A behavioural model of the GABA-facilitating action of benzodiazepines: rotational behaviour after unilateral intranigral injection of chlordiazepoxide

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Recent studies on the mode of action of benzodiazepines have indicated a facilitatory effect on GABA-aminergic transmission (Costa, Guidotti, Mao & Suria, 1975). Rotational behaviour, which has been associated with asymmetric activation of nigrostriatal dopamine (DA) mechanisms, has recently been induced by unilateral manipulation of GABA activity in the substantia nigra zona reticulata (SNR), presumably via a striato-nigral GABA modulation of activity in DA neurones located in the adjacent zona compacta (SNC). Thus blockade of nigral GABA receptors by unilateral intranigral injection of picrotoxin induces contralateral rotation (Tarsy, Pycock, Meldrum & Marsden, 1975), while elevation of nigral GABA level by injection of a GABA transaminase inhibitor produces ipsilateral rotation under the action of amphetamine and apomorphine (Dray, Oakley & Simmonds, 1975). If benzodiazepines exert a facilitation on GABA-minergic transmission then their unilateral injection into SNR should induce ipsilateral rotation.

Male Sprague-Dawley rats (150 ± 20 g) were anaesthetized with ether and unilateral injections of the soluble benzodiazepine chlordiazepoxide hydrochloride (CDP; 1 μg in 1 μl saline) were made stereotaxically into SNR. Control animals received 1 μl saline. Immediately post injection they were placed in automated rotameter bowls and rotation measured continuously for 60 minutes.

Animals receiving CDP injection showed a weak ipsilateral circling/postural deviation on recovery. When pretreated with (+)-amphetamine (5 mg/kg) prior to CDP injection, however, rats showed intense ipsilateral circling that significantly exceeded the mild circling induced by control procedures ($P < 0.01$). Only weak circling was seen after apomorphine pretreatment. With histologically confirmed injections into the region of DA-containing cell bodies (SNC), both CDP and saline induced a mild, indistinguishable, ipsilateral circling. An analysis of variance showed a statistically significant ($P < 0.05$) depth × treatment interaction at 30 minutes. The induction of intense circling in amphetamine pretreated animals by CDP injection was mimicked by injections into SNR of the GABA-analogue baclofen (β)-*p*-chlorphenyl)-GABA; 0.1 μg in 1 μl saline; $P < 0.01$ compared with controls). These effects of both CDP and Lioresal injections into SNR were reduced to control levels by i.p. injection of the GABA antagonist picrotoxin (2 mg/kg).

There is some debate on the exact nature of synaptic GABA-DA interactions in SNR (Dray & Straughan, 1975). This CDP effect is, however, mimicked by the GABA-analogue baclofen and both effects are attenuated by the GABA antagonist picrotoxin. These effects are confined to the GABA containing SNR. Such results indicate a facilitatory effect of chlordiazepoxide on GABA transmission and suggest that this rotational model may be useful in the preclinical assessment of benzodiazepines.

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