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The influence of the new benzodiazepine derivative BD-1158 on the behaviour of rabbits in spontaneous conditions

The ataractics are a class of anxiolytic drugs, widely used in clinical practice and in this group there are distinguished derivatives of the 1,4 benzodiazepine (BDA) (2,3,7,13,15,17). The benzodiazepines show anxiolytic, anticonvulsant, sedative and muscle relaxant effects (2,3,7,16,19). The substance BD-1158, applied in this study also belongs to the BDA.

The purpose of the present experiments was to test the spontaneous behaviour, typical of a rabbit, after administration of BD-1158 and thus defining the activity and side effects of this substance in physiological conditions.

MATERIAL AND METHODS

The experiments were performed using 10 male Chinchilla rabbits of mean body weight 3,250 grams, which were randomised for the study. Adaptation of the animal to the surrounding conditions lasted 1 hour and then three-hour recording of the behaviour of the rabbit was initiated. The time of observation was divided into 10-minute intervals. Several phases of behaviour were estimated: tension, orientation-searching behaviour, comfort, grooming, water and food uptake. Duration of each phase was measured in seconds with a stopwatch during 10-minute intervals.

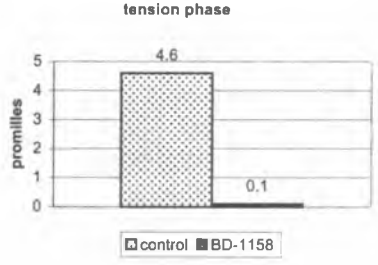
The experiment in spontaneous conditions was performed for 3 subsequent days in a group of 10 rabbits. On the first day spontaneous behaviour was tested. On the second day 1 ml of 1% starch solution was administered intraperitoneally. On the third day BD-1158 was administered intraperitoneally at a dose 10 mg/kg of rabbit body weight diluted in 1% starch solution up to 1ml, 35-40 minutes before initiation of the experiment.The significance of dissolvent and substance influence on the duration of the phases was checked with t-Student test.

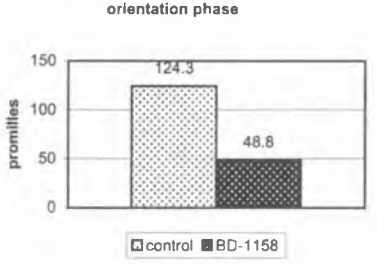
RESULTS

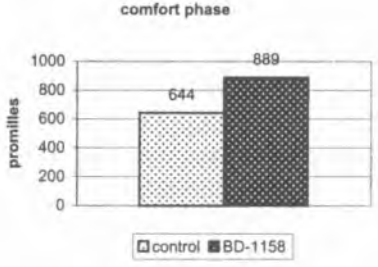
Before studying the influence of BD-1158, the reaction of dissolvent was excluded. The duration of the specific phase of behaviour was evaluated and expressed in ‰, as the share of a given phase in the 3-hour period of observation.

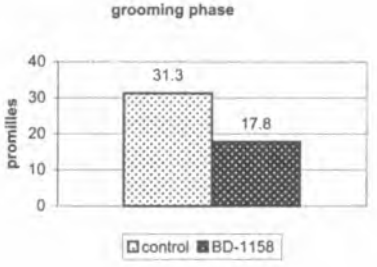
The tension phase constituted almost 5‰ of the 3-hour period of observation under spontaneous conditions. The BDA derivative decreased this phase to the value 0.1‰,which is almost a zero value. In spite of the fact that this change is not statistically significant, probably due to low initial values, it can be concluded that BD-1158 completely eliminated the tension phase.

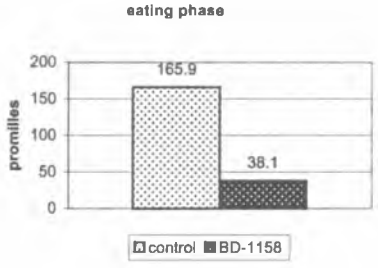
The BDA derivative decreased significantly the duration of the orientation-searching reactions from 124.3‰ to 48.8‰ ($p \leq 0.05$). The duration of the comfort phase has been prolonged after BD-1158 administration from 644‰ to 889‰. This is a statistically significant change ($p \leq 0.05$). No significant influence of BD-1158 on the duration of grooming was found, in spite of its slight reduction from 31.3‰ to 17.8‰. The BDA derivative significantly decreased food and water uptake (changes from 165.9‰ to 38.1‰ and from 29.9‰ to 6.3‰ respectively) ($p \leq 0.05$).

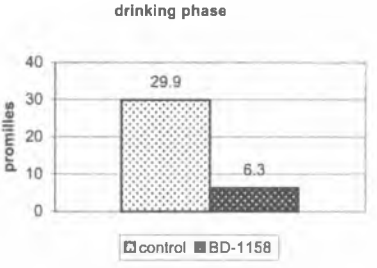












DISCUSSION

The experiments demonstrated that BD-1158 significantly prolonged the comfort phase. Supposedly this effect results from its sedative activity and maybe also due to its activity causing drowsiness, sluggishness and fatigue. These effects are typical of drugs from the benzodiazepine class. Tallman et al. (17), Rattan and Sribanditmongkol (16), Burke et al. (3), Bronson (2) emphasised the sedative and hypnotic effects of BDA. BDA exert their main action through a specific receptor complex, by intensification of the reaction of gamma-aminobutyric acid (GABA) (3, 13, 17). According to T a l l m a n et al. the character of this reaction depends on the influence on the given structure of the brain (17) and according to Curtis et al. on the differences of the GABA receptor structure (6). Probably there are endogenic ligands of the benzodiazepine receptor, which have the function of neurotransmitters (1, 12, 14). Endogenous derivatives of BDA act as agonists that activate specific receptors and as antagonists blocking the tonic influence of natural ligands which causes a general CNS depression, the result of which is sedative activity (14).

BD-1158 reduced the duration of orientation-searching reactions. It should be then admitted, that BDA derivative considerably reduces the interest of the animal in the environment.

Prolongation of the comfort phase and reduction of the orientation-searching phase showed in the studies comply with the described in the literature decrease in motor activity of animals after BDA administration. According to L o p e z et al. clonazepam and triazolam decrease open-field activity in mice, expressed by a decrease in distance travelled, ambulatory time, stereotypic time and vertical movements. Moreover, the authors observed an increase in resting time (9). M i l l e r et al. (10,11) find that motor activity is dose-related for triazolam and clonazepam. L o p e z et al. explain that this behaviour after administration of classical benzodiazepines is caused by blocking of specific receptors by these drugs (9).

BD-1158 almost completely eliminated the tension phase in the behaviour. It decreased grooming and thus reduced the animal's interest in its own body.

According to H u n t et al. (8), C o o p e r and C r u m m y (4), W i s e and D a w s o n (18) the benzodiazepine group of drugs generally facilitates food uptake. H u n t et al. report that chlordiazepoxide induces eating independently of taste while the hungry animals show a high degree of differentiation of tasty food and less tasty food (8). Cooper and Francis indicate the absence of preferences as to the kind and structure of food after chlordiazepoxide administration in spite of general stimulation for eating (5). Wise and Dawson report that diazepam treatment is not as effective as is food deprivation in motivating acquisition of operant responding maintained by food presented over six 90 min daily sessions. This difference, according to the authors, is attributed to the failure of BDA treatment to induce the increased general activity (18).

The results proved that BD-1158 did not influence in typical of BDA way food and water uptake. The decrease of duration of both phases by over 70% was confirmed. These changes were significant.

CONCLUSIONS

1. BD-1158 has a strong anxiolytic and sedative effect (the tension and comfort phase).

2. The state of animal's attention (the orientation-searching phase and grooming) is strongly decreased after BD-1158 administration.

3. In spontaneous conditions BD-1158 significantly decreases eating and drinking.

REFERENCES

1. Bielajev C. et al.: Diazepam facilitates stimulation-induced feedings in rats. Pharmacol. Biochem. Behav., 48, 557, 1994.
2. Bronson M. E.: Chlordiazepoxide, but not bretazenil, produces acute dependence, as evidenced by disruptions in schedule-controlled behavior. Pharmacol. Biochem. Behav., 48, 397, 1994.
3. Burke T. F. et al.: Acute effects of benzodiazepines on operant bahavior and *in vivo* receptor binding in mice. Pharmacol. Biochem. Behav., 48, 69, 1994.
4. Cooper S. J. et al.: Enhanced choice of familiar food in a food preference test after chlordiazepoxide administration. Psychopharmacology, 59, 51, 1978.
5. Cooper S. J. et al.: Feeding parameters with two food textures after chlordiazepoxide administration, alone or in combination with d-amphetamine or fenfluramine. Psychopharmacology, 62, 253, 1979.
6. Curtis D. R. et al.: Central actions of benzodiazepines. Brain Res., 118, 344, 1976.
7. Giusti L. et al.: Characterization of peripheral-type benzodiazepine binding sites from rat and pig pancreas. Biochem. Pharmacol., 48, 583, 1994.
8. Hunt T. et al.: Benzodiazepine-induced hyperphagia: a test of the hunger-mimetic model. Pharmacol. Biochem. Behav., 30, 515, 1988.
9. Lopez F. et al.: Low-dose alprazolam augments motor activity in mice. Pharmacol. Biochem. Behav., 30, 511, 1988.
10. Miller L. G. et al.: Benzodiazepine receptor binding of triazobenzodiazepines *in vivo*: increased receptor number with low-dose alprazolam. J. Neurochem., 49, 1595, 1987.
11. Miller L. G. et al.: Benzodiazepine receptor binding *in vivo*. J. Pharmacol. Exp. Ther., 240, 516, 1987.
12. Mohler H. et al.: Properties of 3H-diazepam binding to benzodiazepine receptors in rat cerebral cortex. Life Sci., 20, 2101, 1977.
13. Pokorski M. et al.: Endogenous benzodiazepine system and regulation of respiration in the cat. Respiration Physiology, 97, 33, 1994.
14. Rosenberg H. C. et al.: Decreased 3H-diazepam binding is a specific response to chronic benzodiazepine treatment. Life Sci., 24, 803, 1979.
15. Smith P. F. et al.: Rapid tolerance to the depressive effects of diazepam on guinea pig motor control using divided doses. Pharmacol. Biochem. Behav., 48, 535, 1994.

16. R a t t a n A. K. et al.: Effect on morphine-induced catalepsy, lethality and analgesia by a benzodiazepine receptor agonist midazolam in the rat. Pharmacol. Biochem. Behav., 48, 357, 1994.
17. T a l l m a n J. F. et al.: Receptors for the age of anxiety: pharmacology of the benzodiazepines. Science, 207, 274, 1980.
18. W i s e R. A. et al.: Diazepam-induced eating and lever pressing for food in sated rats. J. Comp. Physiol. Psychol., 86, 930, 1974.
19. W o o d s J. H. et al.: Benzodiazepines: use, abuse and consequences. Pharmacol. Rev., 44, 151, 1992.

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SUMMARY

BD-1158 is a new 1,4 benzodiazepine derivative. The purpose of the present experiments was to test the spontaneous behaviour (typical of a rabbit) after administration of BD-1158 and thus to define the activity and side effects of this substance under physiological conditions. The experiments were performed for 3 subsequent days in a group of 10 rabbits. On the first day spontaneous behaviour was tested. On the second day 1 ml of 1% starch solution was administered intraperitoneally. On the third day BD-1158 was administered intraperitoneally at a dose 10mg/kg diluted in 1% starch solution up to 1 ml, 35-40 minutes before the beginning of the experiment. Six phases of behaviour were estimated. It was concluded that BD-1158 has a strong anxiolytic and sedative effect, decreases the state of animal's attention, water and food uptake.

Wpływ nowej pochodnej benzodwuazepinyBD-1158 na zachowanie królików w warunkach spontanicznych

BD-1158 jest nowo zsyntetyzowaną pochodną 1,4 benzodwuazepiny. Celem pracy było zbadanie zachowania spontanicznego (typowego dla królika) po podaniu tej substancji i przez to określenie jej działania i ubocznego wpływu w warunkach fizjologicznych. Doświadczenia przeprowadzono w grupie zwierząt liczącej 10 królików. Pierwszego dnia nie podawano substancji, drugiego dnia kontrolowano ewentualny wpływ rozpuszczalnika (podawano dootrzewnowo 1ml 1% roztworu skrobi), trzeciego podawano dootrzewnowo BD-1158 w dawce 10mg/kg masy ciała królika, rozcieńczony w 1% roztworze skrobi do objętości 1 ml, 35 minut przed rozpoczęciem doświadczenia. Wyodrębniono sześć rodzajów zachowań. Stwierdzono, że BD-1158 wykazuje silne działanie uspokajające i przeciwlękowe, silnie ogranicza stan uwagi zwierzęcia oraz obniża pobieranie pokarmu i wody.