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Anxiolytic effect of BPC-157, a gastric pentadecapeptide: shock probe/burying test and light/dark test

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KEY WORDS BPC-157; diazepam; anxiety; exploratory behavior; motor activity

ABSTRACT

AIM: To study anxiolytic effect of a gastric pentadecapeptide, BPC-157. **METHODS**: In shock probe/burying test, pentadecapeptide BPC-157 (10 μg/kg, 10 ng/kg, ip), diazepam (0.075, 0.0375 mg/kg, ip), and an equivolume of saline (5 mL/kg, ip) were given at 30 min prior test. In light/dark test, the same dosage of diazepam, BPC-157, and saline were given at 45 min prior procedure. **RESULTS**: Shock probe/burying test: rats treated with either diazepam or pentadecapeptide BPC-157 were much less afraid after the shock: almost not burying and the total time spent in burying was clearly less than in controls. However, while in the diazepam treated rats the number of shocks received increased over control values, in pentadecapeptide BPC-157 treated groups the number of shocks remained not modified compared with the control values. Light/dark test: after exposure to the intense light, diazepam treated mice had longer latencies of crossing to the dark compartment, a greater number of crossing and a greater number of exploratory rearing, and spent longer time in the light compartment, as compared to the control mice, while BPC-157 mice had a similar behavior to that of the control mice. In contrast with the effect in light area, in dark zone diazepam produced no change with respect to controls, while BPC-157 (10 μg/kg) mice had a greater number of crossing and a greater number of exploratory rearing. **CONCLUSION**: Both diazepam and BPC-157 displayed a bidirectional effect, but the activity of pentadecapeptide BPC-157 was particular, and different from diazepam.

INTRODUCTION

A gastric pentadecapeptide, GEPPPGKPADDAGLV, M_r = 1419, coded BPC-157[1-20], highly stable in gastric juice[20], besides mucosal protective[1-10], wound healing[11-13] and anti-inflammatory effect[14], and interaction with NO[9], and somatosensory neurons system[10], may attenuate motoric disturbances induced by neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP), a Parkinsongenic neurotoxin, affecting nigrostriatal dopamine[17], or reserpine, a depletor of dopaminergic intraneuron granules[17], and dopamine receptors blockade, haloperidol, flufenazine, sulpirid, clozapine catalepsy and/or somatosensory disturbance[16]. It also counteracts helpless behavior in rats subjected to Porsolt's forced swimming test and immobility in open field chronically stressed rats[19].

Interestingly, it also counteracts fully amphetamine-induced disturbances in rats[15]. Besides blocking stereotypy development and reversing already established stereotypy, it counteracts amphetamine-fear reaction (ie, a heightened startle response to acoustic stimulus). Given alone, it shows no influence on gross behavior in normal animals[15]. Recently, given pentadecapeptide BPC-157 simultaneously with diazepam, a lack of tolerance development was demonstrated in tolerance studies, while residual anticonvulsive activity was prolonged, and physical dependence/withdrawal hallmark postponed in diazepam + BPC-157 chronically treated mice[18]. Therefore, considering the commonly known dopamine/GABA implication[21,22], we investigated pentadecapeptide BPC-157 activity in light/dark test, and shock probe/burying

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test, along with diazepam as standard agent, in two models commonly used to predict anxiolytic property[23-39].

MATERIALS AND METHODS

Animals Male Albino Wistar rats, 200 – 250 g (shock probe/burying test), male NMRI mice weighing 22 – 24 g (light/dark test), randomly assigned were used in all of the experiments (approved by local committee), kept in a temperature and humidity controlled room under 12 h light/dark cycle (light on at 7:00 AM), with free access to food and water.

Shock probe/burying test The procedure was carried out as described before[23-25]. Briefly, four days before the experiment, to rats housed individually testing was done between 10 and 19 h in a separate room in an appropriate test box (40 cm × 30 cm × 40 cm). The box floor was evenly covered with 5 cm of kitty litter. In the center of the front wall of the box, 2 cm above the bending material, a test probe was located (6.5 cm × 6.5 cm × 0.5 cm) with two metal wires wrapped around. Electric current was administered through the wires (220 V). Habituation to the box was for 30 min on each of four days before the test day without the probe present, while on the fifth day rats were placed into the box with the probe inserted and contionusly electrified at 2 mA. Touching the probe rats would get an electrical shock producing intense fear and anxiety. Each animal's behavior was observed for 15 min. Number of burying rats, time spent burying and number of shocks received were assessed by a "blind" observer and evaluated[23-25]. Medication was at 30 min prior rats were individually placed into the test box: pentadecapeptide BPC-157 (10 μg/kg, 10 ng/kg, ip), diazepam (0.075, 0.0375 mg/kg, ip), while controls received at the same time an equivolume of saline (5 mL/kg, ip).

Light/dark test A described procedure was followed[26-28]. The apparatus was an open-toppe box (45 cm × 27 cm × 27 cm) divided into a small (2/5) area and a large (3/5) area by a partition that extended 20 cm above the walls. There was a 7.5 cm × 7.5 cm opening in the centre of the partition at floor level. The small compartment was painted black and the large compartment white. The floor of each compartment was marked into 9 cm squares. The white compartment was illuminated by a 60 W tungsten bulb (400 lux) 17 cm above the box and the black compartment by a similarly placed 60 W (0 lux) red bulb. The laboratory was illuminated by red light. All test were performed between 13:00 and 18:00 in a quiet darkened room. Mice were taken from a dark holding room in a dark container to the dark testing room and placed into the test box after a 1 h adaptation. Each mouse was tested by placing it in the center of the white area and allowing it to explore the novel environment for 10 min[26-28]. The number of exploratory rearings in the light and dark sections, the number of line crossing in the light and dark sections, the time spent in the light and dark areas, and the latency of the intitial movement from the light to the dark area was recorded. Its behavior was recorded on videotape and the behavioral analysis was performed subsequently from the recording. Medication was at 45 min before experimental procedure intitiation: pentadecapeptide BPC-157 (10 μg/kg, 10 ng/kg, ip), diazepam (0.1 mg/kg, ip), while controls received at the same time an equivolume of saline (5 mL/kg, ip).

Statistical analysis Fisher exact probability test was used for data of presence/absence of burying and number of received shock. P values of 0.05 or less were be significant. Kruskal-Wallis ANOVA test and Mann-Whitney test was used (time spent burying, the number of exploratory rearings in the light and dark sections, the number of line crossing in the light and dark sections, the time spent in the light and dark areas, and the latency of the intitial movement from the light to the dark area). P values of 0.008 or less were considered to be statistically significant (Bonferroni correction).

RESULTS

Defensive burying Control rats, similarly to data already described in the literature[23-25], showed an intense fear after the first shock. Most of them exhibited the so-called burying behavior (16/24 animals). Along with the literature data, diazepam reversed this behavior (0/24 for both regimens). Compared with them, rats treated with pentadecapeptide BPC-157 were also much less afraid after the shock and were almost not burying 2/24 in mg regimen, or 4/24 in ng regimen). Of note, since obtained with both regimens, using very low dosage (previously shown to effectively oppose above mentioned behavioral disturbances[15-19], and especially diazepam induced tolerance/withdrawal)[18], a particular anxiolytic effect may be suggested. Likewise, the total time spent in burying was clearly less than in controls (Tab 1). Besides, panic jumping and escaping seen in controls following the shock, were not present in pentadecapeptide BPC-157 or diazepam rats.

Interestingly, in the diazepam treated rats the number

Tab 1. Results of shock probe/burying test: number of shocks received, time spent in burying, and counteracting effect of diazepam and pentadecapeptide BPC-157. ^cP values of 0.008 or less *vs* control (saline).

Medication at 30 min before shock/burying procedure		Number of rats		Time spent in burying/s $\bar{x} \pm s$		Shock per rat Number of rats receiving	
		burying	no burying	per burying rat	per rat	2 shocks or less	more than 2 shocks
Saline 5.0 mL (Control)		16	8	91 ± 38	61 ± 54	24	0
BPC-157	10 μg/kg	2	22	10 ± 4^c	1 ± 3^c	24	0
	10 ng/kg	4	20	10 ± 4^c	2 ± 4^c	24	0
Diazepam	0.075 mg/kg	0	24	0	0	19	5
	0.0375 mg/kg	0	24	0	0	19	5

of shocks received was increased over control values, along with literature[23-25], while in pentadecapeptide BPC-157 treated groups the number of shock remained not modified compared with the control values (Tab 1).

Thus, although with respect to a lack of burying after shock seen in either pentadecapeptide BPC-157 or diazepam rats, their activities seem to be essentially the same, further analysis did not support this contention. A further increase of the number of shock over control values was seen only in diazepam rats. On the other hand, a lack of further increase was noted in pentadecapeptide BPC-157 rats. Together, these indicate that in pentadecapeptide BPC-157 and diazepam rats, an intense fear after the first shock was counteracted in a different way. Obviously, since for a specific anxiolytic effect (ie, diazepam) a lack of burying was axiomatically coined with an increased number of shocks received[23-25], such departure noted in pentadecapeptide BPC-157 regimens needs to be further clarified.

Light/dark test Different effects of diazepam and pentadecapeptide BPC-157 in light zone and dark zone emerged an interesting point. After exposure to the intense light, diazepam treated mice had longer latencies of crossing to the dark compartment, a greater number of crossing and a greater number of exploratory rearing, and spent longer time in the light compartment, as compared to the control mice, while BPC 157 mice had a similar behavior to that of the control mice. In contrast with the effect in light area, in dark zone diazepam produced no change with respect to controls while BPC-157 (10 μg) mice had a greater number of crossing and a greater number of exploratory rearing (Tab 2).

Considering a bidirectional effect, already noticed for diazepam like agents, ie, measured by a decrease in a specific activity in one paradigm (shock probe/burying), and an increase in specific activity in the other paradigm (a light/dark test), and thereby not related to nonspecific effects on general activity or arousal[23-28], the observed

Tab 2. Light/dark test. The time spent in the light and dark areas and the exploratory rearings in the light and dark sections, the number of line crossing in the light and dark sections. Different effects of diazepam and pentadecapeptide BPC-157 in light zone and dark zone. ^cP values of 0.008 or less *vs* control (saline).

Medication given ip at 45 min before light/dark procedure	Latency of the initial movement from the light to the dark area/s $\bar{x} \pm s$	Time spent/s $\bar{x} \pm s$		Number of line crossing Min/Med/Max		Number of exploratory rearings Min/Med/Max	
		in the light	in the dark	in the light	in the dark	in the light	in the dark
Saline 5.0 mL (Control)	151 ± 32	257 ± 31	343 ± 31	33/44.0/54	20/32.5/46	4/11.0/22	5/09.0/12
BPC-157 10 μg/kg	161 ± 28	241 ± 33	359 ± 33	38/48.5/60	48/63.5/71	6/12.0/20	8/19.0/26
10 ng/kg	138 ± 48	258 ± 33	342 ± 33	32/39.0/51	23/48.0/61	6/10.0/16	5/10.0/14
Diazepam 0.1 mg/kg	252 ± 41^c	319 ± 44^c	280 ± 44^c	50/66.5/73^c	22/28.5/37^c	14/19.5/27^c	5/07.5/11

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effects of diazepam in light area are along with reported effect. However, an increased activity in dark department (and not in light area), seen in BPC-157 mice, had been not previously reported in diazepam like agents studies[26-28]. Therefore, this bidirectional effect, noted in BPC-157 (10 μg) rats is thereby interesting and its significance for anxiety research remains to be further seen.

Thus, like the shock probe/burying test, study of the light/dark test also indicated some differences in potential anxiolytic activity of pentadecapeptide BPC-157 and diazepam.

DISCUSSION

In general, an antianxiety effect of diazepam-like agents should be a bidirectional one, measured by an increase in specific activity in one paradigm (a light/dark test), and a decrease in a specific activity in the other paradigm (shock probe/burying)[23-25]. Consistently with previous studies, and bidirectional effect as characteristic for an antianxiety activity devoiced of nonspecific effects on general activity or arousal[23-25], diazepam showed a bidirectional effect (increased presence on the light; less burying, but increased number of shocks received).

Therefore, taking advantage from combining the paradigms of a light/dark test, and a shock probe/burying test, the evidenced bidirectional effect of pentadecapeptide BPC-157 is interesting for the research on animal anxiety. However, this bidirectional effect is different, ie, decreased burying, along with the same number of shock received (shock probe/burying); an increased activity in a dark zone (light/dark test). Likely, it is acting at least to some extent differently from diazepam. This is indicative, and deserves further investigation. Recently, in diazepam induced-tolerance/withdrawal studies[18], given pentadecapeptide BPC-157 simultaneously with diazepam, lack of tolerance development was demonstrated in tolerance studies, while residual anticonvulsive activity was prolonged, and physical dependence/withdrawal hallmark postponed in diazepam + BPC-157 chronically treated mice. Thus, pentadecapeptide BPC-157 did neither agonize nor antagonize diazepam effect. Rather, it opposes the negative consequences of diazepam application.

Together, these should be coupled with the evidenced variable rather than consistent influence of many agents[23,30-39] in both shock probe/burying- and light/dark-test with respect to their suggested anxiolytic and nonanxiolytic properties. However, besides these commonly noted inconsistencies in these two models, they were regularly used to predict anxiolytic property[23-39]. Finally, in support of a particular anxiolytic effect, the potential effectiveness only in the very large doses is claimed for nonanxiolytic agents[23]. Unlike this, pentadecapeptide BPC-157 was strongly effective in very low dosage range (10 ng/kg - 10 μg/kg, ip). To show, 5-HT_3 receptor antagonists are usually active within mentioned range[29]. Therefore, the effect of pentadecapeptide BPC-157 should be still positively interpreted.

Thus, unlike diazepam influence in light only, pentadecapeptide BPC-157 did not influence the behavior of the mice in the light compartment. However, a finding of potential interest, particularly seen from the view point of a bidirectional activity, pentadecapeptide BPC-157 did increase the line crossing and exploratory rearings in dark section, a finding previously not reported[23-39]. Theoretically, the potency of diazepam to disinhibit in mice a natural behavioral responding to the aversive situation leading to an increase of the amount of time spent in the light, may be potentially dangerous. Unlike this, pentadecapeptide BPC 157 affects the same parameters, but in dark condition. Thus, it seems that pentadecapeptide BPC-157 effect better follows the natural mouse behaviour in preferred dark condition. Likewise, in a shock probe/burying test, seen from this point of view, diazepam bidirectional activity with an increased number of shocks received in diazepam rats may be hardly taken for a useful anxiolytic activity as it had been suggested[23]. Rather, it should be regarded as a disorientation effect. Not only in theory, a failure of natural capability further to avoid more aversive stimuli (ie, resulting with an increased number of the shock received in diazepam rats) along with "anxiolytic" effect may be a harmful disadvantage. On the contrary, lack of a panic reaction to an aversive stimulus, avoiding more aversive stimuli (ie, not more shocks received), noted in pentadecapeptide BPC-157 treated rats, may be a logical goal for an anxiolytic agent. Supportingly, similar effect was noted also in barbiturate type anxiolytic[23].

Finally, the pentadecapeptide BPC-157 effect seen in amphetamine-treated rats[15] correlates with the effect noted in shock probe/burying procedure. Pentadecapeptide BPC-157 application both prevents and reverses amphetamine-violent twitching, panic jumping, and escaping seen in controls following an acoustic stimulus. It also blocks an increased effect of amphetamine, amphetamine

climbing behavior, a delayed result of striatal dopamine receptors upregulation following dopamine antagonist haloperidol application and dopamine receptors blockade[15]. As mentioned, this fully correlates with no burying and no panic jumping and escaping after shock in pentadecapeptide BPC-157 rats subjected to shock probe/burying procedure, otherwise seen in corresponding controls. Furthermore, this should be seen together with suggested particular pentadecapeptide BPC-157/dopamine system interaction[8,15-17,19], GABA-ergic transmission longly implicated in the regulation of dopamine mediated events within extrapyramidal system and behaviors dependent on striatal functions (catalepsy, stereotypes)[21,22], and the effect of pentadecapeptide BPC-157 on GABA-system disturbances, such as diazepam induced tolerance/withdrawal[18]. Thus, despite mentioned limitations concerning the used two commonly known models to predict anxiolytic activity, since effective in a very low dose range, and not in large dosage like nonanxiolytic agents[23], the reported distinction between pentadecapeptide BPC-157/diazepam treatment may be a basis for further studies to fully define possible gastric pentadecapeptide BPC-157 anxiolytic effect.

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BPC-157，一种胃十五肽的抗焦虑作用：休克探查/埋藏试验和明暗试验

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关键词 BPC-157；地西泮；焦虑；探究行为；运动活动

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