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Feeding Elicited by Benzodiazepine-like Chemicals in Puppies and Cats: Structure-Activity Relationships

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DELLA-FERA, M. A., C. A. BAILE AND C. L. MCLAUGHLIN. *Feeding elicited by benzodiazepine-like chemicals in puppies and cats: structure-activity relationships.* PHARMAC. BIOCHEM. BEHAV. 12(2) 195–200, 1980.—To assess the relationship between the structure of benzodiazepines and their activity as feed intake stimulants, benzodiazepines of different structural subclasses were given *per os* as a drench to puppies and young cats. The chemicals included diazepam (D), elfazepam (E), a 1,5 benzodiazepine (WE405), a triazolobenzodiazepine (U31889), a l-pyridyl triazolobenzodiazepine (U37576), and a thienotriazolodiazepine (WE941). Although all chemicals increased feed intake, there were definite structure-activity differences as well as differences in sensitivity between the cats and puppies. In the puppies, U37576 was the most potent chemical (least chemical required), while E elicited greater feeding responses compared with U37576. In the cats E also stimulated the most feeding, but WE941 and U31889 were the most potent chemicals. WE405 was the least effective chemical in puppies but worked well as a stimulant of 24-hr feed intake in cats. The cats were approximately 2 (U37576) to 7 (D) times more sensitive (mg/kg b.w.) than the dogs to the effects of the chemicals. Time patterns of feeding varied among the chemicals and in general were similar for both puppies and cats. All the chemicals except E caused some degree of either ataxia or excitement in both puppies and cats. Thus, based on its effectiveness as a feed intake stimulant, as well as its lack of undesirable side effects, E is proposed to be most useful therapeutically as an oral feed intake stimulant for these species.

Benzodiazepines Chemically stimulated feeding Cats Dogs Food intake Diazepam Elfazepam

ALTHOUGH benzodiazepines have been extensively studied for their activities as antianxiety agents, muscle relaxants, sedatives, and antiepileptic agents, interest in their action as feed intake stimulants has been increasing only recently. In 1960 Randall [21] showed that injections of benzodiazepines in rats elicited feeding behavior and this was later shown to occur in other animals also [4, 9, 11]. While the mechanism of benzodiazepine-induced feeding is not yet known, several explanations have been suggested. For example, Margules and Stein [16] proposed that benzodiazepines acted by attenuating emotionally inhibitory influences on feeding, but more recent evidence indicates that these chemicals have a direct effect on hunger-satiety mechanisms [27].

Pharmacological studies have revealed structure-activity relationships among the benzodiazepines, and this information has been used to develop derivatives that are highly potent in one activity relative to others. Certain changes made in the basic structure, e.g., substitution of halogen at specific sites, will consistently increase biological activity. Banziger [5] was one of the first to show that various substitutions produced compounds having diverse anticonvulsant activities. For example, diazepam was found to differ from chlordiazepoxide in duration of action against pentylenetetrazol (metrazol)-induced seizures in both mice and rats, and in cats chlordiazepoxide produced sedation while diazepam produced ataxia as well as sedation. Although Banziger did not associate any particular type of substitution with activity, it was later noted that incorporation of halogen in the ortho position of the 5-phenyl ring of diazepam enhanced the biological activity of the resulting compound [25]. Structure-activity relationships have been shown for the feeding effect of the benzodiazepines also [4].

While the reason for these structure activity differences is not certain, it has been suggested to be related to specificity at binding sites. Recently, specific CNS benzodiazepine receptors have been discovered in a wide range of species [18, 19, 20, 24], and a study showing correlation of in vitro binding affinity of benzodiazepines to the receptor with in vivo anxiolytic activity may provide an explanation for structural variations in activity [18]. In this paper we report our findings of structure-activity relationships of benzodiazepines of different subclasses and feeding behavior in puppies and cats.

METHOD

Puppies

Four mixed-breed puppies were used (two males and two females of the same litter). They were housed in individual cages with a balanced dry puppy chow (Purina Puppy Chow) in self-feeders that were filled periodically to maintain continuous ad lib feeding.

Treatments for each test were assigned randomly in a four by four Latin square design and included carrier and three chemical treatments administered *per os* as a drench once daily on consecutive days. Feed intake was measured 30, 60 and 90 min, and 24 hr after treatment. Treatments included three doses each of diazepam (D), Fig. 1, elfazepam (7-chloro-1-[2-(ethyl-sulfonyl)ethyl]-5-(2-fluorophenyl)-1,3-dihydro-2 *H*-1,4 benzodiazepin-2-one) (E), WE405 (7-chloro-1-methyl-5-(2-trifluormethylphenyl)-1H-1,5 benzodiazepine -2,4-[3H, 5H]-di-one), U37576 (8-chloro-1,-(3-pyridyl)-6-phenyl-4H-S-triazolo [4,3-α][1,4]benzodiazepine), and WE941 (8-brom-6-(2-chlorophenyl)-1-methyl-4H-thieno- [3, 2-F][1, 2, 4] triazolo [4,3-a][1,4]diazepin). The carriers were 2.0 ml 50% propylene glycol (PG) in water (D, E, WE405) or 1.0 ml ethanol (WE941, U37576). Average puppy weights were 7.5, 5.0, 7.2, 6.3 and 5.0 kg, respectively, during testing of each chemical above. In the final test, doses of WE941, U37576 and elfazepam eliciting the greatest food intake response during the first 60 min were compared directly; where two doses had nearly equal feeding responses at 60 min, the dose which had greater effects at other time periods was chosen. These treatments and the carrier (1.0 mg ethanol) were assigned randomly in a four by four Latin square design (average puppy weight=8.0 kg). The data were tested for significant differences by analysis of variance and Duncan's multiple range test.

Cats

Twelve domestic shorthair cats were used. They were housed in individual cages with continuous availability of a balanced dry cat chow (Purina Cat Chow). Based on body weight, two groups of six cats were formed. Treatments for each test were assigned randomly to each group in six by six Latin square designs and included sham, carrier, and four chemical doses administered *per os* as a drench once daily. Fresh feed was provided one hour before treatment to assure satiation; all cats ate during this period. Feed intake was measured 30, 60 and 120 min and 24 hr after treatment. The chemicals tested included D, E, WE405, U31889 (8 chloro-6phenyl-1-methyl 4H-s-triozolo 4.3-α,[1,4]benzodiazepine), U37576 and WE941, Fig. 1. The cats increased in weight from an average of 2.5 kg at the beginning of the study to an average of 3.6 kg at the end. In the final test WE941, U37576, U31889, E, and D were compared directly using a randomized six by six Latin square design to assign treatments.

The data were tested for significant differences by analysis of variance and Duncan's multiple range test.

RESULTS

Puppies

Feed intakes during the first 60 min are shown in Table 1. Each chemical elicited a significantly greater feeding response compared with the carriers following the administration of at least one dose. To facilitate comparison of responses among chemicals, the feed intake for the dose of each chemical eliciting the most feeding was adjusted for the animal's metabolic mass ($g/kg_{bw}^{.75}$) [14] during each of the chemical treatment sets, Table 2. Analysis of variance performed on the adjusted carrier intakes from each of the chemical treatment sets revealed no significant differences; therefore, a mean control intake was calculated for each puppy at each time period. All chemicals caused an increase of feed intake for the first 90 min although the degree of increase varied. E and WE405, the only 1,5 benzodiazepine of the series, elicited greater feeding responses during the first 90 min than the other chemicals, $p<0.05$, Table 2. E elicited greater 24 hr intakes than the other chemicals, $p<0.01$. U37576, a 1-pyridyl triazolobenzodiazepine, was

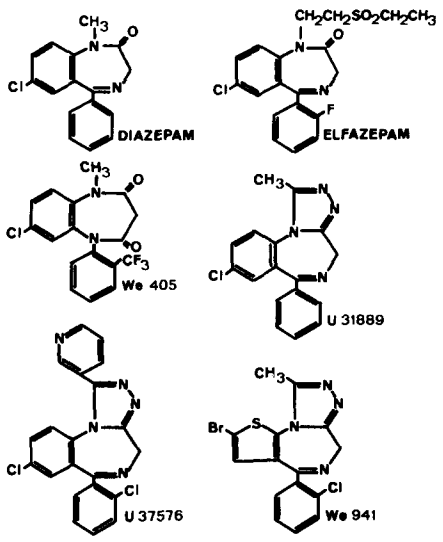

FIG. 1. Structures of benzodiazepine derivatives.

TABLE 1

FOOD INTAKE (G ± SEM) OF DOGS FOLLOWING INTRAGASTRIC TUBING WITH CARRIER AND THREE DOSES EACH OF DIAZEPAM, ELFAZEPAM, WE405, U37576 AND WE941

Chemical	Dose mg/kg	Food intake (g/dog) 0–60 min
Diazepam	0	24 ± 3.8[a]
	7.0	66 ± 34.2[ab]
	14.0	113 ± 28.7[b]
	28.0	89 ± 9.5[ab]
Elfazepam	0	25 ± 2.9[x]
	5.0	91 ± 2.9[xy]
	10.0	133 ± 3.3[y]
	20.0	127 ± 2.4[y]
WE405	0	23 ± 8[a]
	10.5	63 ± 13[ab]
	21.0	96 ± 22[b]
	42.0	71 ± 13[ab]
U37576	0	12 ± 8.5[a]
	0.16	67 ± 11.9[b]
	0.32	66 ± 6.7[b]
	0.64	117 ± 17.5[b]
WE941	0	33 ± 2.9[a]
	0.25	58 ± 17.1[ab]
	0.50	76 ± 13.8[b]
	1.00	82 ± 6.6[b]

[ab]Means not having a common superscript are different, $p<0.05$.
[xy]Means not having a common superscript are different, $p<0.01$.

TABLE 2

FOOD INTAKE [G/(KG BODY WT)$^{.75}$] FOLLOWING THE INTRAGASTRIC TUBING OF DOGS WITH THE DOSES OF DIAZEPAM, ELFAZEPAM, WE405, U37576, AND WE941 ELICITING THE GREATEST FEEDING RESPONSE

Time period min	Treatment 0.0	Diazepam 14 mg/kg	Elfazepam 20 mg/kg	WE405 21 mg/kg	U37576 0.65 mg/kg	WE941 1.0 mg/kg
0–30	3.6^{x} ±0.5	16.1^{xy} ±4.5	27.5^{y} ±3.6	8.3^{x} ±1.8	24.2^{y} ±2.7	24.1^{y} ±2.1
0–60	5.9^{x} ±1.9	24.9^{yz} ±6.3	38.2^{z} ±3.5	8.3^{xy} ±1.8	29.4^{z} ±4.4	24.1^{yz} ±2.1
0–90	7.8^{a} ±3.0	25.9^{b} ±6.2	42.9^{c} ±6.0	42.9^{c} ±4.9	27.0^{b} ±4.4	24.9^{b} ±1.9
24 hr	87.5^{x} ±8.5	89.5^{x} ±9.0	143.0^{y} ±12.3	91.0^{x} ±11.4	105.0^{x} ±10.0	104.0^{x} ±7.2

[abcd]Means not having a common superscript are different, $p<0.05$.
[xyz]Mean not having a common superscript are different, $p<0.01$.
*Treatment probability based on 2-way analysis of variance.

TABLE 3

FOOD INTAKE (G) FOLLOWING INTRAGASTRIC TUBING OF DOGS WITH CARRIER AND ONE DOSE OF ELFAZAPAM, WE941 AND U37576

Time period min	Treatment Carrier	Elfazepam 20 mg/kg	WE941 1.0 mg/kg	U37576 0.65 mg/kg
0–30	9^{a} ±4.8	168^{c} ±25.2	92^{b} ±11.1	105^{bc} ±33.8
0–60	23^{a} ±13.9	206^{c} ±13.0	92^{b} ±11.5	122^{b} ±38.4
0–90	36^{a} ±26.9	215^{c} ±12.1	92^{a} ±11.8	125^{b} ±39.6
24 hr	335^{a} ±43.7	600^{c} ±33.1	342^{a} ±29.3	459^{b} ±32.2

[abc]Means not having a common superscript are different, $p<0.05$.
*Treatment probability based on 2-way analysis of variance.

the most potent chemical with only 0.16 mg/kg required to increase feed intake after 60 min, Table 1. WE941, a triazolo-derivative of a thienodiazepine, was nearly as potent, although the feeding responses were not quite as great.

The type and amount of secondary behavioral changes produced by the chemicals also differed. Treatment with D resulted in ataxia which lasted up to 1 hr after treatment. WE405 caused excitement in the first 30 min as did U37576; however, after 30 min, treatment with U37576 resulted in ataxia lasting at least 1 hr. WE941 produced the most serious behavioral changes. In the first 30 min, the puppies showed a considerable amount of excitement, as manifested by barking, salivation and nonspecific biting. This was followed by a period of ataxia and sedation. E was the only chemical which produced no secondary behavioral changes.

In the study comparing directly the best doses of WE941, U37576 and E (Table 3), the initial responses were generally confirmed. The three chemicals selected for this test had had the greatest effect on 24 hr intakes during the initial test. U37576 increased feed intake over all time periods, but E caused significantly more feeding than U37576 during the 60 and 90 min and 24 hr postinjection periods. WE941 elicited a shorter and lesser feeding response. The types of secondary behavioral changes seen in the dose response tests were also seen in the comparison test.

Cats

The 60 min feed intakes of the dose response tests are shown in Table 4. All chemicals except U37576 and WE405 elicited a marked feeding response during the first 60 min postinjection. No differences were found between the sham and carrier treatments, $p<0.05$. As with the puppies, the feed intake data were adjusted for metabolic mass ($g/kg_{bw}^{.75}$) to facilitate comparisons between the "best doses" for each chemical. Overall there were no significant differences among the sham and the carrier treatments, $p<0.05$. The analysis of variance included the means for the sham and carrier treatments, Table 5. D, E, and WE941 increased intake at all time periods. While WE405 had no effect in the early postinjection period but increased the 24 hr intake, U31889 only increased intake in the first 2 hr ($p<0.01$) and not in the 24 hr postinjection period. Although U31889 elicited a marked feeding response at even the 0.06 mg/kg dose, U37576, which has a very similar structure, did not elicit feeding in the cats even at the 0.16 mg/kg dose, Table 4.

In the final cat experiment, doses of D, E, U31889, and WE941 which elicited the most feeding were compared directly. In addition, because of the unexpected lack of response to U37576, a higher dose of this chemical was included as a treatment. All chemicals elicited a marked feeding response at all time periods including the 24 hr postinjection period, Table 6. The means were highest for E for all periods except 30 min.

These chemicals also caused a variety of secondary behavioral changes in the cats, as in the puppies. In some cats

TABLE 4

FOOD INTAKE (G ± SEM) FOLLOWING INTRAGASTRIC TUBING OF CATS WITH CARRIER AND FOUR DOSES EACH OF DIAZEPAM, ELFAZEPAM, WE405, U31889, U37576 and WE941

Chemical	Dose mg/kg	Food intake (g/cat) 0–60 min
Diazepam	sham	12.4 ± 2.1^{x}
	0	9.2 ± 2.1^{x}
	0.25	13.8 ± 1.7^{xy}
	0.50	25.8 ± 5.4^{xyz}
	1.0	32.0 ± 5.0^{yz}
	2.0	35.5 ± 8.1^{z}
Elfazepam	sham	7.7 ± 1.0^{w}
	0	10.8 ± 1.3^{wx}
	0.50	14.3 ± 1.4^{wxy}
	1.0	16.1 ± 1.9^{xy}
	2.0	20.4 ± 2.7^{yz}
	4.0	26.4 ± 3.9^{z}
WE405	sham	8.5 ± 1.5
	0	8.2 ± 1.2
	0.50	7.6 ± 2.8
	1.0	14.3 ± 2.7
	2.0	8.5 ± 2.2
	4.0	13.9 ± 3.3
U31889	sham	7.5 ± 3.3^{x}
	0	5.4 ± 0.5^{x}
	0.03	15.9 ± 2.6^{xy}
	0.06	26.0 ± 4.0^{yz}
	0.12	36.4 ± 7.5^{z}
	0.25	40.6 ± 6.6^{z}
U37576	sham	8.7 ± 2.4
	0	8.7 ± 1.9
	0.02	12.4 ± 3.7
	0.04	11.7 ± 4.4
	0.08	15.3 ± 3.1
	0.16	13.3 ± 2.6
WE941	sham	9.0 ± 1.7^{x}
	0	8.5 ± 2.6^{x}
	0.03	29.9 ± 4.5^{y}
	0.06	26.5 ± 4.6^{y}
	0.12	34.1 ± 2.8^{y}
	0.25	35.4 ± 4.4^{y}

^{wxyz}Means not having a common superscript are different, $p<0.01$.

D caused tranquilization and ataxia for at least 2 hr after treatment. Neither E nor WE405 caused any significant changes. U31889, U37576 (0.32 mg/kg), and WE941 all caused excitement and ataxia of varying degrees of severity with U31889 causing the least and WE941 the most severe changes.

DISCUSSION

Our results confirm and extend reports of structure-activity relationships of various benzodiazepines and show that both puppies and cats will respond to the feed intake stimulating properties of benzodiazepines administered orally. Elfazepam, containing an orthofluorphenyl, was indeed more potent than diazepam, which has only an unsubstituted phenyl. The lack of sedation and ataxia following elfazepam administration also supports the finding that a terminal ethyl in 1-alkylsulfonylalkyl derivatives could cause a separation in sedative and feed intake stimulating properties. The 1,5 benzodiazepine WE405 was one of the less effective chemicals tested. The triazolo compounds U37576, U31889, and WE941 were the most potent; however, the maximum feeding response was not as great as that following elfazepam treatment. Although elfazepam and U37576 consistently elicited the greatest feeding response in the puppies, U37576 proved to be one of the less effective feed intake stimulants in the cats, while elfazepam was the most effective. Cats generally required much smaller doses per unit of body weight than did the dogs for a maximum feeding response; cats were also more sensitive to the other behavioral effects of the chemicals. However, we have no explanation for the unexpectedly similar dose of U37576 required to elicit feeding in cats and dogs. The structurally similar chemical U31889 elicited feeding in cats at one fifth the dose required for U37576.

The acute effects on feeding patterns also varied between chemicals. In general, treatment with WE941 caused feeding primarily in the first 30 min, while feeding after WE405 occurred later: after 30 min in the puppies and after 1 hr in the cats. Feeding after U37576 and diazepam occurred in the first 60 min. Feeding after elfazepam began immediately and continued for up to 2 hr after treatment. The secondary behavioral effects (e.g., excitement) following treatment with U37576 or WE941 were somewhat unexpected; however, there have been reports of "paradoxical" rage or excitement in humans treated with benzodiazepines [23]. Although we did not test for the possibility of development of tolerance to the feeding effect of these chemicals, this problem has been discussed by Wise and Dawson [27], who showed that tolerance did not develop to the feeding elicited by benzodiazepines in rats. Due to its effectiveness in both stimulating feeding within 2 hr and increasing 24-hr intake as well as its lack of undersirable side effects, elfazepam is a good candidate for use as a feed intake stimulant in treating anorexia in diseased and debilitated cats and dogs.

Since the early 1960's, the benzodiazepines have been shown to stimulate feeding in a variety of animals [21]. This property had earlier been explained in terms of ability of these chemicals to disinhibit suppressed behavior [16], and thus it reflected their anxiolytic effect. There is now evidence that this effect on feeding is specific [27]. Benzodiazepines vary widely in relative potency of their activities, i.e., muscle relaxant vs anxiolytic vs sedative. Many studies have shown that these variations reflect structural differences between benzodiazepine derivatives. For example, the addition of halogen to the 7 position or the orthophenyl position has been shown to change the relative effectiveness of various types of benzodiazepines [2, 8, 13]. In studies with several l-(alkyl-sulfonyl alkyl) 1,4 benzodiazepines, definite structure-activity relationships were shown with these compounds in the feeding behavior of sheep [4]. The most advantageous compounds were those with a C-7 halogen, a C-5 ortho-halophenyl, and a l-ethylsulfonyl ethyl substitution. The halogen substitutions, in order of increasing activity, were iodo, bromo, fluoro, and chloro. For example, chlorine added to the ortho position of the phenyl group doubled feed intake in sheep. An orthophenylchloro substitution in the case of N-meth-

TABLE 5

FOOD INTAKE [G/(KG BODY WT)$^{.75}$] OF CATS FOLLOWING INTRAGASTIC TUBING WITH THE DOSES OF DIAZEPAM, ELFAZEPAM, WE941, WE405, U37576, AND U31889 ELICITING THE GREATEST FEEDING RESPONSE

Time period min	None	Carrier	Treatment Diazepam 2 mg/kg	Elfazepam 4 mg/kg	WE941 0.25 mg/kg	WE405 4 mg/kg	U37576 0.08 mg/kg	U31889 0.25 mg/kg
0–30	2.1^{a} ±0.2	2.1^{a} ±0.2	15.3^{c} ±3.4	8.7^{b} ±1.4	15.8^{c} ±2.4	4.3^{ab} ±1.3	3.2^{a} ±1.4	8.9^{b} ±1.8
0–60	4.2^{x} ±0.2	4.4^{x} ±0.4	17.5^{z} ±3.7	13.2^{yz} ±2.3	16.7^{z} ±2.0	6.4^{xy} ±1.5	6.4^{xy} ±1.4	11.6^{yz} ±1.8
0–120	5.9^{x} ±0.3	6.2^{x} ±0.6	18.3^{z} ±3.9	14.5^{yz} ±2.4	19.7^{z} ±1.6	11.0^{xy} ±1.3	7.7^{x} ±1.3	14.7^{xy} ±1.9
24 hr	57.2^{a} ±1.8	55.9^{a} ±1.2	68.4^{b} ±4.9	79.6^{c} ±4.6	78.6^{c} ±3.9	71.5^{bc} ±4.5	63.3^{ab} ±2.1	58.8^{a} ±2.4

^{abc}Means not having a common superscript are different, $p<0.05$.
^{wxyz}Means not having a common superscript are different, $p<0.01$.
Treatment probability based on 2-way analysis of variance.

TABLE 6

FOOD INTAKE (G) FOLLOWING INTRAGASTRIC TUBING OF CATS WITH CARRIER, DIAZEPAM, ELFAZEPAM, WE941, U37576 AND U31889

Time period min	Carrier	Treatment Diazepam 2 mg/kg	Elfazepam 4 mg/kg	WE941 0.25 mg/kg	U37576 0.32 mg/kg	U31889 0.25 mg/kg
0–30	7.6 ± 1.2^{a}	28.5 ± 5.2^{b}	26.8 ± 2.2^{b}	23.1 ± 3.4^{b}	17.7 ± 4.5^{b}	22.0 ± 4.2^{b}
0–60	12.6 ± 1.8^{a}	34.9 ± 6.8^{b}	35.9 ± 2.2^{b}	27.6 ± 3.4^{b}	26.6 ± 5.8^{b}	30.7 ± 5.6^{b}
0–120	16.6 ± 1.7^{a}	36.7 ± 6.5^{bc}	42.3 ± 2.4^{c}	31.4 ± 3.2^{bc}	29.1 ± 5.8^{b}	36.0 ± 5.5^{bc}
24 hr	123.0 ± 6.3^{a}	145.6 ± 7.2^{b}	160.2 ± 9.0^{c}	145.5 ± 5.3^{b}	143.3 ± 6.7^{b}	141.8 ± 7.4^{b}

^{abc}Means not having a common superscript are different, $p<0.05$.

yl-lorazepam did not increase the feeding response over that of D in cats in previous studies [7,11]. The doses of D used were 0.3 and 1.0 mg/kg body weight given IP, and the feeding responses reported were similar to those presented here. In these studies with cats, the 2-carbonyl function apparently increased the feeding response threefold as shown by the responses to D and medazepam.

Other structural changes have been found to enhance or suppress certain actions of the benzodiazepines. In the study described above in sheep, compounds having a terminal ethyl group (1-alkylsulfonyl ethyl) had a separation of polyphagic and sedative properties; those with a terminal methyl were active sedatives [4]. In studies on the effects on feeding behavior of sheep of three 8-chloro-6-(ortho-chlorophenyl) imidazo 1,4 benzodiazepines, including a 1-methyl derivative, a 2-methyl derivative, and the parent compound, each caused intense feeding; however, rate of eating and drinking time varied greatly among them [3].

Bauer *et al.* [6] studied the biological properties of another class of benzodiazepines, the 1,5 benzodiazepines. They found similar properties between the 1,4 and 1,5 derivatives, but compared with diazepam, the 1,5 benzodiazepines were much less potent in a test used to determine antianxiety effectiveness (metrazol antagonist test [28]). The introduction of a 1-methyl increased activity of 5-(o-fluorophenyl) 1,4 benzodiazepines, while longer side chains reduced potency [2]. This effect occurred primarily in the tests measuring antianxiety activity, while their activity as muscle relaxants was unchanged and activity as sedatives was depressed [1].

Triazolobenzodiazepines have been found not only to be more potent than the corresponding diazepam derivatives, but also to have better therapeutic ratios and to have marked differences in the spectrum of activity [22]. For example, certain triazolobenzodiazepines were found to be at least as potent antianxiety agents as diazepam, but were much less active as depressants or muscle relaxants. Their potency as feed intake stimulants is also greatly increased. Certain triazolobenzodiazepines have been found to be at least 10 times as potent feed intake stimulants as corresponding diazepam derivatives [4,9].

Recent reports of specific CNS benzodiazepine receptors in a wide range of species [18, 19, 20, 24] may provide an explanation for the differences in activity found among benzodiazepines. It has already been shown that in vitro affinities of benzodiazepines for the receptor correlate well with their potencies in vivo in several pharmacological tests

predictive of anxiolytic activity in humans.

While there were definite structure-activity differences among the chemicals, as well as differences in sensitivity between the cats and puppies, each of the chemicals elicited feeding in both species. There are applications in both veterinary and human medicine for chemical feed intake stimulants for the treatment of anorexias [4,9], although often the depressant effects of these chemicals would jeopardize their potential value. Of the present representatives of the subclasses of benzodiazepines tested, elfazepam is proposed to be of most potential use therapeutically in these species.

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