PHARMACOLOGICAL EVIDENCE THAT THE ANXIOLYTIC EFFECT OF TOFISOPAM IS RELATED TO A SUBGROUP OF BENZODIAZEPINE RECEPTORS

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The observation that tofisopam, a 3,4-benzodiazepine derivative, was found to be completely ineffective in the Vogel test, whereas it proved to exert anxiolytic activity in man (for review see Pellow and File, 1986) prompted us to search for an animal model capable to detect the anxiolytic effect of this benzodiazepine derivative.

Using this new method, details of which are described elsewhere (Miklya and Knoll, in press), the anxiolytic effect of tofisopam could be demonstrated. The anxiolytic dose range was found to be between 15-25 mg/kg and 400 mg/kg was the smallest dose which inhibited unpunished responding. The anxiolytic effect of tofisopam disappeared by raising the dose and it could be completely antagonized by 0.1 mg/kg Ro 15-1788, whereas picrotoxin left it unchanged, indicating that this effect is related to benzodiazepine receptors.

Chlordiazepoxide behaved in an unusual manner in our test, it inhibited punished responding in two dose ranges. The anxiolytic activity was first detectable with a dose as small as 0.1 mg/kg, and 20 mg/kg Ro 15-1788 was needed to antagonize this effect. The anxiolytic effect of 0.1 mg/kg chlordiazepoxide disappeared by raising the dose to 0.5-1 mg/kg, and a second anxiolytic dose range was detected by reaching the dose of 2.5 mg/kg. This effect could be antagonized by 10 mg/kg Ro 15-1788. This behavior

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of chlordiazepoxide speaks in favor of the assumption that two populations of benzodiazepine receptors, BR1 and BR2, are involved in the observed effects. Chlordiazepoxide has a higher affinity to the BR1 population, as 0.1 mg/kg is sufficient to stimulate this subgroup of benzodiazepine receptors which then seem to be inhibited by higher doses of the drug. In agreement with the high affinity of chlordiazepoxide to this population of receptors we need high amount of Ro 15-1788 (20 mg/kg) to antagonize the anxiolytic effect of 0.1 mg/kg chlordiazepoxide. The anxiolytic effect of the high, 2.5 mg/kg, dose of chlordiazepoxide, antagonized by 10 mg/kg Ro 15-1788, is proposed to be related to BR2 receptors. The anxiolytic tests, like the Vogel test, used today in pharmacological praxis seem to reveal the binding of the anxiolytics to the BR2 receptor subgroup.

We suggest that tofisopam which exerts only in one dose range an anxiolytic effect, acts selectively on BR1 receptors and this is why it is ineffective in the usually used anxiolytic tests, like the Vogel test, which seems to measure the effects on BR2 receptors.

Using our new method we try now to develop new anxiolytics acting selectively on the BR1 subgroup of benzodiazepine receptors, but being more potent than tofisopam.

REFERENCES

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