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Zetidoline blocks the action of apomorphine on neurons in the rat substantia nigra

N. HARRIS, P. G. DOREY, G. N. WOODRUFF*, *Department of Physiology and Pharmacology, University of Southampton, Southampton SO9 3TU, U.K.*

Zetidoline (1-(3-chlorophenyl)-3-[-2-(3,3-dimethyl-1-acetidinyl-ethyl]-imidazolidin-2-one HCl) is a member of a new class of psychotropic agents. In various behavioural tests, zetidoline displays neuroleptic-like properties. For example, it inhibits apomorphine-induced emesis in dogs and amphetamine-induced stereotypy in rats (Barone et al 1982). Furthermore, zetidoline, like other centrally-acting dopamine antagonists, increases striatal dopamine turnover and elevates plasma prolactin concentrations (Barone et al 1982). Although zetidoline is active in dopamine receptor binding assays, it is not an effective antagonist of the stimulatory effect of dopamine on the dopamine-sensitive adenylate cyclase in striatal homogenates (Barone et al 1982). In this respect zetidoline resembles the substituted benzamide sulpiride. Recently, we have shown that sulpiride is a potent antagonist of the inhibitory effect of dopamine on the dopamine-containing neurons in the rat substantia nigra. In the present study we have investigated the action of zetidoline on neurons in the substantia nigra, by studying its effect on the responses of the cells to the intravenous injections of the dopamine receptor agonist apomorphine.

Methods

Male Wistar rats, 150 and 180 g were anaesthetized with chloral hydrate (350 mg kg^{-1}) and a femoral vein cannulated for drug administration. Each rat was then placed in a stereotaxic frame. Anaesthesia was maintained with oxygen containing 1–2% halothane. Single barrelled glass microelectrodes, containing pontamine sky blue 2% in 2 M NaCl were used to obtain extracellular recordings of spikes from single neurons in the substantia nigra, zona compacta. The cells were identified as dopamine-containing by their characteristic firing pattern, their behaviour following antidromic stimulation of the ipsilateral striatum and their responsiveness to intravenous injections of apomorphine (Bunney et al 1973; Guyenet & Aghajanian 1978). At the end of each successful experiment, pontamine sky blue was ejected from the recording electrode; the position was later identified histologically. Only one neuron was studied in each rat. Apomorphine was dissolved in 0·9% NaCl containing 8 mM tartaric acid and diluted as required with 0·9% NaCl. Zetidoline was dissolved in 0·9% NaCl.

* Correspondence.

Results and discussion

A total of 12 spontaneously active neurons in the substantia nigra, zona compacta, were used in this study. The firing of all of the cells was potently inhibited by intravenous injections of the dopamine receptor agonist apomorphine. The ID50 (dose causing a 50% depression of the firing rate) for apomorphine was approximately 10 μg kg^{-1}. The inhibitory action of apomorphine was often associated with an increase in the size of the spike (Fig. 1). Zetidoline, in doses of from 100 to 1000 μg kg^{-1} intravenously, potently and rapidly blocked the inhibitory effect of apomorphine on zona compacta neurons. When given during a period of apomorphine-induced depression of the spontaneous firing rate of cells, zetidoline (100 μg kg^{-1}) caused a rapid (within 20 s) reversal of apomorphine-induced depression (Fig. 2). Furthermore, following this same dose of zetidoline, subsequent intravenous injections of apomorphine (1–10 μg kg^{-1}) no longer produced the usual depression of firing of the cells (Fig. 2). This blocking action of zetidoline, which was demonstrated on all 12 neurons on which it was studied, could be overcome by increasing the dose of apomorphine to 100 μg kg^{-1}. On 7 of the 12 cells, zetidoline caused an increase in the spontaneous firing rate of the neurons.

According to one classification (Kebabian & Calne 1979), dopamine receptors have been classified into those which are linked to adenylate cyclase and those which are not. However, there is currently no direct evidence that the neuropharmacological actions of dopamine are mediated by an increase in cyclic AMP. For example sulpiride, which unlike many neuroleptic drugs, does not block the stimulatory effects of dopamine on the dopamine-sensitive adenylate cyclase in

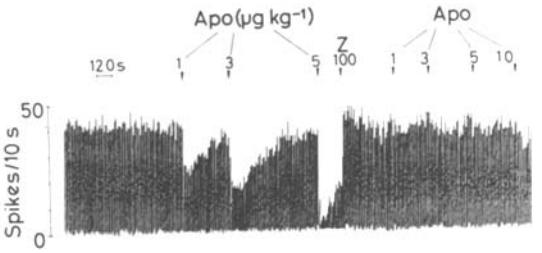

FIG. 1. Ratemeter recordings of a SNC neuron inhibited by apomorphine (1, 3 and 5 μg kg^{-1} i.v.). Zetidoline (100 μg kg^{-1} i.v.) rapidly reversed the inhibition and blocked the effect of subsequent doses of apomorphine.

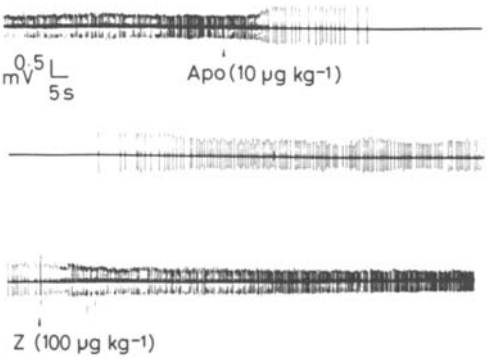

FIG. 2. Continuous spike record of a SNC neuron, showing an inhibition caused by apomorphine (10 μg kg^{-1} i.v.). Note the increase in spike height during the inhibition. Zetidoline (100 μ kg^{-1}) caused a reversal of apomorphine-induced inhibition and a return of the spike height to its pre-drug level.

striatal homogenates (Trabucci et al 1975), is nevertheless a potent dopamine antagonist when applied microiontophoretically onto dopamine-containing neurons in the substantia nigra and is a potent blocker of the behavioural effects produced by the local application of dopamine receptor agonists into the nucleus accumbens (Woodruff & Pinnock 1981). Zetidoline is a novel psychotropic drug with properties indicative of central dopamine receptor antagonism. For example it inhibits apomorphine-induced emesis in dogs and amphetamine-induced stereotypy in rats (Barone et al 1982). Recently Barone et al (1982) have shown that zetidoline, like classical neuroleptic drugs, causes an increase in striatal dopamine turnover and an increase in plasma prolactin levels. However the same authors also showed that, like sulpiride, zetidoline showed virtually no activity on the striatal dopamine-stimulated adenylate cyclase. The dopamine-containing neurons in the rat substantia nigra, zona compacta, provide a useful system on which to study the actions of dopamine receptor agonists and antagonists. The cells can be identified by their characteristic firing pattern, their responses to antidromic stimulation of the ipsilateral striatum and their responsiveness to intravenous injection of dopamine agonists such as apomorphine (Bunney et al 1973; Aghajanian & Bunney 1977). A wide variety of dopamine antagonists have been shown to block and reverse the inhibitory effect of apomorphine on zona compacta cells (Bunney 1979).

In the present study we have provided evidence that zetidoline is an antagonist of the dopamine receptors on the dopamine-containing neurons in the substantia nigra.

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