BENZODIAZEPINES POTENTIATE 5HT-RECEPTOR STIMULATION

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It is well known that benzodiazepines reduce 5HT turnover in the central nervous system (Saner & Pletscher 1979), probably by potentiating GABA-mediated inhibition of raphe cell firing (Gallager 1978), and it has been suggested that this property may contribute to the anxiolytic action of the benzodiazepine group (Thiebot et al 1982). It has been reported, however that behavioural sequelae of direct central 5HT receptor stimulation are potentiated by benzodiazepines (Nakamura and Fukushima 1977), suggesting perhaps a postsynaptic facilitaton. The experiments described here were designed to investigate this apparent disparity between pre- and post-synaptic mechanisms.

Head twitch induced in male CFLP mice by i.p. injection of either 2.5 $mg.kg^{-1}$ 5-methoxy-N,N'dimethyltryptamine (5MeODMT) or a combination of 5HTP (50 $mg.kg^{-1}$) and carbidopa (25 $mg.kg^{-1}$) was used as a measure of $5HT_2$ receptor stimulation. The effects of four benzodiazepines-diazepam (2-16 $mg.kg^{-1}$) oxazepam (1-30 $mg.kg^{-1}$), clonazepam and clobazam (0.3-10 $mg.kg^{-1}$) were investigated; each was injected 60 min before the observation period. Table 1 shows that all four benzodiazepines significantly potentiated the response to 5MeODMT, but produced no significant increase in response to 5HTP.

Table 1 Effect of benzodiazepines on 5HTP- and 5MeODMT-induced Head Twitch

	control	diazepam $8mg.kg^{-1}$	oxazepam $10mg.kg^{-1}$	clonazepam $10mg.kg^{-1}$	clobazam $3mg.kg.^{-1}$
5HTP	5.8 ± 0.4	5.6 ± 1.7	7.1 ± 0.9	2.0 ± 0.6	7.0 ± 1.0
5MeODMT	3.8 ± 0.5	11.8 ± 1.3	12.9 ± 0.6	16.6 ± 1.5	13.3 ± 0.5

Number of head twitches in a 3min period ∓ sem, n not less than 6. All increases over control in the 5MeODMT response are significant at the $p < 0.001$ level. The inhibition in response to 5HTP produced by clonazepam is significant at the $p < 0.05$ level.

Clonazepam (10 $mg.kg^{-1}$) significantly increased head twitch response to the $5HT_2$ agonists quipazine (5$mg.kg^{-1}$) and mescaline (10 $mg.kg^{-1}$); conversely the $5HT_2$-receptor antagonist pirenperone (5$\mu g\ kg^{-1}$) inhibited to an equal extent the head twitch response induced by 5MeODMT alone, and that in response to 5MeODMT combined with clonazepam. Depletion of 5HT by pretreatment with p.chlorophenylanine (3 x 300 mg kg^{-1}) slightly increased basal response to 5MeODMT, but the percentage increase in response to combination of clonazepam with 5MeODMT was unchanged. Finally, the $GABA_A$ antagonist (+)-bicucculine (2 and 4 $mg.kg^{-1}$) did not antagonise the head twitch response to clonazepam and 5MeODMT.

These results show that benzodiazepines are capable of potentiating behavioural responses to direct stimulation of the $5HT_2$ receptor. Since the potentiation is unaffected by (+)-bicucculine, it is presumably not mediated via the $Gaba_A$ receptor, and a direct interaction at the $5HT_2$ receptor site remains a possibility. The lack of potentiation of the response to 5HTP is presumably due to benzodiazepines decreasing presynaptic turnover of 5HT and thereby decreasing the post-synaptic availability of 5HT derived from exogenous 5HTP.

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