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PRESYNAPTIC CONTROL OF DOPAMINE METABOLISM IN THE NUCLEUS ACCUMBENS. LACK OF EFFECT OF BUSPIRONE AS DEMONSTRATED USING IN VIVO VOLTAMMETRY.

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SUMMARY

Buspirone is a non-benzodiazepine drug with anxiolytic properties. It has been reported to induce a marked increase in the metabolism of dopamine in the striatum and the nucleus accumbens which is similar to that induced by neuroleptics. It has been suggested that the effect observed in the striatum reflects an action of buspirone on dopaminergic autoreceptors in both terminals and cell bodies. In the present study, presynaptic effects of buspirone on dopaminergic metabolism in the nucleus accumbens were investigated, and they were compared to the effects of the classical neuroleptic, haloperidol. Dopaminergic terminals were isolated by infusion of tetrodotoxin into the median forebrain bundle in order to evaluate the effects of buspirone and haloperidol on presynaptic receptors. Changes in dopamine metabolism were determined by <u>in vivo</u> voltammetry. Buspirone administered after interruption of the impulse flow did not affect dopamine metabolism. In contrast haloperidol treatment led to an increase in metabolism of dopamine. It is concluded that buspirone did not act at the presynaptic level and furthermore on dopaminergic autoreceptors.

Buspirone, an anxiolytic drug lacking affinity for benzodiazepine or GABA bindings sites (1), has been shown to markedly increase dopamine metabolism in the striatum or the nucleus accumbens (2, 3, 4). This effect is similar to the one obtained with classical dopaminergic antagonists such as the neuroleptics (2, 3, 4). The increase in dopamine metabolism induced by neuroleptics in the striatum or the nucleus accumbens is generally thought to reflect a blockade of postsynaptic dopaminergic receptors and of presynaptic dopaminergic autoreceptors situated on both terminals and cell bodies (5). However, the importance of the classical feed-back activation induced by blockade of postsynaptic receptors by neuroleptics has been challenged (6). Concerning buspirone it has been suggested from <u>in vitro</u> and <u>in vivo</u> studies that this drug affects dopamine metabolism in the striatum by blocking presynaptic dopaminergic autoreceptors (7).

The aim of the present study was to investigate the effects of buspirone on dopaminergic terminals in the nucleus accumbens, in order to evaluate the action of the drug at the presynaptic level. The effects on dopamine metabolism were studied <u>in vivo</u> after isolation of the nerve terminals in the

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nucleus accumbens by local infusion in the median forebrain bundle (MFB) of tetrodotoxin (TTX), a classical blocker of nerve conduction (8). While TTX blocks the neuronal firing, buspirone would be still able to modify dopamine metabolism at the presynaptic level by an effect on dopamine release and/or synthesis. An increase in the dopamine metabolism in the nucleus accumbens would indicate a direct action of buspirone on dopaminergic autoreceptors or an indirect action via another type of neuron modulating presynaptically the dopamine release. An absence of an increase in dopamine metabolism would indicate a lack of presynaptic action involving dopaminergic autoreceptors. Since the effects induced by buspirone on dopamine metabolism are similar to those elicited by well-known neuroleptics (2, 3, 4), the effects of buspirone at the presynaptic level were compared to those induced by the classical neuroleptic haloperidol.

Dopamine metabolism was assessed by measuring the presynaptic metabolite of dopamine, 3,4-dihydroxyphenylacetic acid (DOPAC). DOPAC levels were monitored by in vivo differential pulse voltammetry (DPV) with pretreated carbon fibre electrodes. This technique allows the selective and continuous measurement of DOPAC in striatal structures (9, 10, 11, 12, 13, 14).

In the present work, it was shown that buspirone as opposed to haloperidol did not affect dopamine metabolism in the nucleus accumbens. The results suggested that this drug does not act on dopaminergic autoreceptors in this structure.

METHODS

Male Sprague-Dawley rats (Janvier, France) weighing 400-440 g housed at 22°C and maintained on a 12 h light-dark cycle (light on at 8:00 a.m.) were used. The animals were tracheotomized under halothane anesthesia, intubated with a tracheal cannula, artificially ventilated with halothane (0.5-0.75% in air) after injection of d-tubocurarine (10 mg/kg ip) and placed in a stereotaxic frame with the incisor bar 3 mm below the interaural line. All stereotaxic pressure points and incision margins were locally anesthetized with lidocaine (xylocaine). Body temperature was monitored and maintained constant (37°C) by a thermostatically controlled blanket. The carbon fibre microelectrodes (8 µm diameter, 500 µm length) were implanted in the nucleus accumbens (ACC). The following stereotaxic coordinates were used : 10.8 mm anterior to the interaural line, 1.6 mm lateral to the midline, 7 mm below the cortical surface. The microinjection cannulae (30 gauge) were implanted in the MFB at the level of the lateral hypothalamus with the following coordinates : 5.2 mm, 1.7 mm, 8.7 mm.

A classical three-electrode potentiostatic setting was used. Carbon fibre microelectrodes were prepared as previously reported (15, 16). The reference electrode was a AgCl-coated silver wire obtained from a Teflon coated silver wire and prepared as previously described (14). The auxilliary electrode was a platinum wire. Differential pulse voltammograms (DPV) were recorded every minute using a commercially available voltammetric apparatus (PRG5 Tacussel, Villeurbanne, France). The following parameters were set : scan rate, 10 mV/s ; voltage range, -50 to +150 mV with respect to the reference electrode ; pulse modulation duration, 48 ms. The height of the DOPAC peak height which appeared at +50 mV with the reference electrode used (14) was measured as previously reported (11). For each experiment the mean of the 30 peak heights measured during a recording period of 30 min over which the signal varied less than 10% was calculated and taken as the 100% value.

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