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Novel Benzodiazepine Receptor Ligands: Palatable Food Intake Following Zolpidem, CGS 17867A, or Ro23-0364, in the Rat

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YERBURY, R. E. AND S. J. COOPER. *Novel benzodiazepine receptor ligands: Palatable food intake following zolpidem, CGS 17867A, or Ro23-0364, in the rat.* PHARMACOL BIOCHEM BEHAV **33**(2) 303–307, 1989.—The potent imidazopyridine hypnotic, zolpidem, binds to central benzodiazepine receptors and has predominantly sedative properties, as determined in animal models. In tests of palatable food consumption in nondeprived male rats, the present results indicate that zolpidem (0.3–3.0 mg/kg) had no effect on food intake. Its lack of effect contrasts sharply with other benzodiazepine agonists which strongly stimulate palatable food intake. Two other novel compounds, both of which bind to benzodiazepine receptors, and which have reduced propensity to induce sedative effects, increased palatable food consumption, although in differing ways. The imidazobenzodiazepine Ro23-0364 (0.3–10.0 mg/kg) dose-dependently increased feeding in the standard procedure, but failed to stimulate food intake in presatiated animals. The pyrazoloquinoline CGS 17867A (1.0–30.0 mg/kg) increased food intake in both test procedures, although the dose-effect relationship was nonmonotonic. Taken together, the data indicate a probable separation between hyperphagic and sedating effects of benzodiazepine receptor agonists. If zolpidem's sedative effect is linked to an action at a receptor subtype (benzodiazepine Type 1 or ω_1), then the hyperphagic effect of benzodiazepines may depend more on the alternative subtype.

Zolpidem Ro23-0364 CGS 17867A Benzodiazepines Feeding Palatability Rats

FAMILIAR benzodiazepines, e.g., chlordiazepoxide, diazepam, midazolam, increase food consumption in food-deprived rats eating standard laboratory chow (9,29) and in nondeprived animals eating palatable sweet mash (12,15). The increased consumption of palatable food is due to increased duration of eating bouts, and not to an increase in the frequency of eating bouts (16). There is evidence to suggest that the hyperphagic response may be a consequence of interactions with taste-related palatability (7, 18, 39).

The discovery of specific benzodiazepine recognition sites in the central nervous system (8,27) has been followed by a fertile period of drug development, which has considerably expanded our view of the pharmacology of these receptors (24). Amongst the several categories of drugs which are now known to bind to these sites, there are several differences in their behavioral effects. As far as feeding responses are concerned, we know that not only benzodiazepines but also several kinds of nonbenzodiazepines which act as agonists at benzodiazepine sites (e.g., CL 218,872, zopiclone, the β-carbolines ZK 93423, ZK 91296) stimulate food consumption (10,15). On the other hand, the pyrazoloquinolines CGS 9895 and CGS 9896 (3, 5, 6, 41) do not reliably increase the level of food intake and can act as benzodiazepine antagonists (17). So-called "inverse agonists" acting at benzodiazepine receptors significantly reduce food consumption in rats (10,12).

The new compounds acting at benzodiazepine receptors help to throw light on the important behavioral factors which underlie the hyperphagic effect of benzodiazepines. Thus, partial agonists with little propensity to induce muscle-relaxation or ataxia [e.g., the imidazobenzodiazepines Ro16-6028 and Ro17-1812 (23)] nevertheless bring about marked increases in food consumption (40). The pyrazoloquinolines, CGS 9895 and CGS 9896, produce effects in animal tests which are predictive of anxiolytic activity (3, 5, 6, 31, 32, 38), but do not reliably increase food consumption (17). In short, the new drugs provide tools for dissecting separable behavioral effects mediated by drug actions at benzodiazepines receptors (19). There is a strong motive, therefore, for continued investigation of the properties of novel benzodiazepine receptor ligands as they become available.

One of the most interesting new drugs is the imidazopyridine, zolpidem (2). It binds with high affinity to benzodiazepine recognition sites, with selectivity for the Type 1 site (1,21). [It can be noted that an alternative designation for benzodiazepine recep-

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tor subtypes has recently been proposed, namely ω_1 and ω_2 recognition sites (25).] Zolpidem is a selective hypnotic, and also has behavioral effects indicative of some anxiolytic activity (20, 21, 28, 33). Our first aim was to determine whether or not zolpidem, as an agonist selective for Type 1 (or ω_1) recognition sites, would affect food consumption in nondeprived rats. Two other newly-described drugs were tested, both of which have been described as having anxiolytic properties with reduced capacity to induce side-effects. The first is Ro23-0364 (26,37), and the second CGS 17867A (4). Since neither compound has been tested for its effects of food consumption, they were included in the present series of experiments.

Each of the three compounds was tested in nondeprived animals trained to eat a familiar sweetened mash, under conditions of no presatiation and of partial presatiation, respectively (10,12).

METHOD

Animals

The subjects were 50 adult male rats (hooded General strain) which were bred in the Department of Psychology. They were housed individually in stainless steel cages with continuous access to standard laboratory food pellets (modified diet 41B, Heygate and Sons, U.K.). They were maintained under a 12-hr light–12 hr dark cycle (lights on at 7 a.m.) and the room temperature was maintained at 21–22°C. The animals were weighed regularly before drug testing to accustom them to being handled. They were in the weight range 250–400 g at the start of testing.

Drugs

Zolpidem (N,N,6-trimethyl-2-(4-methylphenyl) imidazo [1, 2-a] pyridine-3-acetamide hemitartrate) was supplied by courtesy of Dr. S. Langer, Laboratories d'etudes et de recherches Synthelabo, Bagneux, France. It was dissolved in distilled water, and injected IP in doses of 0.3–3.0 mg/kg, 15 min prior to the test of palatable food consumption. The doses and injection-test interval were based on previously-published results (34). Ro23-0364 (6-[2-chlorophenyl]-4H-imidazo[1,5-][1,4]benzodiazepine-3-carboxamide) was obtained through the courtesy of Dr. J. Sepinwall, Hoffmann-La Roche Inc., Nutley, NJ. It was ultrasonically dispersed in distilled water, to which Tween 80 (2 drops of 10 ml) has been added, and injected IP in doses of 0.3–10.0 mg/kg, 25–30 min prior to the test. CGS 17867A (2-p-chlorophenyl-2,3,6,7,8,9- hexahydropyrazole-(4,3-c) quinoline-3 (5H)-one hydrochloride) was supplied by CIBA GEIGY Corp., Pharmaceuticals Division, Summit, NJ. It was ultrasonically dispersed in distilled water to which Tween 80 had been added, and injected IP in doses of 1.0–30.0 mg/kg, 25–30 min prior to the test. Injection volumes were 1 ml/kg.

Procedure

The animals were first familiarized with the highly palatable diet. Over a period of 10 days, each animal was given a daily 30-min test of food consumption. Animals were transferred individually to test cages (identical to the home cages), and freshly-prepared portions (30–40 g) were placed in clear plastic dishes inside the cage. Standard lab pellets and water were not available during the test period. The diet consisted of 50 ml sweetened condensed milk, 150 ml ground rat maintenance diet No. 1 (Special Diet Services Ltd., Essex, U.K.) and 200 ml distilled water. Within a few minutes of thorough mixing, the food sets to a relatively firm consistency. By the end of the familiarization period, the latency to begin eating the diet was minimal for every animal. Consumption of the diet was measured to the nearest 0.1 g, with corrections made for spillage.

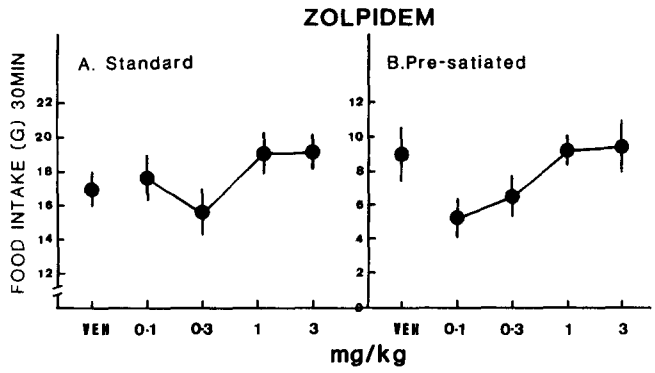

FIG. 1. Zolpidem (0.1–3.0 mg/kg IP) failed to affect palatable food intake in a 30-minute test, in either standard or presatiated conditions. Results are shown as means ± S.E.M. (N = 9, standard; N = 10, presatiated).

Animals were first tested following drug administration in a presatiated condition (10). This procedure is designed to lower the baseline level of consumption and to test animals in a partially-satiated condition. Animals had 10-min access to the palatable diet, prior to drug administration. The 30-min intake test followed the stipulated drug-test intervals. The rats were randomly allocated to 5 equal groups (N = 10), according to injection conditions. At least 48 hr elapsed between consecutive drugs (zolpidem, Ro23-0364, CGS 17867A). Following completion of this series, animals were left for 5 days, and were retested with the same drug series in a standard procedure (i.e., no prefeeding before drug administration) (12,15). Baseline levels of food consumption were higher in this procedure. The rats were randomly allocated to 5 equal groups (N = 9, because 2 animals were lost) for each drug condition. The rationale for utilizing the two test procedures was to optimize detection of either increases or decreases in levels of food consumption, and so avoid failing to detect effects of drug treatments.

The food intake data were analysed by one-way ANOVA, followed by Dunnett's *t*-test to compare individual dose treatments against the corresponding vehicle treatment.

RESULTS

Zolpidem

As Fig. 1 indicates, zolpidem (0.1–3.0 mg/kg) had no significant effect on palatable food consumption in nondeprived rats, $F(4,40) = 1.43$, N.S. In the presatiated condition, baseline food intake was reduced, but zolpidem was still ineffective in the 30 min test, $F(4,45) = 2.19$, N.S.

Ro23-0364

Figure 2 shows that Ro23-0364 (0.3–10.0 mg/kg) produced a dose-related effect on palatable food intake, $F(4,40) = 4.32$, $p < 0.01$. Intake was increased significantly at 3.0 and 10.0 mg/kg. In contrast, in the presatiated condition, Ro23-0364 had no significant effect on food intake, $F(4,45) = 1.25$, N.S.

CGS 17867A

This compound was also effective in increasing palatable food intake, $F(4,40) = 4.72$, $p < 0.005$ (Fig. 3). However, the dose-response function was inverted U-shaped, and the peak effect

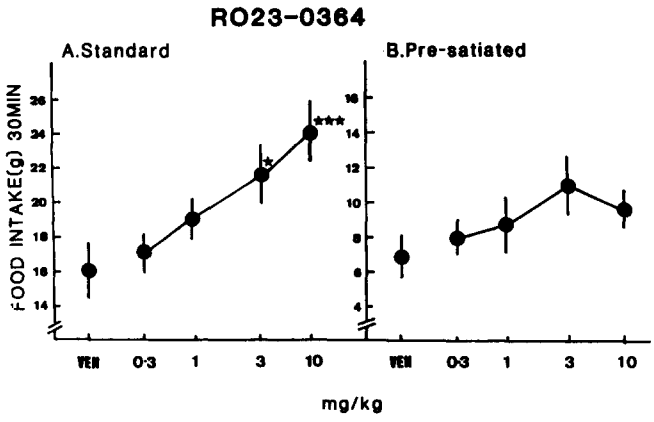

FIG. 2. The novel imidazobenzodiazepine Ro23-0364 (0.3–10.0 mg/kg IP) significantly increased consumption of food in the standard procedure, but had no effect in presatiated animals. Levels of significance: ★$p<0.05$; ★★★$p<0.005$ (Dunnett's t-test).

occurred at 3.0 mg/kg. At 30 mg/kg, CGS 17867A did not significantly increase food intake. In presatiated animals, CGS 17867A increased palatable food consumption at 1 and 3 mg/kg, but not at 10 and 30 mg/kg (Fig. 3).

DISCUSSION

One of the most interesting results to emerge is that the selective hypnotic, zolpidem, had no effect on food consumption under either test condition.This contrasts with a series of experimental reports which indicate that zolpidem produces effects in animal models which are predictive of clinical efficacy as anxiolytics: acquisition of conditioned fear in mice (33); activation of dopamine metabolism of tail-pinch stress (20); punished drinking in rats (21). Zolpidem also has a potent sedative action, reducing locomotion in mice (33), as well as reducing rates of operant responding in rats (34). The discriminative stimulus properties of zolpidem have been investigated by Sanger and his colleagues (30, 34, 35).

He concludes that the zolpidem stimulus is probably more closely associated with sedation, rather than with its anxiolytic action (30). Since zolpidem binds selectively to Type 1 (ω_1)

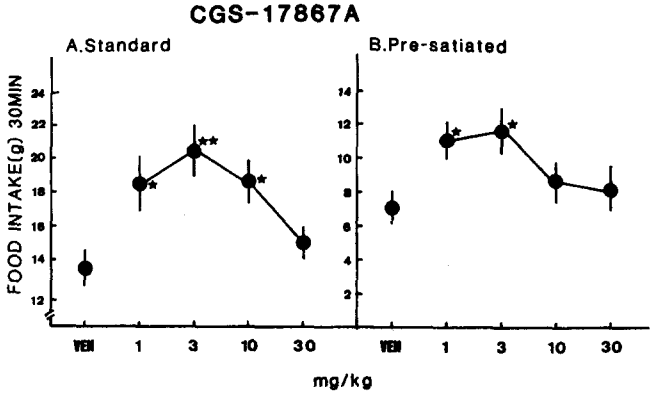

FIG. 3. The novel pyrazoloquinoline CGS 17867A (1.0–30.0 mg/kg) significantly increased palatable food consumption, but the dose-effect relations were inverted U-shaped. Significant effects were found at lower doses. Levels of significance. ★$p<0.05$; ★★$p<0.01$ (Dunnett's t-test).

recognition sites (1, 2, 25), it is possible that zolpidem's selective sedative action is linked to preferential activity at this subtype of benzodiazepine receptors, although this is at present a speculative idea (30).

Behaviorally, zolpidem is of considerable interest since it possesses selective sedative activity, but did not affect food consumption (Fig. 1). Furthermore, over the same dose-range, zolpidem has no effect on saline or water drinking in water-deprived rats (13), even though benzodiazepines like chlordiazepoxide, diazepam or midazolam reliably increase ingestion of saline or water (14,22). Zolpidem does not appear to share, therefore, the effect of typical benzodiazepines to enhance ingestional responses in the rat. Sedation produced by drug action at benzodiazepine receptors may therefore be unrelated to either hyperphagic or hyperdipsic effects. In support of this conclusion, imidazobenzodiazepines which are less potent than full agonists in producing sedation are nevertheless fully effective in increasing the consumption of food or fluids (19,40).

The imidazobenzodiazepine Ro23-0364 exhibits anticonflict properties in both rat and squirrel monkey operant tests of punished responding (37). Unlike diazepam, Ro23-0364 does not reduce motor activity in rats; it antagonizes diazepam-induced deficits in a traction wire test in mice (37). Its profile in the present tests of palatable food consumption is somewhat different from that of classic full agonists like diazepam or midazolam. While Ro23-0364 increased food intake in a dose-dependent manner under the standard procedure, it had no effect in the presatiated condition. In contrast, midazolam, for example, increases food intake irrespective of the degree of presatiation (12). Thus, a relatively small change to the test procedure was sufficient to remove the hyperphagic effect of Ro23-0364.

The pyrazoloquinoline CGS 17867A binds with high affinity to benzodiazepine recognition sites, but the GABA ratio for CGS 17867A is much lower than that for diazepam (4). In behavioral tests, CGS 17867A has effects which are consistent with anxiolytic activity: it antagonizes pentylenetetrazol discriminative stimuli, and has anticonflict effects in rats tested in an operant punishment paradigm (4). Generalization to CGS 9896 discriminative stimuli is also obtained with CGS 17867A (4). In previous experiments, the pyrazoloquinolines CGS 9895 and CGS 9896 failed to affect food consumption, and antagonized the hyperphagic response to the benzodiazepine full agonist, clonazepam (17). CGS 17867A is therefore the first example of pyrazoloquinoline which reliably increases palatable food intake in nondeprived animals. Its effect, however, was not monotonically related to dose, and the largest dose of 30 mg/kg did not increase food consumption. We do not know the reason for the inverted U-shaped dose-response function, but the results suggest that the effects of CGS 17867A are somewhat complex, and a single mechanism of action may not be sufficient to account for the results. In a conflict procedure, CGS 17867A increased punishing responding in rats, but its effect was not markedly dose-related over the range, 3.0–30 mg/kg, PO (4).

In summary, the selective hypnotic zolpidem, which has pronounced sedative effects in rats and mice, did not affect palatable food consumption in nondeprived rats, either in the standard condition or the presatiated condition. On the other hand, both the imidazobenzodiazepine Ro23-0364 and the pyrazoloquinoline CGS 17867A did stimulate increased food consumption. Drugs which act as agonists as benzodiazepine receptors clearly differ in their effects in tests of palatable food consumption. The results indicate the hyperphagic effects of some benzodiazepine agonists may be separable from sedative effects. Differences between Ro23-0364 and CGS 17867A emerged particularly with regard to feeding in the presatiated condition. CGS 17867A increased food intake, whereas Ro23-0364 did not. Both drugs,

however, increased food consumption in the standard test procedure. Hence, combined use of the two procedural variants may be methodologically valuable in discriminating amongst novel benzodiazepine receptor ligands.

After submission of the present paper, a report was published which showed that zolpidem (0.3–3.0 mg/kg) had no effect on food intake in rats habituated to a daily feeding schedule (36). In contrast, chlordiazepoxide (2.5–1.0 mg/kg) significantly increased food intake. Hence, both sets of results are in agreement that zolpidem, unlike other benzodiazepine receptor agonists, does not increase food consumption.

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