Diazepam-Induced Hyperphagia in Mice is Sensitive to Quinpirole

Min RAHMINIWATI and Masakazu NISHIMURA*

Department of Pharmacology, University of Obihiro School of Veterinary Medicine, Obihiro, Hokkaido 080–8555, Japan

(Received 18 November 1998/Accepted 23 February 1999)

ABSTRACT. The present trial examined the possibility that diazepam (DZP, 1 mg/kg) induces hyperphagia by acting on the dopaminergic system. Quinpirole (QP), dopamine D-2 receptor agonist, was used for this purpose. Mice fasted for 24 hr were treated with QP 1 (QP-1) or 2 (QP-2) mg/kg 30 min prior to termination of the starvation. DZP was given to untreated mice and half of the QP-1 and QP-2 treated mice 10 min before the termination of the starvation. Food consumed during six 30 min intervals (30 min-feeding), food consumed for 3 hr (total feeding), time required to enter the room containing food by passing through a maze with four multiple routes (time to banquet), latent period to commencement of eating food after entering the banquet room (latent period), and feeding frequency for the 30 min intervals as well as for 3 hr were measured. DZP stimulated feeding, shortened the latent period without affecting the time to banquet and increased the feeding frequency. The hyperphagic effect was restricted to the first 30 min interval only. Both QP-1 and QP-2 first reduced, then progressively stimulated, and finally reduced feeding without modifying total feeding, thus making a bell-shaped profile. They also prolonged both the time to banquet and the latent period, and reduced the feeding frequency of the first 30 min interval but not that for 3 hr. Both QP-1 and QP-2 canceled all the effects of DZP. These results imply that dopamine D2 receptor is involved in the induction of hyperphagia by DZP. — KEY WORDS: diazepam, dopamine receptor, hyperphagia, mouse, quinpirole.

Benzodiazepines elicit hyperphagia in rats and mice [4, 5, 29]. They shorten the latent period to commencement of eating [4, 5] and enhance food anticipatory [18] and lever-pressing responses [37], as well as increasing tolerance to quinine-adulteration of food [12]. Therefore, this type of hyperphagia may be related with stimulation of feeding motive and appetite which in turn stimulate locomotor activity in searching for food and water.

The central dopaminergic system may be involved in initiating and keeping conditioned incentive motivation and motor activity and also may contribute to keeping motive in initial feeding and during intermeal intervals [14]. Feeding motive enhanced by diazepam (DZP) may appear in part via the dopaminergic system since dopamine antagonists such as SCH23390 and haloperidol can inhibit the hyperphagic effect of DZP [17]. Dopamine D-2 receptor may function not only in feeding but also in exploring for food and water [20].

We examined the effects of DZP combined with or without quinpirole (QP, D-2 receptor agonist) on feeding profile and exploratory behavior for food and water in mice.

MATERIALS AND METHOD

Male ddY mice weighing 29–33 g were maintained individually in plastic cages in a room with a 12:12-hr light-dark cycle (light on at 6.15 a.m.) and constant temperature (23 ± 1°C). Food and tap water were available ad libitum. Two days before start of the experiment mice were acclimatized for 1 hr in a maze with four multiple routes which were connected to a box with tap water and food (banquet room). Mice reaching this box 3 times in 1 hr were used as subjects. The mice were deprived of their food for 24 hr. The starvation started from 8 a.m. Mice were divided into 6 groups of 9 mice. Thirty minutes before end of starvation the control group injected s.c. with physiological saline solution, and two groups each were injected s.c. with QP at 1 (QP-1) or 2 (QP-2) mg/kg b.w., respectively. Ten minutes prior to the end of starvation the remaining group and one each of the QP-1 and QP-2 groups were injected i.p. with DZP at 1 mg/kg b.w.

Mice starved for 24 hr were introduced individually into the system with four multiple mazes to explore for food. The time from the subject entering the system to reaching the banquet room was shown as the latent period. The time till beginning to eat food after entering the banquet room was shown as the latent period. In separate experiments, feeding times during 3 hr after the starvation were measured at consecutive 30-min intervals. Statistical analysis was performed using analysis of variance (ANOVA). The data were then analyzed further using Fishers PLSD as a post hoc test following ANOVA. A probability of less than 0.05 was defined as statistically significant. All the data were expressed as means ± SE.

RESULTS

DZP showed a hyperphagic effect (Figs. 1 and 2), and this effect was restricted to the first 30-min interval (Fig. 1). QP had no significant effect on total feeding for 3 hr, but reduced the feeding up to the 2nd 30-min interval, then facilitated it and was followed by a decline, thus producing a bell shaped profile for feeding (Fig. 1). The hyperphagic effect of DZP was canceled by pretreatment with QP (Figs.
1 and 2). It was noteworthy that QP alone induced hyperactivity in locomotion. This included running in the banquet room and restless at the food. A small dose (0.1 mg/kg) of QP had no intrinsic effect on food consumption, but it blocked the hyperphagic effect of DZP (data not shown).

DZP had no significant effect on the time to banquet but markedly shortened the latent period (Fig. 3). In contrast to this effect QP alone markedly lengthened both the time to banquet and the latent period (Fig. 3). The shortening of the latent period by DZP was reduced by pretreatment with QP (Fig. 3, right panel). QP (0.1 mg/kg) never lengthened these times, but canceled the effect of DZP (data not shown).

DZP had a stimulatory effect on feeding frequency for all the 30-min intervals except the third one (Fig. 4). Both QP-1 and QP-2 reduced the frequency at the first 30-min interval, thereafter increasing it above that of the control, more markedly in the case of QP-2 (Fig. 4). The stimulatory effect of DZP for only the first 30-min interval was inhibited by the pretreatment with QP-1 and QP-2 (Fig. 4). This protective effect was confirmed in measuring feeding frequency for 3 hr (Fig. 5). A small dose of QP (0.1 mg/kg) had no effect on the feeding frequency at any of the intervals, but inhibited the stimulatory effect of DZP (data not shown).

DISCUSSION

The present experiment showed that 1) DZP had a hyperphagic effect; 2) this effect was related not to shortening of the time to banquet but to shortening of the latent period; 3) the hyperphagic effect was canceled by QP; and 4) the shortening of the latent period was also inhibited by QP. Thus the hyperphagia induced by DZP might be related to persistence in the search for food. It is possible that DZP acts on dopamine D2 receptors in this process. This possibility is supported by the following
Amphetamine can induce hyperactivity possibly via the dopamine D2 system [16]. In this type of hyperactivity the D2 system might work in the caudate-putamen [24], striatum [1, 23, 28] and nucleus accumbens [6, 8, 15, 21, 24, 28]. Such a system in the nucleus accumbens might be available for spontaneous locomotion [11]. QP has a biphasic effect on locomotion [15, 32]. This effect depends on the dose and initial level of activity [31] as well as temporal and environmental conditions [27]. The nucleus accumbens may have a major role in foraging since activation of the perifornical lateral hypothalamus increases during the release of dopamine and its metabolism in the nucleus accumbens but not in the striatum [8, 13, 20, 21]. The shell of this region has been proposed as having preferential involvement in feeding [26]. The interaction of \(\gamma\)-aminobutyric acid (GABA), an agonist, with dopamine D-2 and D-1 receptors in this region can elicit feeding responses [25] and exploratory behavior [30]. In contrast, D2 activation in the striatum inhibits the release of GABA [22]. D2 activation in the perifornical lateral hypothalamus [2, 3] can induce feeding [19, 33] and drinking as well as exploratory behavior [16]. The nucleus accumbens may have a role in food reward, and interference in this region can affect harmfully feeding-related memory processes and feeding motives [8, 9]. The striatum may contribute to an impairment of feeding and food handling [23], whereas the GABA system was believed to be a target of DZP to induce hyperphagia. Therefore, it is possible that hunger induced by DZP will activate the dopamine D2 system in the perifornical lateral hypothalamus which in turn activates the nucleus accumbens [8, 9] to search for food and water as well as the striatum for stimulating the ingestive behavior [7].

In conclusion these observations support the idea that DZP-induced hyperphagia is mediated in part by the dopamine D2 system [10] by interfering with the feeding motive.

REFERENCES

7. Ferrari, F., Pelloni, F. and Giuliani, D. 1975. Lesions of the...
terminal fields are necessary for normal locomotor and investigatory exploration in rats. Brain Res. 199: 359–384.