Potentiation of muscimol-induced hyperactivity by benzodiazepines

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When GABA-mimetic agents, inhibitors of GABA-transaminase or GABA agonists, are administered systemically, animals show catalepsy, sedation and hypokinesia (Naik et al 1976; Benton & Rick 1976; Matsui & Deguchi 1977). However, when these drugs are injected intracerebrally, animals show varying behaviour according to the injection site; for example, pallidal injection induces akinesia (Pycock & Horton 1976) while nigral injection induces hyperactivity (Scheel-Krüger et al 1977; Matsui & Kamioka 1978a).

Benzodiazepines are thought to bring about their various effects by facilitation of GABA-ergic transmission in the central nervous system (Haefely et al 1975) and potentiating the effect of GABA-mimetic agents (Polc et al 1974; Naik et al 1976). We have found that benzodiazepines potentiate the effect of the GABA agonist, muscimol, injected into the globus pallidus to induce catalepsy (Matsui & Kamioka 1978b). In this paper, we examine whether benzodiazepines also potentiate the hyperactivity induced by muscimol injected into the substantia nigra.

Non-anaesthetized male Wistar-Imamichi rats (250–300 g) were injected with muscimol (0·5 μl/10 s) bilaterally into the substantia nigra through guide cannulae (o.d. 0·7 mm), which were stereotaxically implanted under sodium pentobarbitone (Abbott laboratories, 40 mg kg^{-1}, i.p.) 4 days before injection, using stainless steel needles (o.d. 0·35 mm) and the stereotaxic atlas of Pellegrino & Cushman (1967). The muscimol was given 60 min after rats were placed singly in a Perspex box on the Valimex (Columbus Instruments, Ohio). The rats were returned immediately to the Perspex box and locomotor activity recorded cumulatively over 60 min.

Nitrazepam (Sankyo Co., Ltd.), diazepam (Takeda pharmaceutical Ind., Ltd.) or chlordiazepoxide (Takeda) were suspended in 1% carboxymethyl cellulose (CMC) and administered orally 30 min before injection of muscimol. Muscimol was synthesized in our laboratories. The brains were later examined histologically and data obtained from rats with placement errors were discarded.

Fig. 1 shows the effects of intranigral injection of muscimol on locomotor activity and the interaction with benzodiazepines. When 3 ng of muscimol was injected into the substantia nigra, rats showed continuous sniffing and headmovements and the counts measured on the Valimex increased significantly compared with those of the saline-injected group. Muscimol, 10 and 30 ng, further increased the hyperactivity.

Nitrazepam, 0·3 mg kg^{-1}, diazepam, 1 mg kg^{-1}, and chlordiazepoxide, 2 mg kg^{-1}, did not, but nitrazepam, 1 mg kg^{-1}, diazepam, 3 mg kg^{-1}, and chlordiazepoxide, 5 mg kg^{-1}, did significantly potentiate the hyperactivity induced by 3 ng of muscimol. When each benzodiazepine was administered alone, rats did not show hyperactivity, and the locomotor activity of rats so treated was not different from that of rats injected with 0·9% NaCl into the nigra (Fig. 1a).

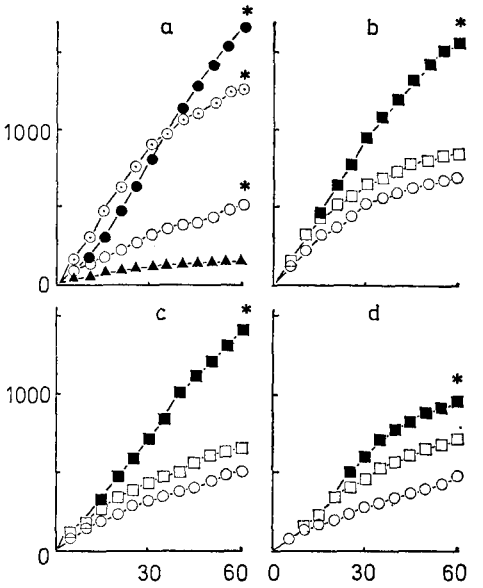

FIG. 1. Cumulative locomotor activity. (a) Intranigral injection of muscimol 3 ng (○), 10 ng (⊙), 30 ng (●) and saline (▲). (b) 3 ng of muscimol plus CMC (○), nitrazepam 0·3 mg kg^{-1} (□), and 1 mg kg^{-1} (■). (c) 3 ng of muscimol plus CMC (○), diazepam 1 mg kg^{-1} (□) and 3 mg kg^{-1} (■). (d) 3 ng of muscimol plus CMC (○), chlordiazepoxide 2 mg kg^{-1} (□) and 5 mg kg^{-1} (■). Each point represents an average value obtained from 5 rats. 1 group consisted of 5–7 rats originally and rats without placement errors were dropped from other groups to produce an equal number. * P <0·05 (the Mann-Whitney U-test. Analysis were based on a total score for the 60 min period.) Ordinates: locomotor counts. Abscissa: time (min).

Many reports indicate the inhibitory effect of GABA on the nigral dopamine neurons (Precht & Yoshida 1971; Andén & Stock 1973) and, therefore, it seems probable that potentiation of the nigral GABA-ergic system would depress behaviour. However, recent studies indicate that increase of the nigral GABA content or nigral injection of muscimol induce hyperactivity (Dray et al 1977; Scheel-Krüger et al

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1977). We have observed similar behaviour and, furthermore, shown that three benzodiazepines potentiated the effect of muscimol.

Benzodiazepines are well-known to have excitatory effects as well as depressant effects on behaviour and these effects depend on the test situation, the dose and whether the drug is administered acutely or chronically (Schallek et al 1972). In the present experiments, benzodiazepines potentiated the effect of muscimol at doses close to those that produce increase in ambulation (Christmas & Maxwell 1970) or exploration (Marriott & Spencer 1965). However, the increase in ambulation or exploration by benzodiazepines is not seen in experienced rats, and our muscimol-treated rats were habituated to the Perspex box before locomotor activity was recorded. Therefore, it is unlikely that potentiation of muscimol-induced behaviour by benzodiazepines is due to increase in ambulation or exploration. Babbini et al (1971) found the potentiation of amphetamine-induced stereotyped behaviour by benzodiazepines and the stereotyped behaviour resembles muscimol-induced behaviour, e.g. continuous sniffing and head movement. These excitatory effects of benzodiazepines are thought to be related to anxiety reducing action. Although it is not clear whether hyperactivity induced by intranigral injection of muscimol is related to anxiety, the excitatory effects of benzodiazepines may be due to facilitation of nigral GABA-ergic transmission.

On the other hand, large doses of benzodiazepines do not show the excitatory effects but often produce the depressant effects (Schallek et al 1972; Christmas & Maxwell 1970). These actions of benzodiazepines may be due to the facilitation of GABA-ergic systems in areas other than the substantia nigra, and where the GABA-ergic sytem has a depressant effect on behaviour, for example, the globus pallidus (Matsui & Kamioka 1978b).

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