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Selective Permeation of the Blood-Brain Barrier as a Cause of the Anomalous Properties of 'Atypical' Neuroleptics

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HERBERG, L. J. AND T. B. WISHART. *Selective permeation of the blood-brain barrier as a cause of the anomalous properties of 'atypical' neuroleptics.* PHARMAC. BIOCHEM. BEHAV. **12**(6) 871–873, 1980.—Metoclopramide is a widely used anti-emetic drug with potent dopamine-blocking effects on brain structures involved in emesis and prolactin secretion but it is apparently devoid of therapeutic effect in schizophrenia, thus calling into question the supposed role of dopamine blockade in the action of antischizophrenic drugs. This investigation compared the depression of hypothalamic self-stimulation produced by metoclopramide and by a 'typical'' neuroleptic, spiroperidol (spiperone), when injected by different routes. Metoclopramide was found to be nearly 30 times more potent when administered directly into the brain via the cerebral ventricles than when injected intraperitoneally; on the other hand the potency of spiroperidol was virtually unaffected by the route of administration. The blood-brain barrier is known to be absent from brain sites controlling emesis and prolactin secretion; thus the potency of metoclopramide as an anti-emetic and in releasing prolactin, and its relative ineffectiveness as an antipsychotic can be accounted for by a failure to enter the brain freely except at privileged sites. Thus its anomalous properties are not necessarily inconsistent with the dopamine theory of schizophrenia.

Blood-brain barrier Intraventricular injection Metoclopramide Neuroleptic Schizophrenia Self-stimulation Spiroperidol

THE Dopamine Theory of schizophrenia [22] rests largely on evidence that the antipsychotic potency of drugs is correlated with their ability to block transmission at dopamine-(DA-) sensitive synapses in the brain [7]; thus the recent discovery of certain 'atypical' neuroleptic agents effective against schizophrenia but which fail to produce other signs of DA blockade (such as catalepsy in animals or extrapyramidal symptoms in man) has caused the theory to be reconsidered [6,14]. The most serious [14] and "crucial" [25] inconsistency has been said to be the finding that metoclopramide, a widely used anti-emetic with a modest but significant affinity for DA receptors *in vitro* [11] fails to relieve the symptoms of schizophrenia when given in doses effective against vomiting [19]. Metoclopramide has proved effective *in vivo* against several behavioural [1, 12, 13, 21, 30] and biochemical [15,29] models of limbic and extrapyramidal function but the pattern of its effects across these tests shows marked differences from that of most other neuroleptics [11], and shows no clear relation to its clinical properties [11]. In clinical use metoclopramide in doses of 5–10 mg is virtually free from extrapyramidal side-effects [19], even in patients with Parkinson's disease [2], but it may occasionally induce severe dyskinetic reactions in children or young adults [19]. We report evidence that some of these anomalous properties of metoclopramide may be simply a consequence of its failure to gain physical access in adequate concentrations to certain parts of the brain.

Various other possibilities have previously been considered. The ineffectiveness of metoclopramide in schizophrenia is unlikely to be due to its blocking the 'wrong' type of DA receptor: the antipsychotic potential of neuroleptics correlates better with their affinity for ^{3}H-spiroperidol-binding DA-receptors rather than with their affinity for adenyl cyclase-linked postsynaptic receptors [10,26] and this is precisely the pattern of affinities displayed by metoclopramide [11,20]. Nor does metoclopramide favour the extrapyramidal rather than the limbic division of the DA-containing systems: it affects the turnover of DA in the two divisions equally [12,29]. Some atypical DA-blockers are thought to owe their anomalous behaviour to their anticholinergic properties [17,23] but this cannot be true of metoclopramide which has none [19].

An alternative explanation is that metoclopramide may be incompletely absorbed from the blood stream and distributed differentially to different brain areas, and this possibility is supported by the relatively poor penetration of the brain by sulpiride [3,9], a chemically related compound effective against schizophrenia when administered in very high doses (up to 2.0 g/day). Although metoclopramide strongly affects at least two areas within the brain—the chemosensitive trigger area for vomiting in the area postrema of the medulla [5] and the hypothalamic median eminence controlling prolactin secretion [16] these structures are exceptional sites where the blood-brain barrier is known to be lacking [4]. The entry of metoclopramide into other parts of the brain including the extrapyramidal and limbic systems could be so poor as to

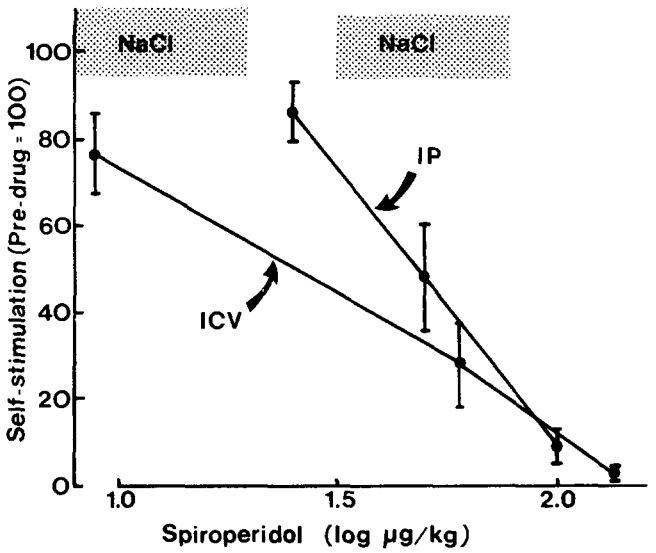

FIG. 1. Self-stimulation rates after intracerebroventricular (ICV) and intraperitoneal (IP) injection of NaCl and different doses of spiroperidol. Shaded areas indicate response rates after NaCl. Ranges are standard errors. N=6.

account for its failure to induce dyskinesias [2] or to relieve schizophrenia [19]. We tested this possibility by administering metoclopramide directly into the brain via the cerebral ventricles so as to bypass the blood-brain barrier. For comparison we also examined the effects of a typical neuroleptic, spiroperidol, selected because it is known to be extremely potent both as an antipsychotic and in producing symptoms of extrapyramidal blockade.

METHOD

Central effects of injected drugs were assessed in an electrical self-stimulation procedure in which the rat operated a pedal to administer reinforcing electrical pulses through electrodes implanted in a 'reward' area of its own brain [18]. Response rates in self-stimulation are highly sensitive to drugs that increase of decrease transmission in dopaminergic pathways, and all DA-receptor blocking agents, including spiroperidol and metoclopramide, have been shown to cause a dose-dependent depression of responding [28]. To ensure a steady even performance we used a variable-interval schedule of reinforcement that limited the rat to a single 0.5-sec response-contingent pulse at random intervals averaging 10 sec in duration. Different doses of metoclopramide, spiroperidol or of NaCl in 5 µl isotonic solutions were injected slowly through stainless steel cannulas implanted in the lateral ventricle. Systemic injections served as controls and were administered intraperitoneally in a volume of 1.0 ml/kg. Injections were preceded by a 30-min pre-drug baseline session of self-stimulation, and their effects were recorded in a further 30-min session 2.5 hr later. Each rat was given NaCl and all intraventricular and intraperitoneal doses of either metaclopramide or spiroperidol, different doses being given in a randomized sequence at intervals of not less than 3 days. At the end of the experiment correct placement of electrodes and cannulas was verified by injecting a dye through the cannula and by histological examination.

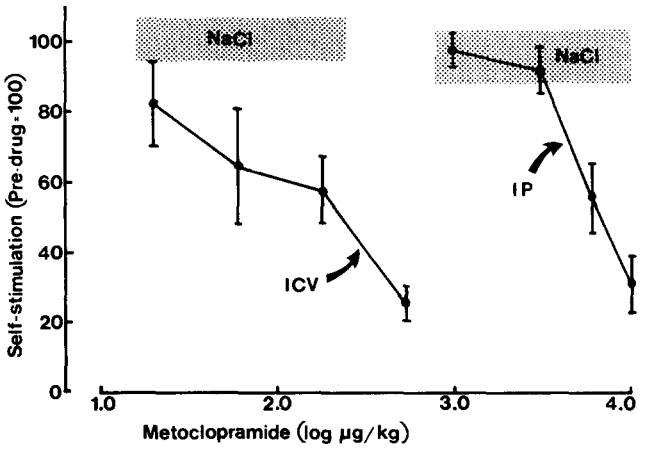

FIG. 2. Self-stimulation after metoclopramide. N=7. Details as in Fig. 1.

RESULTS

Figure 1 shows dose-response curves for the effects of spiroperidol on self-stimulation recorded 2.5 hr after injection. After this interval there was little difference in potency between injections of spiroperidol given intraventricularly and intraperitoneally, and the interpolated values for doses that would inhibit responding by 50% were not significantly different (respectively 44 ± 18 and 56 ± 7 µg/kg $t_{10}=1.52$, $p<0.1$). This result is in line with similar previous findings after intraventricular injection of drugs that pass freely in and out of the brain [8,24]. Metoclopramide, on the other hand, was nearly 30 times less potent when given systemically than when given intraventricularly (see Fig. 2), the respective ID_{50} values being 7.3 ± 0.7 and .27 ± .06 mg/kg ($T_{12}=17$, $p<0.001$).

DISCUSSION

These results demonstrate the existence of brain structures highly sensitive to metoclopramide but relatively inaccessible to it when the drug is administered systemically. If these structures include the sites of action of antipsychotic drugs, the variable effects of metoclopramide on extrapyramidal function and its seeming ineffectiveness as an antipsychotic as compared to its potency as an anti-emetic, would be accounted for. Central concentrations of metoclopramide will depend critically on the permeability of the blood-brain barrier and will therefore vary not only between one brain region and another but also according to age, species, previous treatment with other drugs, and with changes in blood chemistry and tonicity [4,27]. It is therefore unnecessary to suppose that metoclopramide-sensitive DA-receptors differ uniquely from DA receptors blocked by antipsychotic drugs, nor is it necessary to regard the seeming ineffectiveness of metoclopramide as a crucial challenge [14,25] to the Dopamine Theory of schizophrenia.

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