Altered serotoninergic activity in mouse brain induced by clonazepam

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The mechanism by which some conventional anticonvulsant drugs elevate cerebral serotonin (5HT) levels (Bonnycastle, Giarman & Paasonen, 1957; Jenner, Chadwick, Reynolds & Marsden, 1975) is poorly understood. We now report the actions of the potent benzodiazepine clonazepam on the functional activity of the cerebral 5HT system.

Clonazepam (4 mg/kg i.p. 3 h previously) administered to male Swiss S mice (20–25 g) elevated cerebral 5-hydroxyindoleacetic acid (5HIAA) and tryptophan levels ($P < 0.001$) but not 5HT levels, both at room temperature and in animals with a normal body temperature maintained by a constant environmental temperature of 33°C.

In the presence of the monoamine oxidase inhibitors (MAOI) pargyline hydrochloride (100 mg/kg i.p. 15 min previously) and tranylcypromine sulphate (25 mg/kg i.p. 15 min previously) clonazepam increased both 5HT and 5HIAA levels ($P < 0.05$) compared to animals receiving MAOI alone. The increase in 5HIAA produced in the presence of a MAOI suggests that clonazepam blocks the egress of 5HIAA from brain.

In the presence of probenecid (200 mg/kg i.p. 1 h prior to and 2 h following clonazepam administration) clonazepam caused an elevation of cerebral 5HT, 5HIAA and tryptophan levels ($P < 0.01$) compared to animals receiving probenecid alone. Comparison of the elevation of 5HIAA obtained following administration of clonazepam with and without probenecid or MAOI administration suggests that at least 50% of the rise is due to the altered metabolism of cerebral 5HT whereas the remainder results from the blockade of 5HIAA egress caused by clonazepam.

Clonazepam (4 mg/kg i.p.) reduced the depletion of 5HT ($P < 0.02$) induced by p-chlorophenylalanine methyl ester hydrochloride (200 mg/kg daily for 3 days) suggesting a reduction of 5HT utilisation. However, the accumulation of 5-hydroxytryptophan ($P < 0.001$) induced by prior treatment with the central decarboxylase inhibitor NSD 1034 (150 mg/kg i.p. 0.5 h prior to and 1.5 h following clonazepam) was unaltered suggesting that clonazepam has no effect on 5HT synthesis.

Following a pulse injection of L-G-[^{3}H]-tryptophan (8.8 Ci/mmol; 25 μCi s.c. 1 h following clonazepam) clonazepam increased the brain content of labelled 5HT and tryptophan ($P < 0.05$) compared to animals receiving [^{3}H]-tryptophan alone, confirming that the drug decreases 5HT utilisation.

These data suggest that in the mouse clonazepam elevates brain tryptophan levels, although this is not reflected by altered 5HT synthesis, decreases 5HT utilisation and blocks the egress of 5HIAA from the brain.

References

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