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The Benzodiazepine Partial Agonists, Ro16-6028 and Ro17-1812, Increase Palatable Food Consumption in Nondeprived Rats

ROSALIND E. YERBURY AND STEVEN J. COOPER[1]

Department of Psychology, University of Birmingham, Birmingham B15 2TT, U.K.

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YERBURY, R. E. AND S. J. COOPER. *The benzodiazepine partial agonists, Ro16-6028 and Ro17-1812, increase palatable food consumption in nondeprived rats.* PHARMACOL BIOCHEM BEHAV **28**(4) 427–431, 1987.—Two novel imidazobenzodiazepines, Ro16-6028 and Ro17-1812, have been described recently as partial agonists acting at benzodiazepine receptors. In a test of palatable food consumption using nondeprived rats, Ro16-6028 (0.01–10 mg/kg) and Ro17-1812 (0.01–10 mg/kg) were shown to produce dose-dependent increases in food intake. Ro16-6028 was more potent than Ro17-1812. Suriclone, midazolam, and the β-carbolines ZK 93423 and ZK 91296 also significantly increased food intake. The maximum effects of Ro16-6028 and Ro17-1812 were at least equivalent to those obtained with full agonists acting at benzodiazepine sites. Neither Ro16-6028 nor Ro17-1812 reduced locomotion or rearing frequency in an open field test, although there was a reduction in grooming frequency. In contrast, the full agonist midazolam dose-dependently reduced all measures of general activity. The results indicate that some novel benzodiazepine partial agonists strongly stimulate food intake in the absence of side effects typical of the classical benzodiazepines.

Benzodiazepines Ro16-6028 Ro17-1812 β-Carbolines ZK 93423 ZK 91296 Midazolam Suriclone Rats Food intake Palatability

BENZODIAZEPINE-induced hyperphagia [8, 9, 29, 34, 38] is mediated by agonist activity at central-type high affinity benzodiazepine receptors, exhibits stereoselectivity and is blocked by benzodiazepine receptor antagonists, e.g., Ro15-1788 and CGS 8216 [10, 16, 18, 24]. Full agonists, like diazepam, chlordiazepoxide and midazolam, not only increase food consumption but also produce characteristic side effects (sedation, ataxia, muscle relaxation) which greatly affect concurrent behavioural responses [8,17].

Benzodiazepine receptor partial agonists have been introduced which generally retain anxiolytic and anticonvulsant properties, but which have a markedly diminished capacity to produce side effects. The pyrazoloquinolines CGS 9895 and CGS 9896 [2–5, 22] and the β-carboline ZK 91296 [11, 23, 25, 26, 28, 33, 35, 36] are examples of these novel compounds. It is interesting that there is a distinction which can be drawn between these partial agonists, so far as ingestional responses are concerned. While ZK 91296, like full agonists, increased palatable food consumption in nondeprived rats [10,11] and increased ingestion of a hypertonic salt solution in thirsty rats [12], CGS 9895 and CGS 9896 had no effect on either response [12, 14–16]. The pyrazoloquinolines antagonised benzodiazepine-induced hyperphagia [16], consistent with their profile as mixed agonist-antagonists [3,5].

The aim of the present report was to establish the possible effects of two novel benzodiazepine derivatives, Ro16-6028 and Ro17-1812, on palatable food consumption and on general activity in an open field test. Both compounds have recently been described as partial agonists acting at benzodiazepine receptors [29]. They show anxiolytic and anticonvulsant activity, in which they are more potent than diazepam. We were interested in determining if these compounds resemble either the β-carboline ZK 91296 in terms of their effects on food intake, or the pyrazoloquinolines CGS 9895 and CGS 9896 which produce little or no change in food consumption.

For purposes of comparison, and to help in the interpretation of the results obtained with Ro16-6028 and Ro17-1812, the effects of several additional compounds on palatable food consumption were also investigated in the first experiment. These were the benzodiazepine receptor full agonists midazolam, ZK 93423 [35,36] and suriclone [19,21], and the β-carboline partial agonist ZK 91296 [28].

EXPERIMENT 1

The effects of the two novel benzodiazepines, Ro16-6028 and Ro17-1812, on palatable food consumption were investi-

[1]Requests for reprints should be addressed to S. J. Cooper.

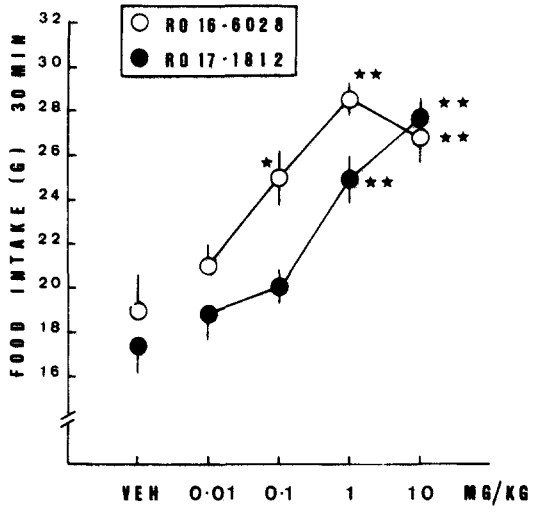

FIG. 1. Ro16-6028 and Ro17-1812 dose-dependently increased the level of palatable food consumption in nondeprived rats over a 30 min test period. Results are shown as mean intake (g) ±S.E.M. N=10 per group. Levels of significance: *$p<0.05$; **$p<0.01$ (Dunnett's t-test).

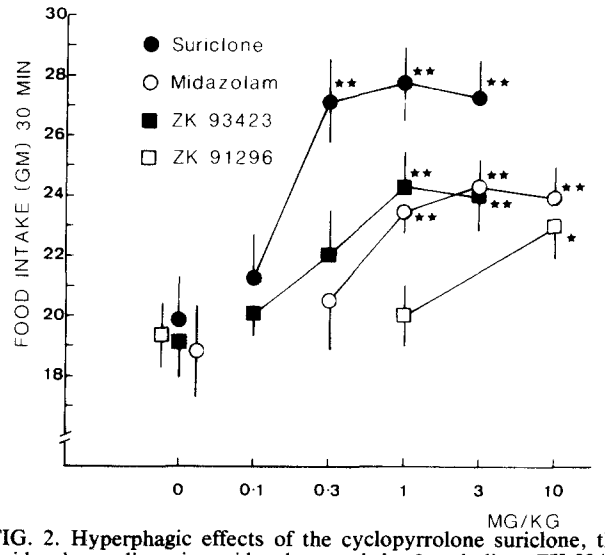

FIG. 2. Hyperphagic effects of the cyclopyrrolone suriclone, the imidazobenzodiazepine midazolam, and the β-carbolines ZK 93423 and ZK 91296 in a palatable food consumption test. ZK 91296 was also tested at 0.1 mg/kg, but had not effect (data not shown). Other details as described in legend to Fig. 1.

gated in nondeprived rats, using methods which have been described in detail previously [13, 14, 16].

METHOD

Animals

The subjects were 50 adult male rats (hooded General strain) which were bred in the animal laboratory of the Psychology Department. 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 220–390 g at the start of testing.

Drugs

The following drugs were used: midazolam bimaleate (supplied by Roche Products Ltd., U.K.); the β-carbolines ZK 93423 and ZK 91296 (6-benzyloxy- and 5-benzyloxy-4-methoxymethyl-β-carboxylic acid ethyl ester, respectively), which were supplied through the courtesy of Dr. D. N. Stephens, Schering, West Berlin; the imidazobenzodiazepines Ro16-6028 (tert-butyl(S)-8-bromo-11, 12,13,13a-tetra-hydro-9-oxo-9H-imidazo [1,5-a] pyrrolo-[2,1-c][1,4] benzodiazepine-1-carboxylate) and Ro17-1812 (cyclopropylmethyl (S)-8-chloro-12, 12a-dihyrdo-9-oxo-9H, 11H - aceto[2,1-c] - imidazo - [1,5 - a][1,4]benzodiazepine - 1 - carboxylate), which were kindly supplied by Professor W. Haefely, Hoffmann-LaRoche, Basel; suriclone (6-(2-chloro-7-naphtyridine [1,8] yl)-5-[(4-methyl-1-piperazinyl) carbonyl-oxy]-7-oxo-2,3,6,7-tetrahydro dithino [1,4] [2,3-c] pyrrole), which was provided by C. Garrett, Rhone-Poulenc Sante, Vitry-sur-Seine, France.

Midazolam bimaleate was dissolved in isotonic saline, and its doses expressed in terms of the salt. The other drugs were prepared by ultrasonic dispersion in distilled water to which Tween 80 was added (2 drops in 10 mg). The suspensions were made up immediately before use. Injections were given by intraperitoneal route 20 min before the test of palatable food consumption.

Procedure

The animals were first familiarized with the highly palatable diet. Over a period of 9 days, each animal was given a daily 30 min test of food consumption. Freshly-prepared portions (30–40 g) were placed in clear plastic dishes inside the home cage. The diet consisted of 50 ml Nestlés 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, this food sets to a relatively firm consistency. By the end of the familiarization period, the latency to begin eating the diet was minimal in every case. Consumption of the diet was measured to the nearest 0.1 g, with corrections made for spillage.

For each drug test, the animals were allocated at random to equal-size groups (N=10), according to vehicle and drug doses conditions. At least 48 hr was allowed between consecutive drug tests. Intake data were analysed by one-way analysis of variance (ANOVA) followed by Dunnett's t-test to compare individual dose treatments against the corresponding vehicle treatment [37].

RESULTS AND DISCUSSION

Ro16-6028 and Ro17-1812

Ro16-6028 (0.01–10 mg/kg) had a significant effect on palatable food consumption in nondeprived rats, $F(4,45)=9.20$, $p<0.001$. As Fig. 1 shows, Ro16-6028 produced a dose-related increase in food intake, with significant effects occurring at 0.1 mg/kg and at higher doses. The maximum level of food consumption was 28.6±0.9 g (mean±S.E.M.) in the 30 min test.

Ro17-1812 (0.01–10 mg/kg) also produced a significant ef-

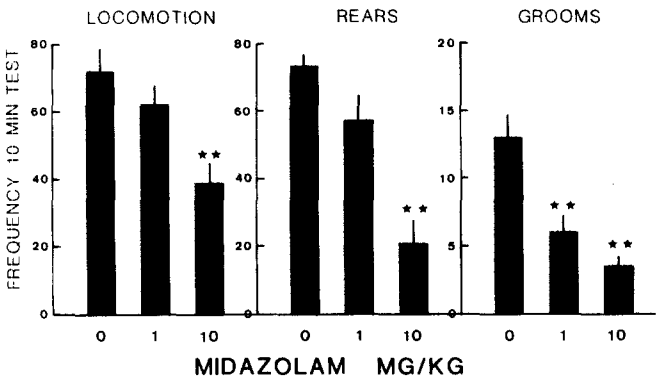

FIG. 3. Effects of midazolam (1 and 10 mg/kg) on frequency of locomotor activity, rearing and grooms in a 10 min test of open field activity. Results are shown as mean+S.E.M. N=per group. Level of significance: $^{**}p<0.01$ (Dunnetts t-test).

fect on food intake, $F(4,45)=14.0$, $p<0.001$. Its effect was dose-related, but it was less potent than Ro16-6028 (Fig. 1). A dose of 1.0 mg/kg was required to produce a significant increase in intake, although the maximum level of intake (27.7±0.9 g) was comparable with that produced by Ro16-6028.

Benzodiazepine Receptor Agonists

Significant increases in palatable food consumption were produced by midazolam, the cyclopyrrolone suriclone, and the β-carbolines ZK 93423 and ZK 91296, respectively (Fig. 2). Effects of suriclone were marked, with a highly significant increase in food intake occurring at 0.3 mg/kg and higher doses. Significant effects were produced by midazolam and ZK 93423 at 1.0 mg/kg, and by the partial agonist ZK 91296 at 10 mg/kg. The maximum effect of these three drugs was slightly less than that produced by suriclone.

These results establish that the two novel benzodiazepines, Ro16-6028 and Ro17-1812, significantly enhanced palatable food consumption in nondeprived rats, and that Ro16-6028 is the more potent of the two. This latter finding confirms results reported in preliminary form by Haefely [20], that Ro16-6028 is more potent than Ro17-1812. Most interestingly, the maximum increases in food consumption produced by the two compounds were equal to, and in some instances, in excess of the hyperphagic effect of several benzodiazepine full agonists. They were clearly more potent than the β-carboline partial agonist, ZK 91296, and are distinguishable from the pyrazoloquinolines, CGS 9895 and CGS 9896, which have relatively little effect on food intake [6, 14, 16, 32].

It was shown previously that ZK 93423 and ZK 91296 increase food intake in partially-satiated animals [10]. The present data confirm their hyperphagic effect, but show that partial satiation before drug administration is not necessary for the effect to occur. The present data also indicate for the first time that suriclone stimulates food consumption. This cyclopyrrolone binds with high affinity to central-type benzodiazepine sites [7], has anxiolytic and anticonvulsant activity [19,21], and is effective as a clinical anxiolytic [1].

EXPERIMENT 2

The aim of the second experiment was to investigate effects of Ro16-6028 and Ro17-1812 on general activity in an open field test. Their effects were compared with those of the full agonist, midazolam. If these novel benzodiazepines are partial agonists [20], we should expect them to have little or no depressant effect on general activity.

METHOD

Animals

The subjects were 50 additional adult male rats of the same strain as those used in the first experiment. They were housed individually under the same conditions as in Experiment 1.

Drugs

Midazolam, Ro16-6028 and Ro17-1812 were prepared as described in the first experiment, and were each tested at two doses, 1.0 and 10.0 mg/kg. These doses were selected as those which produced reliable hyperphagic effects (Figs. 1 and 2). They were injected IP 20 min before the activity test.

Procedure

The general activity test was carried out in a clear, plastic rectangular tank, measuring 45×24 cm in area, and 20 cm high. The floor was subdivided into six equal rectangles (15×12 cm). An animal was placed in the centre of the tank, and the frequencies of locomotion, rearing and grooming were scored over a 10 min period. *Locomotion* was defined as crossing from one floor section to another, when all four paws crossed the dividing line between sections. *Rearing* was recorded when the animal stood on its hindlegs only, and *grooming* was scored for separate episodes of head or body grooming.

The animals were first allocated at random to 5 equal groups, and were allocated to a vehicle condition, Ro16-6028 at 1 and 10 mg/kg and Ro17-1812 at 1 and 10 mg/kg, respectively. Two weeks later, 30 animals were selected at random from this group, and were divided into 3 equal groups, and were re-tested following injection of midazolam at 1 and 10 mg/kg, and isotonic saline vehicle, respectively.

The frequency data were analysed by one-way ANOVA followed by Dunnett's t-test.

RESULTS AND DISCUSSION

Midazolam

Midazolam significantly affected each of the three behavioural categories: locomotion, $F(2,27)=6.84$, $p<0.01$; rears, $F(2,27)=14.17$, $p<0.001$; grooms, $F(2,27)=16.27$, $p<0.001$. In each case, midazolam decreased frequency dose-dependently (Fig. 3). Grooming was most affected, with a reduction to 46.5% of the control value at 1.0 mg/kg of midazolam, and to 27.1% at 10 mg/kg. Locomotion frequency was reduced to 53.5% of the control value at 10 mg/kg, and at the same dose, rearing frequency was reduced to 28.9% of the control value.

Ro16-6028 and Ro17-1812

The data for the two novel benzodiazepines are shown in Table 1. There was no overall difference between groups in terms of locomotion, $F(4,45)=1.81$, N.S. However, there was a tendency for locomotion frequency to increase following 10 mg/kg of Ro16-6028 (a 44% increase above control level). There was a group effect for rearing, $F(4,45)=4.01$, $p<0.01$, and 10 mg/kg of Ro16-6028 produced an increase

TABLE 1

EFFECTS OF THE BENZODIAZEPINE PARTIAL AGONISTS Ro16-6028 AND Ro17-1812 ON GENERAL ACTIVITY MEASURES IN AN OPEN FIELD TEST

Injection Condition	Response Frequency		
	Locomotion	Rears	Grooms
Vehicle	50.2 ±4.9	43.7 ±6.0	12.1 ±2.3
Ro16-6028 (1.0 mg/kg)	58.3 ±5.3	45.8 ±4.0	6.0* ±1.8
Ro16-6028 (10.0 mg/kg)	72.3 ±5.7	65.3† ±6.3	4.8† ±0.9
Ro17-1812 (1.0 mg/kg)	63.3 ±8.6	47.8 ±6.1	7.2 ±2.1
Ro17-1812 (10.0 mg/kg)	55.0 ±5.9	37.1 ±3.3	4.2† ±0.8

Results are shown in terms of mean ± S.E.M. (N=10 per group). Statistical comparisons: *$p<0.05$; †$p<0.01$ (Dunnett's t-test).

that was significant (a 49.4% increase above control level). Ro17-1812 (1.0 and 10 mg/kg) had no effect on either locomotion or rearing. The frequency of grooming was affected by both compounds, $F(4,45)=3.56$, $p<0.05$, and significant decreases occurred at both doses of Ro16-6028 and at the higher dose of Ro17-1812.

Midazolam, as a full agonist, produced dose-related decreases in locomotion, rearing and grooming, at doses which had significantly hyperphagic effects. At 10 mg/kg, rats treated with midazolam show appreciable side effects (sedation, ataxia, muscle relaxation), and these are most probably responsible for the reductions in general activity measures. These results are consistent with our earlier observations concerning midazolam's effects on nonfeeding behaviour within the palatable food consumption test [17].

In contrast Ro16-6028 and Ro17-1812 did not produce general depressant effects at doses which markedly stimulated food consumption. These observations agree with the report of Haefely [20]. Furthermore, recent results of Sanger indicate that neither compound reduced operant response rates in a drug discrimination test [30]. Nevertheless, we detected some effects on behaviour in the open field test. At 10 mg/kg, Ro16-6028 had a slight stimulant action, and locomotion and rearing frequencies were increased to approximately the same degree. This effect was not observed with Ro17-1812. Both drugs reduced grooming frequency, but it is not clear why this response was affected in this way. One possibility is that it may reflect some anxiolytic activity, but a residual depressant effect cannot be discounted.

GENERAL DISCUSSION

The two novel benzodiazepines, Ro16-6028 and Ro17-1812, markedly increased the consumption of a palatable diet by nondeprived rats, at doses which did not depress locomotion and rearing frequency in an open field test. In these respects, they are similar to the β-carboline partial agonist, ZK 91296, which also has a hyperphagic effect (Figs. 1, 2).

Sanger has demonstrated that Ro16-6028 and Ro17-1812 produce effects which generalise to the discriminative cue of chlordiazepoxide [30]. At 1.0 mg/kg, both compounds produced 88% responding on the drug lever, and 100% generalisation at 10 mg/kg. Response rates were not produced at these doses. Our present data indicate that at the same doses, both compounds produced substantial hyperphagic effects, and that a significant effect of Ro16-6028 was also detected at the lower dose of 0.1 mg/kg. Taken together, both studies indicate that the two benzodiazepines produce behavioural effects (hyperphagia, generalisation to a benzodiazepine discriminative cue) which match the maximal effects of full agonists, in the absence of appreciable side effects.

In terms of anxiolytic and anticonvulsant activity, Ro16-6028 and Ro17-1812 share effects with other benzodiazepine partial agonists, ZK 91296, CGS 9896 and CGS 9895 [2–5, 28, 39]. In addition, they share with ZK 91296 and CGS 9896 the property of giving rise to benzodiazepine discriminative cues in drug discrimination studies [4, 28, 30]. Most importantly, however, a fundamental distinction emerges between these compounds when ingestional responses are considered. While Ro16-6028, Ro17-1812 and ZK 91296 act as agonists and stimulate food consumption, the pyrazoloquinolines (CGS 9896 and CGS 9895) have little or no agonistic activity in studies of food intake, but exhibit marked antagonist effects [6, 14–16, 32]. In a similar way, it has been shown recently that Ro16-6028, Ro17-1812 and ZK 91296 act as agonists in a test of hypertonic saline consumption, while the pyrazoloquinolines showed no agonist activity [12].

It remains to be seen if all behavioural effects of these novel benzodiazepine receptor ligands can be explained solely in terms of partial agonist activity at a single receptor. There is interest in the alternative view that selective agonist (or mixed agonist and antagonist) action may occur at functionally distinct sub-types of benzodiazepine receptors [15, 22, 27, 30, 33]. Further research should help to resolve this critical issue.

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