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DOPAMINE AGONISTS AND COBALT-INDUCED EPILEPSY IN THE RAT

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1 Electrocorticogram (ECoG) recordings were made from conscious rats which had cortical implants of cobalt. The epileptiform spike activity was then assessed by means of an automated technique, based on peak angle measurements.

2 Apomorphine (0.5, 1.0 and 2.0 mg/kg i.p.) and lisuride (0.1, 0.25, 0.5 and 1.0 mg/kg i.p.) inhibited spike activity in established primary and secondary foci in a dose-dependent manner. Bromocryptine (10 and 20 mg/kg i.p.) and CF 25-397 (40 mg/kg i.p.) had a similar effect but only after a latent period of several hours. Chronic administration of bromocryptine (20 mg/kg i.p. daily) attenuated the normal development of the foci following implantation.

3 Pimozide (1 mg/kg i.p.) potentiated cortical epileptic activity in cobalt-implanted rats and blocked the antiepileptic effects induced by the dopamine agonists.

4 Intrastriatal administration of dopamine (25 μg) or apomorphine (60 μg) suppressed epileptiform spikes in the cortex. Destruction of striatal catecholamine terminals by 6-hydroxydopamine increased the spike activity.

5 It is concluded that the striatum may play an essential part in mediating the anti-epileptic effects of dopamine and its agonists in this model of epilepsy.

Introduction

It has been recognized for some time that brain monoamine activity may be important in determining seizure threshold in animals (see Maynert, 1969). Reserpine, by lowering amine levels, increases susceptibility to seizures produced by electroshock (Azzaro, Wenger, Craig & Stitzel, 1972) and to audiogenic seizures (Schlesinger, Boggan & Freedman, 1968). Conversely, there are reports that raising levels of monoamines decreases seizure intensity (Lehman, 1967) and reverses the effects of reserpine (Boggan & Seiden, 1971).

Implantation of a cobalt-gelatine rod into the rat frontal cortex produces a chronic model of focal epilepsy in which both primary and secondary cortical foci develop and persist (Fischer, Holuber & Malik, 1967; Dow, McQueen & Townsend, 1972). However, the animals rarely have generalized seizures and the direct effects of drugs on the focal discharges can be examined. In a preliminary study Ashcroft, Dow, Emson, Harris, Ingleby, Joseph & McQueen (1974) showed that apomorphine and amphetamine suppressed the epileptic changes while spiroperidol had the opposite effect. We have extended these observations to a study of several dopamine agonists with predominantly direct actions on dopamine receptors in the striatum and mesolimbic system.

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Methods

Male Wistar rats (200 to 250 g) were used in all experiments. A cobalt-gelatine pellet (Fischer *et al.*, 1967) was implanted into the right sensorimotor cortex and four stainless steel recording screws were fixed to the skull 3 mm either side of the coronal and sagittal sutures (Dow *et al.*, 1972). In some animals a hollow stainless steel cannula was stereotaxically fixed to each side of the skull to allow the injection of drugs into the striatum (A 7.7 mm, L 2.7 mm and V 3.5 mm, Konig & Klippel, 1963).

Electrocorticograph (ECoG) recordings were made from conscious unrestrained rats by means of twist pin connectors fitted into the hollow bore of the recording screws. The ECoG was recorded on a Grass Model 7 Polygraph and on magnetic tape (Tandberg series 100 instrument). Four channels were used for recording from two rats simultaneously, each channel measuring the potential difference due to epileptic activity in either the primary or secondary focus of one rat. The taped records were analysed for epileptic spike activity by the method of Hill & Townsend (1973) which is based on peak angle measurements. The resultant spike count correlated well with subjective assessment of spike frequency in the polygraph records.

The following drugs were used: apomorphine solution (Evans); lisuride hydrogen maleate (Scherring); pimozide (Janssen); apomorphine, dopamine, 6-hy-

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droxydopamine (6-OHDA), bromocryptine mesylate and 9, 10-didehydro-6-methyl-8 beta-(2-pyridylthiomethyl) ergoline (CF25-397) (all Sandoz). Lisuride was dissolved in sterile saline (0.9% w/v NaCl solution) to make a concentration of 2 mg/ml. Bromocryptine, CF25-397 and pimozide were dissolved in a few drops of 1 N acetic acid and the acidity reduced with a few drops of 0.5% ethanol. The final volume (1 to 2 ml) was made with 5% glucose solution to a drug concentration of 20, 20 and 2 mg/ml respectively. For intrastriatal use, apomorphine, dopamine and 6-OHDA were dissolved in sterile saline containing 0.5 mg/ml ascorbic acid to a concentration of 30, 12.5 and 10 mg/ml respectively. Prior to injection, 1 ml of the drug solution was drawn into a glass syringe (Agla) which was then fitted on a micrometer and injection made into the striatum at a rate of 1 µl per 30 s with a sterile 18 gauge needle.

Experimental design

Acute effects of dopamine agonists and antagonists. All drugs were tested 8 to 12 days after cobalt implantation when the epileptic activity from the cortical foci was prominent. Pairs of rats were allowed to settle in the Perspex recording box for at least 10 min before the start of recording which then continued for 30 min. After this control period one animal received the drug under study and the other the appropriate vehicle. The ECoG was then monitored for a further 2 h in all cases, except after bromocryptine and CF 25-397 when recordings were made for 6 h. The effect of pimozide on the action of dopamine agonists was demonstrated by its administration 45 min before either apomorphine or lisuride and 20 min before either bromocryptine or CF 25-397.

Chronic effects of bromocryptine. Because of its long duration of action the effects of repeated administration of bromocryptine on the development of cobalt-induced foci were examined. Bromocryptine (20 mg/kg i.p.) was given daily starting on the day of implantation to one group of 5 rats while the control group received equivalent volumes of the vehicle daily. ECoG recordings were made immediately before each injection for 2 weeks and the spikes counted during these 10 min records.

Effects of intrastriatal injection of dopamine and apomorphine. After a control recording, apomorphine (60 µg) or dopamine (25 µg) was injected into each striatum except in one group of experiments when dopamine was given into the right striatum only. Control animals received an equivalent volume (2 µl) of the vehicle and recordings were continued for 1 h. Using this technique Arluison, Agid & Javoy (1978) found that the zone of diffusion of tritiated dopamine extended to about 1.5 mm from the needle tip.

Effects of 6-hydroxydopamine. 6-OHDA (20 µg) was injected into each striatum just before cobalt application to the right frontal cortex in 6 rats and 6 control rats received 2 µl vehicle before cobalt implantation. The 10 min ECoG recordings were made from both groups at regular intervals for 2 weeks to monitor the development of epileptiform spikes in the cortex. The animals were then killed by decapitation and their brains dissected out on a mixture of solid CO_2 (−75°C) and ice. Both striata were removed and stored in liquid nitrogen (−195°C) to be assayed for dopamine and noradrenaline levels by the method of Palkovits, Brownstein, Saavedra & Axelrod (1974).

Statistical comparison

It was noted that the spike frequency varied considerably between different animals in the initial 30 min control period. The average spike count per 5 min in either the primary or secondary focus in this period was thus normalized to a ratio of one. The subsequent spike rates following administration of a drug or vehicle could then be expressed relative to this control rate for each rat. This allowed data from several animals to be pooled and for a comparison to be made between different drugs and also between different doses of the same drug. The differences were then analysed by the Mann-Whitney test.

In the chronic experiments with bromocryptine and 6-OHDA comparison of spike frequencies between different groups of rats was made by the Kruskal-Wallis one-way analysis of variance.

Results

Within a few days of cobalt application to the right frontal cortex a primary epileptogenic focus developed, associated with twitching of the whiskers and contralateral forelimb. Propagation of epileptiform discharges led to the appearance of the secondary (mirror) focus in the contralateral frontal cortex. Spiking from both foci was maximal at 8 to 10 days and was still prominent during the second week after cobalt application. The spike frequency from the secondary focus was always higher than that from the primary focus.

All dopamine agonists suppressed the epileptic whisker and forelimb twitches in cobalt-implanted rats. This effect was also associated with bristling of fur, increased arousal and, at the higher doses, increased locomotion and stereotyped behaviour. Control rats showed no significant changes in epileptic

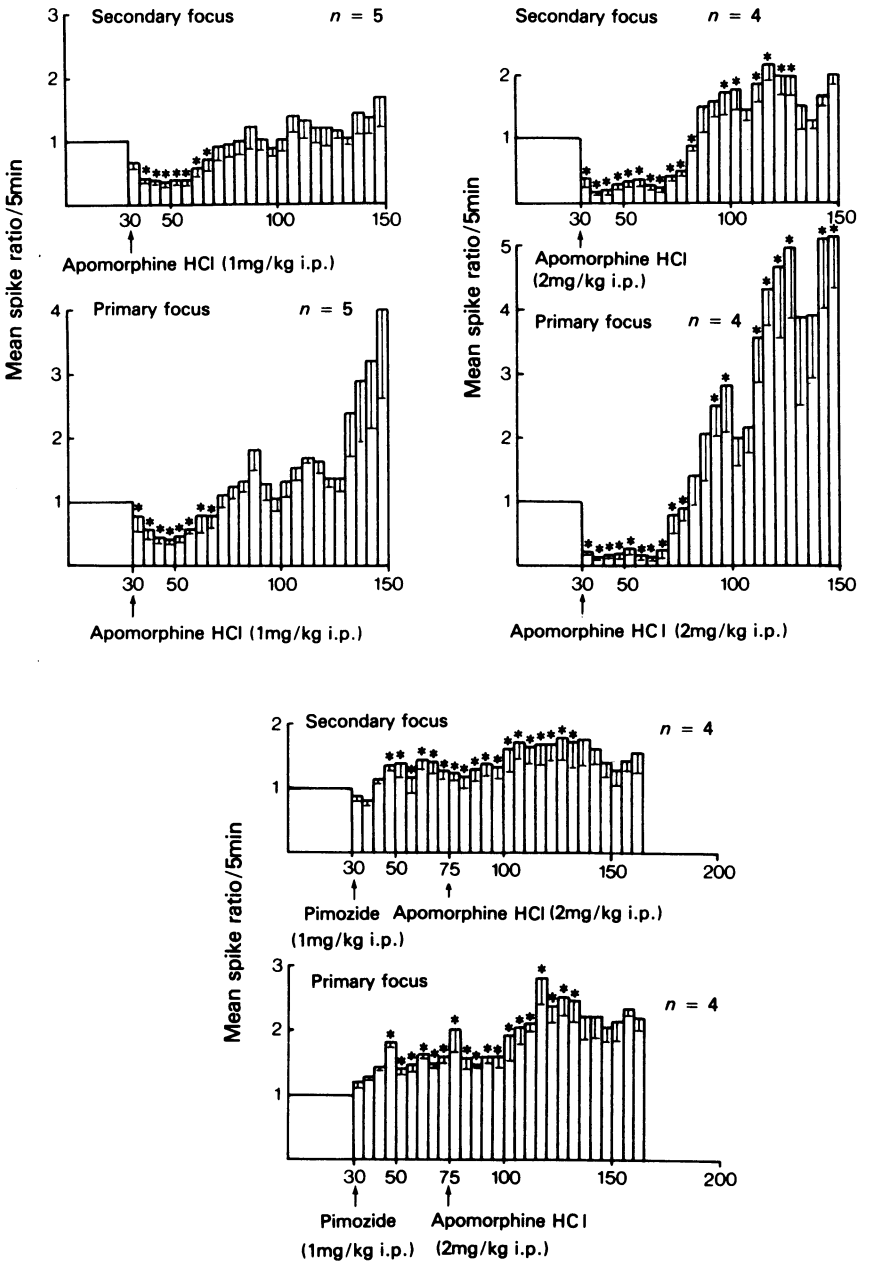

Figure 1 Effects of apomorphine on epileptiform spikes from primary and secondary foci in cobalt-implanted rats. n = number of animals. Mean values are given; vertical lines show s.e. mean. Ordinate scales: mean spike ratio (average spike count for control period equals 1.0). Abscissa scales: time in min. *Significantly different from spike rate following injection of vehicle. $P < 0.05$ (Mann-Whitney Test).

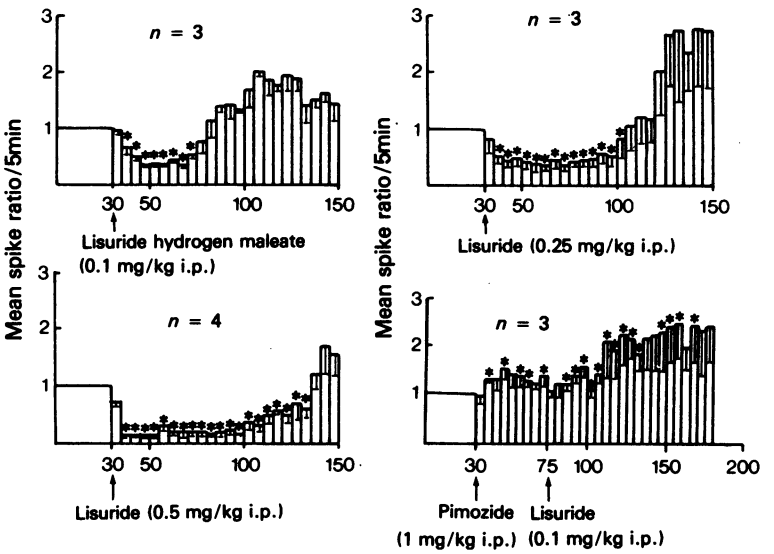

Figure 2 Effects of lisuride hydrogen maleate on epileptiform spikes from the primary focus in cobalt-implanted rats. n = number of animals mean values are given; vertical lines show s.e. mean. Ordinate scales: mean spike ratio (average spike ratio for control period equals 1.0). Abscissa scales: time in min. *Significantly different from spike rate following injection of vehicle, $P < 0.05$ (Mann-Whitney Test).

manifestations or behaviour following administration of the appropriate vehicle.

Effect of apomorphine (0.5 to 2 mg/kg i.p.)

Apomorphine produced a significant suppression of epileptic activity in both the primary and secondary foci (Figure 1). This effect was evident within a few minutes of administration and lasted from 30 to 55 min depending on dose. The magnitude of the suppression was dose-dependent ($P < 0.02$, Kruskal-Wallis). There was a rebound increase in spike frequency about 90 min after injection and this was significant at the highest dose of 2 mg/kg i.p. ($P < 0.05$, Mann-Whitney Test). Saline-treated ($n = 13$) or vehicle-treated rats ($n = 12$) showed some increase in spike frequency with time but this was not significant. Pimozide (1 mg/kg i.p.) blocked the suppressant effects of apomorphine (Figure 1) and also significantly potentiated the epileptic activity of both primary and secondary foci in 4 rats and this effect, evident within 10 min of injection, lasted for about 2 h.

Effect of lisuride (0.1 mg/kg i.p.)

Lisuride also produced a significant reduction in epileptic spike activity in both foci and the effects on the primary focus are shown in Figure 2. Spike suppression was evident within a few minutes of administration and lasted for 50 to 115 min depending on dose. The effect on both foci was dose-dependent ($P < 0.001$, Kruskal-Wallis) and was blocked by prior administration of pimozide (Figure 2).

Effect of bromocryptine (10 to 20 mg/kg i.p.) and CF25-397 (40 mg/kg i.p.)

Bromocryptine, unlike apomorphine and lisuride, had no immediate effect on cortical spiking (Figure 3). However, 3 h after the lower dose and 1 h after 20 mg/kg the numbers of epileptiform spikes in both foci were significantly reduced. This effect persisted for more than 6 h with both doses and was dose-dependent ($P < 0.001$, Kruskal-Wallis). No significant drug effect was seen 24 h after administration. CF25-397 also significantly reduced the epileptic changes in both foci in 4 rats after a latent period of about 1 h. Prior treatment with pimozide completely prevented the suppressant effects of both bromocryptine and CF25-397 on cortical spikes.

Chronic effects of bromocryptine (20 mg/kg i.p.)

The daily intraperitoneal administration of bromocryptine did not completely prevent the development of primary and secondary epileptic foci (Figure 4). However, the spike frequencies in both foci were significantly lower than in the group of control rats ($P < 0.05$, Kruskal-Wallis). This effect was first noted

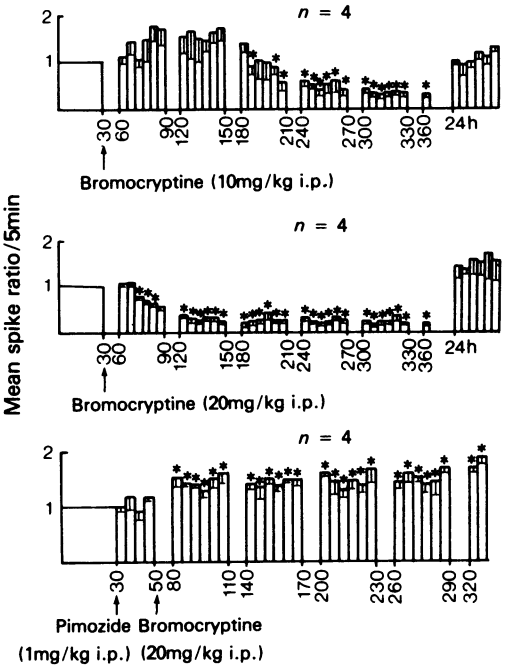

Figure 3 Effects of bromocryptine mesylate on epileptiform spikes from the primary focus in cobalt-implanted rats. n = number of animals. Mean values are given; vertical lines show s.e. mean. Ordinate scales: mean spike ratio (average spike ratio for control period equals 1.0). Abscissa scales: time in min. *Significantly different from spike rate following injection of vehicle, $P < 0.05$ (Mann-Whitney Test).

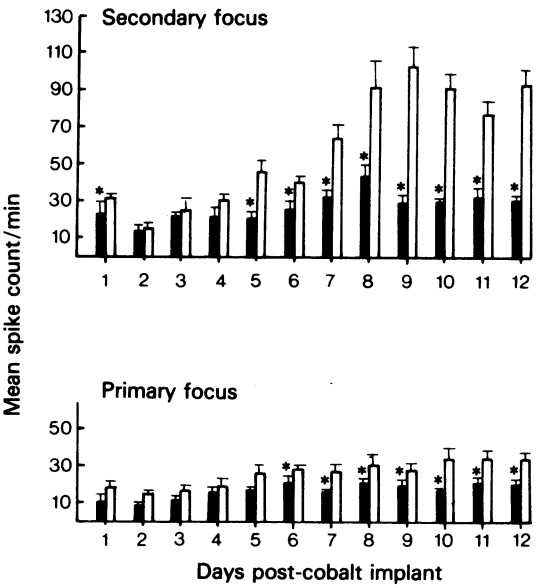

Figure 4 Effects of daily administration of bromocryptine (20 mg/kg i.p. solid column) on the development of cobalt-induced epileptiform spikes; vehicle-treated controls: open columns. Spike counts are based on ECoG recording made immediately before the daily injection. $n = 5$ for both controls and bromocryptine-treated groups. Mean values are given; vertical lines show s.e. mean. *Significantly different from controls, $P < 0.05$ (Kruskal-Wallis).

on the fifth day after implantation and was more marked in the secondary focus where the usual high level of spiking was not apparent.

Effect of intrastriatal dopamine and apomorphine

Intrastriatal injection of 2 µl saline had no effect on cortical spiking 8 to 12 days after cobalt implantation. However, the bilateral injection of 25 µg dopamine or 60 µg apomorphine into each striatum produced a significant reduction in epileptiform activity from both foci and the effects on the primary focus are shown in Figure 5. Spike suppression was evident within 5 min and lasted for about 50 min and was more intense following apomorphine. This effect was associated with the abolition of whisker and forelimb twitches as well as the appearance of signs of dopaminergic stimulation of the striatum such as increased arousal, locomotion and stereotyped behaviour. The injection of 25 µg dopamine into the right striatum only also suppressed cortical spiking from both foci but the effect was less marked than that following bilateral injection. Histological examination demonstrated needle tracts in the corpus striatum in all animals.

Effect of bilateral intrastriatal 6-hydroxydopamine injection

The injection of 20 µg 6-OHDA into each striatum in 6 rats which then had cobalt implanted into the right frontal cortex significantly reduced striatal levels of both dopamine and noradrenaline (Table 1). The levels for cobalt-implanted rats are not significantly different from those reported for untreated control animals (Tassin, Velley, Stinus, Blanc, Glowinski and Thierry, 1975). The spike activity in 6-OHDA-treated rats was slightly, but significantly ($P < 0.05$, Kruskal-Wallis) higher than that in the control rats. This effect was apparent immediately after implantation and persisted throughout the recording period of 2 weeks.

Discussion

Implantation of cobalt into the rat cerebral cortex leads to the development of both primary and second-

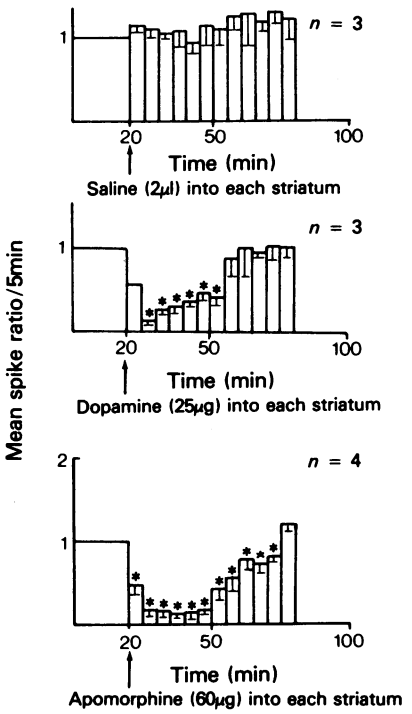

Figure 5 Effects of intrastriatal saline, dopamine and apomorphine on cobalt-induced cortical spiking. n = number of animals. Mean values are given; vertical lines show s.e. mean. *Significantly different from spike rate following injection of vehicle, $P < 0.05$ (Mann-Whitney Test).

ary epileptogenic foci which persist for several weeks. The animals rarely have spontaneous seizures and this semichronic model of epilepsy is ideal for studying the influence of drugs on focal discharges. We have examined the effects of a group of drugs, known to stimulate dopamine receptors, on epileptiform spike activity in the ECoG recorded from the conscious animal.

The dopamine agonists lisuride, apomorphine, bromocryptine and CF25-397 (in descending order of potency) suppressed the epileptic activity; the effects for any one drug were dose-dependent. It is established that these compounds stimulate dopamine receptors (Ernst, 1967; Jaton, Loew & Vigouret, 1975; Horowski & Wachtel, 1976; Johnson, Loew & Vigouret, 1976). Both apomorphine and lisuride suppressed cortical spiking rapidly but the effects of lisuride persisted for longer, perhaps due to slower catabolism of this drug. Bromocryptine, like apomorphine, induces circling behaviour in rats with unilateral lesions in substantia nigra (Johnson *et al.*, 1976). However, bromocryptine is characterized by a delayed onset of effect and this was also demonstrated in the present work. The reason for this delay has not been established but the formation of an active metabolite or an effect on dopamine reuptake cannot be excluded. The anti-epileptic effects of CF 25-397 were similar to those of bromocryptine but milder. It did not induce stereotyped sniffing which may reflect its selectivity for dopamine sites within the nigro striatal system (Jaton *et al.*, 1975). Pimozide, an established dopamine receptor antagonist (Anden, Butcher, Corrodi, Fuxe & Ungerstedt, 1970) exacerbated focal discharges in cobalt-implanted rats as well as preventing the antiepileptic effects of the agonists. Other workers have shown that dopamine agonists block (either partially or completely) audiogenic and photogenic seizures, whereas dopamine blockers potentiate spike and wave EEG activity and increase susceptibility to seizures (Lehman, 1970; Boggan & Seiden, 1971; Anlezark & Meldrum, 1975; Meldrum, Anlezark & Trimble, 1975). The exact mechanism of this effect is unclear and therefore we attempted to localize the site of action in our studies within the brain.

Although dopaminergic terminals have been found in the cingulate and dorsomedial prefrontal cortex (Thierry, Stinus, Blanc & Glowinski, 1973; Fuxe, Hokfelt, Johansson, Jonsson, Lidbrink & Ljungdahl, 1974) they are not found in the sensorimotor area where the cobalt is implanted (Lindvall, Bjorklund, Moore & Stenevi, 1974; Emson & Koob, 1977).

Table 1 Effect of bilateral intrastriatal 6-hydroxydopamine (6-OHDA) injection (20 μg) on the catecholamine content in each striatum of cobalt-implanted rats

Dopamine				*Noradrenaline*			
Controls (6)		*6-OHDA*(6)		*Controls* (6)		*6-OHDA*(6)	
Right striatum	Left striatum	Right striatum	Left striatum	Right striatum	Left striatum	Right striatum	Left stratium
9911 ± 416	9420 ± 625	953* ± 285	1446* ± 445	301 ± 39	329 ± 46	77* ± 19	97* ± 28

Each value represents the mean concentration (ng/g wet weight) ± s.e. mean. Number of animals shown in parentheses.
*$P < 0.001$ when compared with pooled concentration in controls (Student's t-test, two-tailed).

Therefore, it is unlikely that dopamine agonists exert their effects in cobalt-induced epilepsy by stimulation of cortical dopamine receptors.

It has been shown that the major site of action of dopamine agonists is dopamine receptors in the striatum and mesolimbic system. In addition, it has been shown (see Cools, Lohman & van den Bercken, 1977) that the corpus striatum in the rat receives afferent fibres from and sends efferent fibre connections, via the globus pallidus and the thalamus, to the cerebral cortex, particularly the motor area. Schwarz, Creese, Coyle & Snyder (1978) have shown that 35% of tritiated haloperidol binding in the striatum is located on presynaptic terminals originating from neurones in the frontal cortex. It seemed probable then that the site of action of the drugs used in our experiments would be the striatum. Indeed we found that both dopamine itself and apomorphine, when administered directly into the striatum suppressed cortical discharges in a manner similar to that seen following parenteral administration. It is possible that this suppression results from an increase in the tonic inhibition of cortical neurones contributing to desynchronization of the epileptic cortex. The inhibition of epileptic activity in both foci following unilateral injection of dopamine into the striatum emphasizes the role of the thalamus in desynchronizing the epileptic, cortex, in addition to its reported role in hypersynchronizing epileptic changes (Aquino-Cias & Bures, 1967; Kusske, 1976). Moreover, reduction in the activity of striatal neurones by bilateral 6-OHDA lesions might release the cortical neurones from striatal inhibition and perhaps potentiate epileptic changes in the cortex. Our results did demonstrate a small but definite increase in focal discharges following such treatment.

However, the ascending reticular activating system (ARAS) also sends fibre connections to the striatum and in turn receives efferent fibres from striatal neurones (Cools *et al.*, 1977). The ARAS exerts a desynchronizing tone on the cortex thus mediating arousal. It is possible that stimulation of striatal neurones by dopamine or dopamine agonists with its associated increase in the levels of arousal induced a rather non-specific cortical desynchronization. There is also evidence that in models of 'sensory epilepsy', including focal motor epilepsy, proprioceptive impulses arising from motor activity play an important role in the evolution of seizure response (Chauvel, Lamarche & Pumain, 1975; Naquet, Catier & Menini, 1975). Dopamine agonists could act directly or indirectly on this system.

Kobayashi, Schirakabe, Kishikawa & Mori (1976) suggested that dopamine is directly involved in the regulation and development of epileptic activity in penicillin-induced lesions in the cat cerebral cortex. We attempted to determine whether this might also be the case in cobalt-induced epilepsy by following the development of the foci during chronic treatment with the long-lasting dopamine receptor agonist, bromocryptine. Although this treatment suppressed cortical spike discharges the development of both primary and secondary epileptogenic foci was not completely prevented. However, the usual upsurge in epileptic activity seen after five days, particularly from the secondary focus was not observed.

Dopamine agonists cannot be considered as generally effective anti-epileptic agents and variations in response exist between species (McKenzie & Soroko, 1972; Meldrum *et al.*, 1975). Recently it has been shown that apomorphine and bromocryptine have no effect on either developing or established seizures in kindled rats (Farjo, 1978). However, the present study does demonstrate that certain drugs inhibit spike discharges from cobalt-induced epileptogenic foci apparently by stimulating dopaminergic receptors in the corpus striatum. Although dopamine appears to modulate epileptic activity in the cerebral cortex it does not seem to be directly involved in the initiation of such activity and the mechanism of this effect has not been established.

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