THE EFFECT OF BINODALINE ON MONOAMINE UPTAKE AND TURNOVER IN RAT BRAIN

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Binodaline, 1-(ω-dimethylaminoethylmethyl)-amino-3-phenyl-indole-hydrochloride,is a novel antidepressant drug which whilst being of similar potency to imipramine in animal experiments, appears to be devoid of anticholinergic activity (Adrian, Ismail & Jahn 1981). To investigate the possible mechanism by which binodaline exhibits its antidepressant activity, we have carried out in vitro studies in male Wistar rats to determine whether binodaline either interferes with monoamine uptake into cerebral nerve endings, or whether it affects the cerebral turnover of these amines. These experiments have been carried out because the most significant neurochemical effect of the clinically useful tricyclic antidepressants is their ability to inhibit the uptake of one or more of these monoamines. It is suggested that this may be directly related to their ameliorative action in depressive illness. In addition, we have investigated the effects of desmethylbinodaline (Sgd 20578) since this compound is expected to be a primary metabolite of binodaline in man.

Uptake studies were carried out using synaptosomes prepared and purified from various regions of rat brain (Gray & Whittaker 1962). After a 10 min preincubation in Krebs-ringer (with or without test drug) and a 10 min incubation in the presence of ^{14}C-labelled monoamine (NA, 5-HT, DA), synaptosomes were reclaimed and counted for radioactivity by liquid scintillation spectrometry. Whole forebrain was used for the study of 5-HT, cerebral cortex for NA and the corpus striatum for DA. The effects of binodaline and Sgd 20578 on monoamine uptake were compared with imipramine and clomipramine, together with their respective N-desmethyl analogues, in NA and 5-HT uptake studies. Nomifensine was also included in the DA study for reference purposes. Binodaline and Sgd 20578 both inhibited monoamine uptake into cerebral nerve endings, the IC_{50} values for the parent drug being 2.3×10^{-7}M (5-HT), 5.0×10^{-6}M (NA) and 1.45×10^{-6}M (DA). Sgd 20578 was more potent than binodaline in inhibiting NA uptake (8.5×10^{-7}M), of a similar potency against 5-HT (3.2×10^{-7}M) and slightly less potent against DA (8.3×10^{-6}M). In terms of relative potency binodaline was of a similar activity to clomipramine and imipramine in inhibiting NA-uptake but considerably weaker than these two drugs in inhibiting 5-HT uptake. In contrast, binodaline was more potent than either clomipramine or imipramine in preventing DA uptake into synaptosomes although in this respect it was considerably less potent than nomifensine.

To investigate the influence of binodaline and Sgd 20578 on cerebral turnover of monoamines, these agents were administered intraperitoneally (5,10,15 mg/kg) to groups of 5 male rats (300 - 400 g). One hour later, NA, 5-HT, DA and the associated metabolites 5-HIAA, DOPAC and HVA were extracted from brain homogenates by means of disposable Bio-Rad columns packed with Sephadex G-10 and assayed fluorimetrically (Earley & Leonard 1978). Neither binodaline nor Sgd 20578 was found to influence cerebral turnover of NA, 5-HT and DA. Brain concentrations of the related metabolites 5-HIAA, DOPAC and HVA were also unchanged. It therefore appears unlikely that the antidepressant activity of binodaline is associated with increased formation, or decreased metabolism of cerebral NA, 5-HT or DA.

In conclusion, it appears that in common with other antidepressants, binodaline owes its antidepressant property at least in part, to its ability to inhibit monoamine uptake into pre-synaptic cerebral nerve endings.

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