i.v. haloperidol on the single unit activity of spontaneously firing pallidal neurons in control animals (●) and animals pretreated with apomorphine (■). Haloperidol, injected in increasing increments at 2 min intervals so that each dose doubled the previous cumulative dose, was administered to control rats (n = 9) or rats pretreated with 0.32 mg/kg apomorphine. Apomorphine was injected in a divided dose regimen of 5, 35, 280 μg/kg i.v., over a 8 min period ending 5 min before haloperidol was administered (n = 14). The average firing rate of each cell after each dose is expressed as a percent of the predrug baseline firing rate. Each point on the graph represents the mean responses of all cells observed at a given dose. The vertical bars represent the standard error of the mean.

Additional experiments were conducted to determine whether the 'priming' dose effect seen with apomorphine was also observed with the ergot compounds. As presented above, a single bolus injection of lisuride (0.48 mg/kg i.v.) increased unit firing rates 93 ± 24% above baseline control rates (n = 10) (fig. 2E). Significantly attenuated responses to lisuride were obtained when 0.48 mg/kg lisuride was given i.v. 8 min after a non-excitatory 'priming' dose (30 μg/kg i.v.) of lisuride (fig. 2F). An average increase of 13 ± 17% above control baseline rate was noted after the 0.48 mg/kg lisuride injection (n = 14). These results indicated that apomorphine is not unique in its ability to alter pallidal responsiveness to agonist stimulation when injected as a priming dose.

3.3. General anesthetic effects

Pilot studies suggested that pallidal cells were less active and less responsive to systemic drug treatment in rats treated with a general anesthetic as compared to pallidal cells in rats locally anesthetized, artificially respired and paralyzed. To explore this observation further, spontaneously active neurons of the globus pallidus were monitored in chloral hydrate anesthetized rats. Pallidal neurons showed no consistent response to a single i.v. bolus injection of 0.32 mg/kg apomorphine in this animal preparation. Following drug administration, 2 pallidal neurons showed increases in rate

greater than 20%, 4 neurons displayed decreases in rate greater than 20%, and 4 neurons displayed no rate changes (< 20%). Overall, the average effect on the pallidal neurons in the chloral hydrate anesthetized rats was a $5 \pm 8\%$ change from control (n = 10). These results are in contrast to those seen with a single i.v. bolus injection of 0.32 mg/kg apomorphine in the paralyzed, locally anesthetized preparation; pallidal activity increased markedly and consistently after a single bolus injection of apomorphine in the paralyzed animal preparation.

4. Discussion

In previous studies, it was found that systemic administration of d-amphetamine markedly increases the activity of spontaneously firing neurons of the globus pallidus in gallamine-paralyzed rats. The excitatory effects of d-amphetamine on pallidal cells were blocked and reversed by haloperidol. Drugs which should preferentially increase norepinephrine receptor stimulation, such as l-amphetamine, desmethylimipramine and clonidine, produced only minor increases in pallidal firing rates after systemic administration. The serotonin uptake inhibitor, fluoxetine, produced varied changes in firing frequencies. Pretreatment with reserpine and α-methyl-p-tyrosine significantly attenuated the d-amphetamine induced increase in pallidal activity (Bergstrom and Walters, 1981). These results suggested that dopamine was playing a predominant role in mediating the stimulatory effects of d-amphetamine on these tonically active pallidal cells. Subsequent studies, confirmed here, (Bergstrom et al., 1982a) showed that systemic administration of apomorphine, 0.08-1.0 mg/kg, also caused haloperidol-reversible increases in the unit activity of these spontaneously firing neurons in the rat globus pallidus.

Pergolide and lisuride are ergot derivatives, capable of inducing many of the behavioral and biochemical changes typically associated with dopamine receptor stimulation (Horowski and Wachtel, 1976; Kehr, 1977; Fuller et al., 1979) and both have been shown to be as potent as apomorphine at inhibiting the single unit activity of dopamine cells when administered systemically (Walters et al., 1979; Bergstrom, unpublished obs.). The present results showed that lisuride and pergolide also cause increases in the firing rates of pallidal neurons which are essentially comparable to those observed with the same molar dose (1 μmol/kg) of apomorphine (Bergstrom et al., 1982a). The observation that apomorphine, lisuride, and pergolide are all able to stimulate pallidal activity to a comparable degree when administered systemically, suggests that stimulation of dopamine sensitive adenylate cyclase (D_1 receptors) is not necessarily related to the actions of these drugs on tonic pallidal activity. Pergolide and apomorphine effectively stimulate dopamine sensitive adenylate cyclase in striatal homogenates and bovine parathyroid cells, but lisuride acts as an antagonist of this enzyme (Pieri et al., 1978; Brown et al., 1980; Rosenfeld et al., 1980).

The effects of pergolide on pallidal activity, like those of apomorphine, were readily reversed by administration of haloperidol. The effects of lisuride, however, were not reversed by administration of this antagonist, although they were blocked when haloperidol was administered before lisuride. These results are similar to those which have been observed in studies of the effects of lisuride on the activity of dopamine neurons; haloperidol also blocks but does not reverse lisuride's actions on these cells (Walters et al., 1979). Similar interactions between haloperidol and the ergot bromocryptine have been reported by Bannon and coworkers (1980), who have also observed that, with time, bromocryptine appears to interact in an irreversible fashion with central dopaminergic receptors. Lisuride may be exhibiting a similar ability to bind to dopamine receptors irreversibly.

Although apomorphine is not thought to be particularly effective at stimulating serotonin receptors, many ergolines, including lisuride, are quite effective as serotonin agonists (Kehr, 1977; Rosenfeld and Makman, 1981). To further investigate the possibility that serotonin receptor stimulation might play a role in mediating the changes in pallidal activity observed with these ergot dopamine agonists, we examined the effects of LSD on pallidal activity. LSD is a potent

serotonin agonist (Aghajanian et al., 1970) but a weaker dopamine agonist with some antagonist effects at dopamine receptors (Creese et al., 1976; Kehr et al., 1978). This drug has also been shown less effective than lisuride at inhibiting the activity of dopamine neurons in the substantia nigra pars compacta (Walters et al., 1979). The results reported here show that LSD did not effectively stimulate pallidal activity when administered in doses comparable to the doses of the other ergot agonists. These results, together with those observed in previous studies, support the idea that dopamine receptor stimulation is more effective than serotonin or norepinephrine receptor stimulation at inducing increases in pallidal activity. They suggest that changes in the tonic activity of pallidal neurons in paralyzed rats may provide a useful in vivo corroboration of in vitro and behavioral tests for drugs active at inducing dopamine-mediated stimulation in the basal ganglia.

Pallidal neuronal responses to dopamine agonist administration were altered in anesthetized animals. The use of the general anesthetic, chloral hydrate, significantly attenuated the increases in pallidal firing rates by apomorphine. Gnome and McCulloch (1983), analyzing local cerebral glucose utilization, found similar results; the increases in pallidal glucose utilization following apomorphine administration in animals anesthetized with chloral hydrate were markedly attenuated compared to the results obtained in conscious animals. One possible explanation for these results is that apomorphine's effects on pallidal activity are mediated indirectly via neuronal inputs to the globus pallidus from regions rich in dopamine receptors and involve transmitter systems which are significantly affected by chloral hydrate. Another possible explanation is that chloral hydrate is acting as a general depressant of neuronal activity and, therefore, attenuating drug effects uniformly throughout the nervous system. Yet, the latter seems not to be the case, as the effects of the GABA agonist muscimol on pallidal neurons are quantatively similar in chloral hydrate rats and in awake, gallamine paralyzed, locally anesthetized, artifically respired rats (Waszczak et al., 1981). In addition, the depressant effects of several psychoactive drugs, such as clonidine, phenoxybenzamine, and LSD on dorsal raphe unit activity are greatly potentiated in the presence of chloral hydrate anesthesia (Trulson and Trulson, 1983).

Several researchers have shown that pretreatment with 'priming' doses of dopaminergic agents can alter the behavioral and biochemical responses of the organism to subsequent administration of these agents (Ljungberg and Ungerstedt, 1977; Ljungberg, 1979; Barghon and Constentin, 1980; Dunstan et al., 1981). In earlier investigations, we made the interesting observation that small non-excitatory doses of apomorphine (priming doses) were able to attenuate the neurophysiological responses of pallidal neurons to subsequently administered larger excitatory doses of apomorphine (Bergstrom et al., 1982b). The first dose appeared to alter or set this system's response so that the additional injection of apomorphine had little further effect. Present results show that the priming dose of apomorphine can attenuate responses to other drugs, in addition to apomorphine itself. A non-excitatory dose of apomorphine was also able to attenuate the response of pallidal neurons to d-amphetamine. Similarly, we observed that a small non-excitatory dose of lisuride blocked the response of pallidal neurons to a larger, normally stimulatory dose of lisuride. The rapid desensitization associated with administration of low 'priming' doses of apomorphine or lisuride does not occur when larger, stimulatory doses of the agonist are administered; responses induced by higher doses do not decay as rapidly as the desensitization induced by lower doses develops. These results suggest that in order to elicit a maximum response in the globus pallidus, a sufficient number of agonist molecules must reach dopamine receptors over a short period. Small doses of dopamine agonists appear to alter the dopamine receptor effector system in such a way that additional stimulation by either the agonist itself or by dopamine produced only a limited response.

Several researchers have suggested that the dopamine receptors can undergo rapid changes in affinity (Bacapoulos, 1981; Makman et al., 1982). The present results may reflect such a phenomenon. In contrast to the attenuation seen with agonists, the response of pallidal neurons to haloperidol, a dopamine antagonist, is potentiated, at

least transitorily, by low doses of apomorphine. Haloperidol, administered alone, has only slight inhibitory effects on pallidal activity (Bergstrom et al., 1982a). However, when haloperidol was administered after the injection of a dopamine agonist, the antagonist was able to completely inhibit pallidal activity in most cases, at least transitorily. Why the antagonist exerts more of an effect on pallidal firing under these conditions is unclear.

It is also not clear where the dopaminergic agents are acting to induce these changes in the firing rates of pallidal neurons. It is probable that these drugs induce alterations in striatal activity which are transmitted to the globus pallidus and expressed as changes in tonic pallidal firing rates. However, as discussed in the introduction, it is also possible that the agonist may be acting directly in the globus pallidus. Recent iontophoretic studies indicate that dopamine modulates the effects of GABA in the globus pallidus in a manner similar to that which has been demonstrated in the pars reticulata of the substantia nigra (Waszczak and Walters, 1983), and may thereby enhance pallidal activity by attenuating the inhibitory effects of GABA in this brain region (Walters and Bergstrom, 1981; Bergstrom and Walters, 1984).

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