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# Pentadecapeptide BPC 157 attenuates disturbances induced by neuroleptics: the effect on catalepsy and gastric ulcers in mice and rats

Nikola Jelovac, Predrag Sikiric *, Rudolf Rucman, Marijan Petek, Anton Marovic, Darko Perovic, Sven Seiwerth [1], Stjepan Mise, Branko Turkovic, Goran Dodig, Pavle Miklic, Gojko Buljat, Ingrid Prkacin

*Departments of Pharmacology and Pathology, Medical Faculty University of Zagreb, Zagreb, Croatia*

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**Abstract**

A gastric pentadecapeptide, BPC 157, with the amino acid sequence, Gly–Glu–Pro–Pro–Pro–Gly–Lys–Pro–Ala–Asp–Asp–Ala–Gly–Leu–Val, MW 1419, known to have a variety of protective effects in gastrointestinal tract and other organs, was recently shown to particularly affect dopamine systems. For instance, it blocks the stereotypy produced acutely by amphetamine in rats, and the development of haloperidol-induced supersensitivity to amphetamine in mice. Consequently, whether pentadecapeptide BPC 157, that by itself has no cataleptogenic effect in normal animals, may attenuate the immediate effects of neuroleptics application, particularly catalepsy, was the focus of the present report. Prominent catalepsy, otherwise consistently seen in the mice treated with haloperidol (0.625, 1.25, 2.5, 5.0 and 10.0 mg/kg b.w., i.p.) and fluphenazine (0.3125, 0.625, 1.25, 2.5 and 5.0 mg/kg b.w., i.p.) after 1.5, 3, 4.5, 6 and 7.5 h following administration, was markedly attenuated when pentadecapeptide BPC 157 (10 μg or 10 ng/kg b.w., i.p.) was coadministered with the neuroleptic. The number of cataleptic mice was markedly lower throughout most of the experimental period. Moreover, on challenge with lower doses of neuroleptics, catalepsy appearance was postponed and the mice, otherwise cataleptic since the earliest period, became cataleptic later, not before 3 or 4.5 h after neuroleptic administration, especially if protected with higher pentadecapeptide dose. Besides catalepsy, coadministration of the pentadecapeptide BPC 157, given in the abovementioned doses, reduced not only catalepsy but somatosensory disorientation (for 7.5 h after administration of a neuroleptic, assessed at intervals of 1.5 h, by a simple scoring system [0–5]) in haloperidol- or fluphenazine-challenged mice as it did in mice treated with sulpiride (20, 40, 80 and 160 mg/kg b.w., i.p.) or with clozapine (25, 50 and 100 mg/kg b.w., i.p.), in which case catalepsy was absent. In other experiments, considering the gastric origin of this pentadecapeptide, the focus was shifted to the evidence that a dose of haloperidol, cataleptogenic due to dopamine receptors blockade, induces gastric ulcers in rats. Coadministration of pentadecapeptide BPC 157 (10 μg, 10 ng, 1.0 ng, 100 pg/kg b.w., i.p.) to rats completely inhibited the lesions otherwise regularly evident 24 h after haloperidol (5.0 mg/kg b.w., i.p.) in control rats (18 of 20 rats had gastric lesions). This activity accompanied the antagonism of the haloperidol catalepsy in rats (assessed at 60-min intervals from 1 to 5 h after haloperidol), when 10-μg- or 10-ng regimens were given (lower doses could not influence catalepsy). Together, these findings indicate that pentadecapeptide BPC 157 fully interacts with the dopamine system, both centrally and peripherally, or at least, that BPC 157 interferes with some steps involved in catalepsy and/or ulcer formation. 

*Keywords:* Pentadecapeptide BPC 157; Antagonism; Catalepsy; Antipsychotic drug; Gastric lesion; Haloperidol; (Mouse); (Rat)

## 1. Introduction

Because of the physiological significance of gut peptides and their possible therapeutic application, the discovery of so far unknown peptides, their original structure and beneficial actions, has received considerable attention. We have identified a new human gastric juice protein with

* Corresponding author. Department of Pharmacology, Medical Faculty University of Zagreb, Salata 11, POB 916, Zagreb 10000, Croatia. Tel.: +385-1-45-66-833, +385-1-45-66-834, +385-1-45-66-836; fax: +385-1-424-001, +385-1-468-3829; E-mail: psikiric@mef.hr

[1] E-mail: seiwerth@mamef.mef.hr.

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mucosal protective properties and a huge range of organoprotective effects, and with MW 40,000 (determined by gel chromatography), code-named BPC. The regular procedures, i.e., controlled dialysis of gastric juice, lyophilisation, chromatographic separation on weak anion exchange resin (DEAE), cation exchange resin (*S*), followed by gel chromatography and finally high pressure liquid chromatography, were applied. In line with this, a 15-amino acid fragment (BPC 157), with amino acid sequence, Gly–Glu–Pro–Pro–Pro–Gly–Lys–Pro–Ala–Asp–Asp–Ala–Gly–Leu–Val, MW 1419, and apparently no sequence homology to known gut peptides, thought to be essential for activity of an entire peptide, was characterized and synthesized (Sikiric et al., 1993a,b, 1994, 1996a,b, 1997a,b,c,d,e; Grabarevic et al., 1997; Seiwerth et al., 1997; Jelovac et al., 1998). Considering its origin, the first focus in the investigation of the pentadecapeptide BPC 157 was its prominent salutary activity on the various gastrointestinal injuries induced by diverse ulcerogens (Sikiric et al., 1993a,b, 1994, 1996a,b, 1997a,b,c,d,e; Paré and Kluczynski, 1994; Veljaca et al., 1994a,b, 1995a,b; Sandor et al., 1996, 1997; Bodis et al., 1997), suggesting that the noted beneficial effects apparently concern the entire gastrointestinal tract. Likewise, it was claimed to have beneficial effects even outside the gastrointestinal tract (Sikiric et al., 1993a,b, 1996a,b, 1997a,b,e; Bosnjak et al., 1994; Paré and Kluczynski, 1994; Veljaca et al., 1994a,b, 1995a,b; Grabarevic et al., 1997; Seiwerth et al., 1997; Jelovac et al., 1998; Konjevoda et al., 1998), e.g., in acute pancreatitis (Sikiric et al., 1996a) and on liver injuries in rats (Sikiric et al., 1993b). Also seen were reduction of acute and chronic inflammation (Sikiric et al., 1997e) and inflammatory mediators release (Veljaca et al., 1994a,b, 1995a,b), and increased wound healing (Sikiric et al., 1993a, 1997a; Seiwerth et al., 1997; Konjevoda et al., 1998). Intriguingly, this also includes heart protection, following hypoxic and reoxygenation injury in the isolated guinea pig heart (Sikiric et al., 1993b; Bosnjak et al., 1994).

Result of a further analysis, based on the alteration of beneficial effects of the pentadecapeptide BPC 157 by various challenges — somatosensory neuron depletion by the neurotoxin, capsaicin (Sikiric et al., 1996b), blockade or stimulation of nitric oxide (NO)-synthesis (Grabarevic et al., 1997; Sikiric et al., 1997d) or dopaminergic and/or catecholaminergic systems (Sikiric et al., 1997b), inhibition of prostaglandin synthesis (Sikiric et al., 1996b, 1997e) — as an indication, among others, led to the suggestion of an interaction with dopaminergic and/or catecholaminergic systems, particularly central (Sikiric et al., 1997b). Although the binding studies were so far unable to show any binding to dopamine receptors, this possibility was a basis for the recent demonstration that the pentadecapeptide BPC 157, although it has no influence on gross behavior in normal animals, may block the stereotypy produced by the dopamine agonist, amphetamine (Jelovac et al., 1998). Moreover, BPC 157 also blocks the increased effect of amphetamine following dopamine receptor antagonist, haloperidol (i.e., climbing behavior) in mice (Jelovac et al., 1998). Together, from a methodological point of view (Masuda et al., 1991), this action could provide an interesting background for further characterization of pentadecapeptide interaction with a dopamine effect. Since it is generally believed that increased amphetamine-induced climbing behavior is a delayed result of striatal dopamine receptor up-regulation following application of the dopamine receptor antagonist, haloperidol, and dopamine receptor blockade (Masuda et al., 1991), it became interesting to see whether the pentadecapeptide BPC 157 also affects the other close consequences of dopamine receptor blockade, such as catalepsy. Also, it had been shown that pentadecapeptide BPC 157 may improve motor disturbances induced by neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP), a Parkinsongenic neurotoxin, affecting nigrostriatal dopamine (Adams and Odunze, 1991), or by reserpine, a depletor of dopaminergic intraneuron granules (Adams and Odunze, 1991). Neuroleptic-induced catalepsy could also be used as a model of Parkinson's disease (Sebens et al., 1995).

Thus, two typical neuroleptics known to induce prominent catalepsy, haloperidol and fluphenazine, were used along with two other neuroleptics shown to induce fewer extrapyramidal side-effects, sulpiride and clozapine (Fujiwara, 1992; Bartoszyk et al., 1996). Considering the gastric origin of this pentadecapeptide BPC 157 (Sikiric et al., 1993a,b, 1994, 1996a,b, 1997a,b,c,d,e; Grabarevic et al., 1997; Seiwerth et al., 1997; Jelovac et al., 1998; Konjevoda et al., 1998) and the evidence that haloperidol induces gastric ulcers (Sikiric et al., 1986), an effect thought to be also related to dopamine receptor blockade, we also tested whether this pentadecapeptide, besides affecting central disturbances induced by neuroleptic application, could affect the haloperidol-induced gastric lesions.

## 2. Materials and methods

### *2.1. BPC 157 — preparation of the peptide*

The pentadecapeptide BPC 157 (Gly–Glu–Pro–Pro–Pro–Gly–Lys–Pro–Ala–Asp–Asp–Ala–Gly–Leu–Val), MW 1419, is a partial sequence of human gastric juice protein BPC, freely soluble in water at pH 7.0 and in saline. It was prepared by solid-phase peptide synthesis, using t-BOC-Val loaded HYCRAM® polymer carrier (Orpegen, Heidelberg). The t-BOC amino acids were coupled in consecutive steps, using diisopropylcarodimide/1-hydroxybenzentirazole reagent for activation. After sequence completion, the partially protected peptide was cleaved from the polymeric carrier by hydrogenation and purified on polymeric carrier then on a silica gel column; all protecting groups were removed with trifluoroacetic

acid and the peptide was finally purified on a silica gel column; all protecting groups were removed with trifluoroacetic acid and the peptide then finally purified by reverse phase high pressure liquid chromatography (RP HPLC). Peptide with 99% (HPLC) purity (1-des-Gly peptide as impurity) was used (Sikiric et al., 1993a,b, 1994, 1996a,b, 1997a,b,c,d,e; Grabarevic et al., 1997; Seiwerth et al., 1997; Jelovac et al., 1998; Konjevoda et al., 1998).

### 2.2. Animals

NMRI male mice, 22–24 g b.w., or male Wistar Albino rats, 200–220 g b.w., from the facilities of Medical Faculty University of Zagreb, Croatia, were used for all experiments.

### 2.3. Experimental protocol

#### 2.3.1. Drugs

Pentadecapeptide BPC 157 was dissolved in saline as before (e.g., Sikiric et al., 1993a, 1994). Haloperidol (Haldol, Krka-Janssen Pharmaceutica, Novo Mesto, Slovenia), fluphenazine (Moditen, Krka-Squibb, Novo Mesto, Slovenia), sulpiride (Sulpirid, Belupo, Ludbreg, Croatia), for intravenous use, were obtained commercially and diluted with saline. Clozapine (Leponex, Sandoz, Switzerland) was dissolved in slightly acidified saline (pH 6.2), as described before (Sebens et al., 1995). All of the agents were applied according to regimens used in other studies (e.g., Barnes et al., 1990; Elliot et al., 1990; Fujiwara, 1992; Moore et al., 1993; Krish et al., 1994; Sebens et al., 1995; Bartoszyk et al., 1996; Jelovac et al., 1998; Kalkman et al., 1997). Considering pentadecapeptide BPC 157 (Jelovac et al., 1998), the focus was to study its possible effectiveness in neuroleptic-induced disturbances also (e.g., catalepsy, gastric lesions).

*2.3.1.1. Drugs protocol.* In experiments with mice, pentadecapeptide BPC 157 (10 μg or 10 ng/kg b.w.) or an equal volume of saline (5.0 ml/kg b.w.) was given simultaneously with different neuroleptics (/kg b.w.): haloperidol (0.625, 1.25, 2.5, 5.0 and 10.0 mg), fluphenazine (0.3125, 0.625, 1.25, 2.5 and 5.0 mg), sulpiride (20, 40, 80 and 160 mg), clozapine (25, 50 and 100 mg). In rats studies, pentadecapeptide BPC 157 (10 μg, 10 ng, 1.0 ng or 100 pg/kg b.w.) or an equal volume of saline (5.0 ml/kg b.w.) was given simultaneously with haloperidol (5.0 mg) in rats. All agents were applied intraperitoneally (i.p.). To verify the pentadecapeptide, BPC 157, effect when given alone in the rat and mouse, saline or pentadecapeptide was applied alone in the given doses.

#### 2.3.2. Neuroleptic assays in mice

*2.3.2.1. Assessment of catalepsy.* The assessment was carried out according to Fujiwara (1992). Briefly, catalepsy was assessed by placing both front limbs of a mouse over a 3.8-cm high horizontal metal bar, 2 mm in diameter, after intervals of 1.5, 3, 4.5, 6 and 7.5 h following the administration of drugs. Thus, the mouse was forced to rest on its hind legs only and maintenance of this abnormal posture for over 30 s was regarded as a positive sign of catalepsy, and the number of cataleptic mice was counted (Fujiwara, 1992).

*2.3.2.2. Somatosensory orientation.* In separate experiments, somatosensory (dis)orientation was evaluated in mice by their reaction to standardized compression of the tail root. This standardized compression of the tail root was performed with a special device. Each mouse was observed for 5 s, over a period of 7.5 h after administration of a neuroleptic, at intervals of 1.5 h. Behavioral responses were assessed using a simple scoring system (score 0–5), where the lowest score showed the worst condition: score 0 — no reaction; score 1 — escaping, but biting and turning reaction absent; score 2 — whole body turned in the direction stimulated, no biting; score 3 — turning and biting, no vocalization; score 4 — in addition to turning and biting, week vocalization; score 5 — turning and biting with strong vocalization.

#### 2.3.3. Haloperidol application in rats

*2.3.3.1. Haloperidol catalepsy.* Catalepsy time (s) was assessed, using a modification of the procedure previously described by Barnes et al. (1990), for 5 min on a horizontal bar and inclined wiremesh screen at 60, 120, 180, 240 and 300 min post-injection. Bar catalepsy was then measured by gently placing the rat's forepaws on the bar (8 cm high) and counting the time until the rats moved two paws on the screen. Thereafter, screen catalepsy was measured by placing the rat head-down on the screen and catalepsy time was counted until the rat moved two paws on the screen. The wiremesh screen was placed at 45° angle.

*2.3.3.2. Assessment of haloperidol-induced mucosal injury.* Immediately after the rats were killed (with an ether overdose) at 24 h following haloperidol administration, the stomach was removed and the lesions (sum of longest diameters of lesions [means ± S.E.M., mm] and lesion incidence [number of rats with and number of rats without lesions]) were assessed by naive observers as described before (Sikiric et al., 1986, 1993a, 1994, 1996a,b, 1997b,c,d,e). Representative sections of the stomach were processed for further histological analysis.

### 2.4. Statistical analysis

Fisher's exact probability test (presence/absence of catalepsy in mice, or gastric lesions in rats), non-parametric analysis of variance (ANOVA) (Kruskall–Wallis one-way ANOVA by ranks) and post-hoc Wilcoxon rank sum

test (somatosensory orientation in mice), one-way ANOVA and post-hoc Tukey's HSD (honestly significant difference) procedure (duration of catalepsy in rats, gastric lesions size [sum of longest lesions diameters] in rats) were used for statistical analysis. The differences were considered to be significant at $P < 0.01$ (downward adjustment because of multiple comparisons; Dawson-Saunders and Trapp, 1994).

## 3. Results

### 3.1. Pentadecapeptide BPC 157 given alone

It had no influence on gross behavior in normal animals, and could not produce catalepsy in mice or rats, or any somatosensory disorientation in the mice throughout the experimental period (Fig. 1).

### 3.2. Neuroleptic assay in mice

#### 3.2.1. Catalepsy

*3.2.1.1. Haloperidol.* Given in doses known to produce catalepsy, haloperidol had a cataleptogenic effect that increased with higher doses and prolongation of the period following application. In general, the attenuation of otherwise consistent haloperidol catalepsy was evident at all the periods assessed if pentadecapeptide BPC 157 (10 μg or 10 ng/kg b.w.) was coadministered. Of note, in several cases, only the 10-μg regimen produced a significant anticataleptogenic effect. Moreover, on challenge with lower doses of neuroleptics, the appearance of catalepsy was postponed, and the mice that were otherwise cataleptic from the earliest period only became cataleptic later, not before 3 or 4.5 h after neuroleptic administration. Besides, the effect of a nanogram dose appeared to be less efficacious than that of a higher microgram dose, seen from the number of mice with catalepsy (this could be particularly illustrated at the point 3 h post-haloperidol 10 mg/kg, i.p., when nanogram dose was between microgram dose and control values, and when the significance compared either vs. controls values or vs. microgram dose was reached). Interestingly, the beneficial effect of the pentadecapeptide BPC 157 was particularly evident when all mice would otherwise have exhibited catalepsy (Table 1). As mentioned before, complete catalepsy development was regularly noted in the case of the mice damaged with the relatively high dose of haloperidol.

*3.2.1.2. Fluphenazine.* The fluphenazine cataleptogenic effect increased with higher doses, but unlike haloperidol-induced catalepsy, it declined towards the later periods. Coadministered at either the higher dose of 10 μg or the lower dose of 10 ng/kg b.w., pentadecapeptide BPC 157 strongly attenuated fluphenazine catalepsy.

It should be noted that in several cases, only the 10-μg regimen produced a significant anticataleptogenic effect. If coadministered with the 0.3 or 0.6 mg/kg dose of fluphenazine, it could completely inhibit appearance of the catalepsy, particularly when assessed after 1.5 or 3 h post-fluphenazine. Interestingly, as in the case of haloperidol catalepsy, the beneficial effect of the pentadecapeptide BPC 157 was particularly marked when all mice would otherwise have exhibited catalepsy. Consistently, in the case of the mice damaged with the highest dose of the

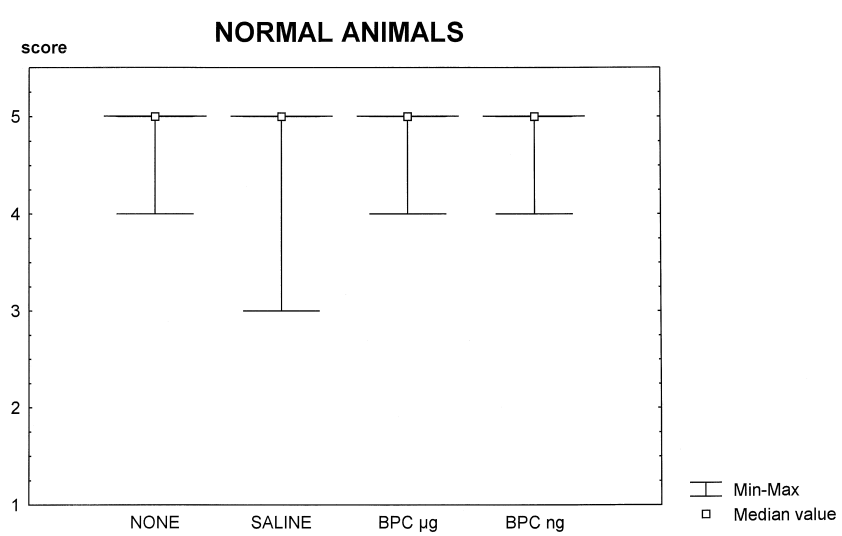


Fig. 1. Somatosensory orientation not affected by application of pentadecapeptide BPC 157 (10 μg or 10 ng/kg, i.p.) or saline (control, 5.0 ml/kg, i.p.) as compared wit normal (non-treated) mice. Behavioral response (assessed using a simple scoring system [score 0–5]) scored by reaction of mice to standardized compression of the tail root. Each mouse was observed for 5 s, for a period of 7.5 h after administration of a agent, in intervals of 1.5 h. Total number, 40 mice per each group. $^{*}P < 0.01$, at least vs. control.

Table 1
Catalepsy induced by various doses of haloperidol, when pentadecapeptide BPC (157 10 μg or 10 ng/kg, i.p.) or saline (control, 5.0 ml/kg, i.p.) was given simultaneously with haloperidol
Number of cataleptic mice (total number, 40 mice per group) in periods assessed (h) following neuroleptic cataleptogenic dose (mg/kg b.w., i.p.).
* $P < 0.01$, at least vs. control.

| Haloperidol | Number of cataleptic mice (total number, 40 mice per each group) at periods assessed (h) following medication (/kg b.w., i.p.) given simultaneously with neuroleptic cataleptogenic dose (mg/kg b.w., i.p.) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1.5 | | | 3 | | | 4.5 | | | 6 | | | 7.5 | | |
| | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng |
| 0.625 | 14 | 0* | 4 | 17 | 0* | 8 | 18 | 6* | 15 | 19 | 7* | 16 | 25 | 14 | 16 |
| 1.25 | 15 | 0* | 5 | 20 | 8* | 16 | 21 | 8* | 17 | 26 | 15 | 16 | 26 | 15 | 16 |
| 2.50 | 17 | 1* | 6 | 33 | 14* | 17* | 35 | 15* | 23* | 40 | 16* | 24* | 40 | 17* | 19* |
| 5.00 | 40 | 14* | 22* | 40 | 15* | 23* | 40 | 16* | 24* | 40 | 17* | 25* | 40 | 24* | 24* |
| 10.0 | 40 | 19* | 25* | 40 | 15* | 31* | 40 | 23* | 29* | 40 | 24* | 32* | 40 | 24* | 31* |

fluphenazine, such as 5.0 mg/kg, the anticataleptogenic effect of the pentadecapeptide BPC 157 was noted throughout the experimental period, at all tested intervals (Table 2).

*3.2.1.3. Sulpiride and clozapine*. Unlike the case with haloperidol or fluphenazine, no catalepsy could be noted in sulpiride- or clozapine-challenged mice.

### 3.2.2. Somatosensory disorientation

*3.2.2.1. Haloperidol*. Like the catalepsy, somatosensory disorientation in haloperidol-challenged mice was sustained, and lasted longer with higher doses. In general, the attenuation of the otherwise prominently expressed somatosensory disorientation could be evidenced at both the higher dose of 10 μg and the lower dose of 10 ng/kg b.w. pentadecapeptide. This was the case for almost all the periods assessed, but in several cases, only the 10-μg regimen had a marked salutary effect. This effect on disorientation regularly correlated with the effect of the pentadecapeptide BPC 157 on haloperidol catalepsy. This beneficial effect of the pentadecapeptide BPC 157 was particularly evident when the mice were damaged with the relatively high dose of haloperidol (Table 3).

*3.2.2.2. Fluphenazine*. In general, fluphenazine-induced somatosensory disorientation parallels fluphenazine catalepsy, and appears to be less expressed than the corresponding disturbance in haloperidol-treated mice. Somatosensory disorientation was seen in the fluphenazine-challenged mice that received the higher doses (1.2, 2.5 or 5 mg/kg). If somatosensory disorientation were present in fluphenazine-challenged mice, it could be improved by pentadecapeptide BPC 157 coadministration, particularly with the higher dose, but also with the lower dose regimen (however, in two cases, the nanogram regimen values were not different from the control somatosensory disorientation values) (Table 4). Regarding somatosensory disorientation following fluphenazine, as in the catalepsy assay, the highest doses of fluphenazine produced the most

Table 2
Catalepsy induced by various doses of fluphenazine, when pentadecapeptide BPC 157 (10 μg or 10 ng/kg, i.p.) or saline (control, 5.0 ml/kg, i.p.) was given simultaneously with fluphenazine
Number of cataleptic mice (total number, 40 mice per group) in periods assessed (h) following neuroleptic cataleptogenic dose (mg/kg b.w., i.p.).
* $P < 0.01$, at least vs. control.

| Fluphenazine | Number of cataleptic mice (total number, 40 mice per each group) at periods assessed (h) following medication (/kg b.w., i.p.) given simultaneously with neuroleptic cataleptogenic dose (mg/kg b.w., i.p.) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1.5 | | | 3 | | | 4.5 | | | 6 | | | 7.5 | | |
| | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng | 0.9% NaCl | BPC 157 10 μg | BPC 157 10 ng |
| 0.300 | 14 | 0* | 0* | 15 | 0* | 0* | 22 | 6* | 12 | 23 | 8* | 16 | 24 | 9 | 17 |
| 0.600 | 17 | 0* | 0* | 18 | 0* | 6* | 24 | 9 | 12 | 26 | 22 | 24 | 26 | 24 | 24 |
| 1.25 | 20 | 7* | 8* | 24 | 8* | 9* | 26 | 16 | 18 | 29 | 24 | 26 | 28 | 16 | 19 |
| 2.50 | 29 | 8* | 9* | 34 | 14* | 16* | 28 | 17 | 23 | 25 | 16 | 24 | 27 | 15 | 18 |
| 5.00 | 40 | 12* | 24* | 40 | 23* | 32* | 32 | 18* | 24 | 25 | 8* | 8* | 25 | 7* | 15 |

Table 3
Somatosensory disorientation induced by various doses (mg/kg b.w., i.p.) of haloperidol, when pentadecapeptide BPC 157 (10 μg or 10 ng/kg, i.p.) or saline (control, 5.0 ml/kg, i.p.) was given simultaneously with neuroleptic
Behavioral response (assessed using a simple scoring system [score 0–5]) scored in mice from their reaction to standardized compression of the tail root. Total number, 40 mice per group.
$P < 0.01$, at least vs. control.

| Each mouse was observed for 5 s over a period of 7.5 h after administration of neuroleptic, at intervals of 1.5 h | | Somatosensory disorientation (score 0–5) after application of neuroleptic at periods assessed (h) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Haloperidol (mg/kg b.w., i.p.) | 0.9% NaCl/ BPC 157/kg, i.p. | 1.5 | | | 3 | | | 4.5 | | | 6 | | | 7.5 | | |
| | | Median | Min | Max | Median | Min | Max | Median | Min | Max | Median | Min | Max | Median | Min | Max |
| 0.625 | **control** | **3** | **1** | **4** | **3** | **1** | **4** | **5** | **4** | **5** | **5** | **4** | **5** | **5** | **4** | **5** |
| | 10 μg | *5* | *4* | *5* | *5* | *4* | *5* | 5 | 3 | 5 | 5 | 3 | 5 | 5 | 3 | 5 |
| | 10 ng | 3 | 2 | 4 | 2 | 1 | 4 | 5 | 4 | 5 | 5 | 3 | 5 | 5 | 4 | 5 |
| 1.2 | **control** | **2** | **1** | **4** | **2** | **0** | **3** | **3** | **1** | **3** | **3** | **1** | **4** | **1** | **0** | **3** |
| | 10 μg | *5* | *3* | *5* | *4* | *3* | *5* | *5* | *3* | *5* | *5* | *4* | *5* | *5* | *4* | *5* |
| | 10 ng | 2 | 1 | 4 | 2 | 1 | 3 | 3 | 1 | 4 | *3* | *2* | *4* | *3* | *2* | *4* |
| 2.5 | **control** | **2** | **0** | **4** | **2** | **0** | **3** | **2** | **0** | **3** | **1** | **0** | **3** | **1** | **0** | **2** |
| | 10 μg | 3 | 1 | 4 | *4* | *3* | *5* | *4* | *3* | *5* | *3* | *2* | *4* | *3* | *3* | *5* |
| | 10 ng | 2 | 1 | 3 | *4* | *3* | *5* | *4* | *3* | *5* | 1 | 0 | 3 | 1 | 1 | 3 |
| 5.0 | **control** | **1** | **0** | **2** | **2** | **0** | **3** | **1** | **0** | **3** | **1** | **0** | **3** | **1** | **0** | **2** |
| | 10 μg | *3* | *2* | *4* | *3* | *3* | *5* | *3* | *2* | *5* | *2* | *1* | *3* | *2* | *1* | *3* |
| | 10 ng | *2* | *1* | *5* | *4* | *3* | *5* | *3* | *2* | *5* | *2* | *0* | *3* | *2* | *1* | *3* |
| 10.0 | **control** | **1** | **0** | **2** | **2** | **0** | **3** | **1** | **0** | **2** | **1** | **0** | **3** | **1** | **0** | **2** |
| | 10 μg | *3* | *2* | *4* | *4* | *3* | *5* | *3* | *2* | *4* | *3* | *2* | *4* | *3* | *2* | *5* |
| | 10 ng | *3* | *2* | *4* | *3* | *3* | *5* | *3* | *2* | *4* | *2* | *1* | *3* | *2* | *1* | *3* |

prominent somatosensory disorientation at all the intervals used and the counteracting effect of the pentadecapeptide BPC 157 was evident throughout the experimental period (Table 4).

Table 4
Somatosensory disorientation induced by various doses (mg/kg b.w., i.p.) of fluphenazine, when pentadecapeptide BPC 157 (10 μg or 10 ng/kg, i.p.) or saline (control, 5.0 ml/kg, i.p.) was given simultaneously with neuroleptic
Behavioral response (assessed using a simple scoring system [score 0–5]) scored in mice from their reaction to standardized compression of the tail root. Total number, 40 mice per group.
$P < 0.01$, at least vs. control.

| Each mouse was observed for 5 s over a period of 7.5 h after administration of neuroleptic, at intervals of 1.5 h | | Somatosensory disorientation (score 0–5) after application of neuroleptic at periods assessed (h) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fluphenazine (mg/kg b.w., i.p.) | 0.9% NaCl/ BPC 157 /kg, i.p. | 1.5 | | | 3 | | | 4.5 | | | 6 | | | 7.5 | | |
| | | Median | Min | Max | Median | Min | Max | Median | Min | Max | Median | Min | Max | Median | Min | Max |
| 0.3125 | **control** | **5** | **3** | **5** | **4** | **3** | **5** | **4** | **3** | **5** | **4** | **3** | **5** | **4** | **4** | **5** |
| | 10 μg | 5 | 3 | 5 | 4 | 4 | 5 | 4 | 4 | 5 | 5 | 4 | 5 | 5 | 4 | 5 |
| | 10 ng | 4 | 3 | 5 | 4 | 3 | 5 | 5 | 4 | 5 | 5 | 3 | 5 | 5 | 4 | 5 |
| 0.625 | **control** | **5** | **3** | **5** | **5** | **3** | **5** | **4** | **3** | **5** | **4** | **3** | **5** | **4** | **3** | **5** |
| | 10 μg | 5 | 3 | 5 | 5 | 3 | 5 | 5 | 3 | 5 | 5 | 4 | 5 | 5 | 4 | 5 |
| | 10 ng | 5 | 3 | 5 | 4 | 3 | 5 | 4 | 3 | 5 | 5 | 3 | 5 | 4 | 3 | 5 |
| 1.25 | **control** | **2** | **1** | **3** | **1** | **1** | **3** | **1** | **1** | **3** | **2** | **1** | **4** | **5** | **2** | **5** |
| | 10 μg | *5* | *3* | *5* | *4* | *3* | *5* | *4* | *3* | *5* | *5* | *3* | *5* | 5 | 4 | 5 |
| | 10 ng | *4* | *3* | *5* | *4* | *3* | *5* | *4* | *3* | *5* | *4* | *3* | *5* | 5 | 3 | 5 |
| 2.5 | **control** | **1** | **1** | **3** | **1** | **1** | **3** | **1** | **1** | **3** | **2** | **1** | **3** | **3** | **2** | **5** |
| | 10 μg | *5* | *4* | *5* | *4* | *2* | *5* | *4* | *2* | *5* | *5* | *4* | *5* | *5* | *4* | *5* |
| | 10 ng | *5* | *3* | *5* | *4* | *3* | *5* | *4* | *3* | *4* | *5* | *3* | *5* | 3 | 2 | 4 |
| 5.0 | **control** | **2** | **1** | **3** | **1** | **1** | **3** | **1** | **1** | **3** | **1** | **1** | **3** | **1** | **1** | **3** |
| | 10 μg | *5* | *4* | *5* | *5* | *4* | *5* | *5* | *2* | *5* | *5* | *3* | *5* | *5* | *4* | *5* |
| | 10 ng | 2 | 1 | 3 | *4* | *2* | *5* | *5* | *3* | *5* | *4* | *4* | *5* | *3* | *2* | *5* |

Table 5
Somatosensory disorientation induced by various doses (mg/kg b.w., i.p.) of sulpiride, when pentadecapeptide BPC 157 (10 μg or 10 ng/kg, i.p.) or saline (control, 5.0 ml/kg, i.p.) was given simultaneously with neuroleptic
Behavioral response (assessed using a simple scoring system [score 0–5]) scored in mice from their reaction to standardized compression of the tail root. Total number, 40 mice per group.
$P < 0.01$, at least vs. control.

| Each mouse was observed for 5 s over a period of 7.5 h after administration of neuroleptic, at intervals of 1.5 h | | Somatosensory disorientation (score 0–5) after application of neuroleptic at periods assessed (h) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sulpiride (mg/kg b.w., i.p.) | 0.9% NaCl/ BPC 157/kg, i.p. | 1.5 | | | 3 | | | 4.5 | | | 6 | | | 7.5 | | |
| | | Median | Min | Max | Median | Min | Max | Median | Min | Max | Median | Min | Max | Median | Min | Max |
| 20.0 | **control** | **3** | **1** | **4** | **2** | **1** | **3** | **2** | **1** | **3** | **4** | **3** | **5** | **4** | **3** | **5** |
| | 10 μg | *5* | *4* | *5* | *5* | *3* | *5* | *5* | *3* | *5* | 4 | 3 | 5 | 5 | 3 | 5 |
| | 10 ng | *4* | *3* | *5* | *3* | *2* | *4* | *3* | *2* | *5* | 4 | 3 | 5 | 5 | 3 | 5 |
| 40.0 | **control** | **2** | **1** | **3** | **2** | **0** | **3** | **2** | **1** | **3** | **5** | **3** | **5** | **4** | **3** | **5** |
| | 10 μg | *5* | *3* | *5* | *4* | *3* | *5* | *5* | *4* | *5* | 4 | 3 | 5 | 5 | 3 | 5 |
| | 10 ng | *4* | *3* | *5* | *3* | *3* | *5* | *3* | *3* | *5* | 4 | 3 | 5 | 4 | 3 | 5 |
| 80.0 | **control** | **2** | **0** | **3** | **2** | **0** | **3** | **2** | **1** | **3** | **4** | **3** | **5** | **5** | **4** | **5** |
| | 10 μg | *4* | *3* | *5* | *5* | *3* | *5* | *5* | *4* | *5* | 5 | 3 | 5 | 5 | 3 | 5 |
| | 10 ng | *3* | *2* | *5* | *3* | *2* | *4* | *3* | *2* | *5* | 4 | 3 | 5 | 5 | 4 | 5 |
| 160.0 | **control** | **2** | **0** | **3** | **2** | **0** | **3** | **2** | **1** | **3** | **4** | **3** | **5** | **5** | **3** | **5** |
| | 10 μg | *4* | *3* | *5* | *5* | *3* | *5* | *5* | *4* | *5* | 5 | 3 | 5 | 5 | 3 | 5 |
| | 10 ng | *4* | *3* | *5* | *3* | *2* | *5* | *3* | *2* | *5* | 4 | 3 | 5 | 5 | 3 | 5 |

*3.2.2.3. Sulpiride and clozapine*. Somatosensory disorientation was seen in those of the sulpiride- or clozapine-challenged mice that received the higher doses. Of note, this somatosensory disorientation was apparently less prominent than the haloperidol- or fluphenazine-induced somatosensory disorientation. In sulpiride- or clozapine-treated mice, unlike those treated with agents that produced catalepsy, somatosensory disorientation was apparently more transitory, and could be not evidenced throughout the experimental period (i.e., it disappeared after 3 [clozapine] or 4.5 [sulpiride] h). However, if somatosensory disorientation were present in mice challenged with either sulpiride or clozapine, it could be improved by pentadecapeptide BPC 157 coadministration, in either the higher, or the lower dose regimen (Tables 5 and 6).

### *3.3. Catalepsy and stomach lesions induction by haloperidol in rats*

#### *3.3.1. Haloperidol catalepsy*

As it did in mice, the i.p. application of 5.0 mg/kg b.w. of haloperidol induced a prominent and sustained catalepsy

Table 6
Somatosensory disorientation induced by various doses (mg/kg b.w., i.p.) of clozapine, when pentadecapeptide BPC 157 (10 μg or 10 ng/kg, i.p.) or saline (control, 5.0 ml/kg, i.p.) was given simultaneously with neuroleptic. Behavioral response (assessed using a simple scoring system [score 0–5]) scored in mice from their reaction to standardized compression of the tail root. Total number, 40 mice per group
$P < 0.01$, at least vs. control.

| Each mouse was observed for 5 s over a period of 7.5 h after administration of neuroleptic, at intervals of 1.5 h | | Somatosensory disorientation (score 0–5) after application of neuroleptic at periods assessed (h) | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Clozapine (mg/kg b.w., i.p.) | 0.9% NaCl/ BPC 157/kg, i.p. | 1.5 | | | 3 | | | 4.5 | | | 6 | | | 7.5 | | |
| | | Median | Min | Max | Median | Min | Max | Median | Min | Max | Median | Min | Max | Median | Min | Max |
| 25.0 | **control** | **2** | **1** | **3** | **2** | **1** | **4** | **4** | **3** | **5** | **5** | **4** | **5** | **5** | **3** | **5** |
| | 10 μg | *4* | *3* | *5* | *4* | *3* | *5* | 4 | 3 | 5 | 5 | 4 | 5 | 5 | 4 | 5 |
| | 10 ng | *3* | *2* | *4* | *3* | *2* | *4* | 4 | 3 | 5 | 5 | 3 | 5 | 5 | 3 | 5 |
| 50.0 | **control** | **2** | **1** | **3** | **2** | **1** | **3** | **4** | **3** | **5** | **5** | **3** | **5** | **4** | **3** | **5** |
| | 10 μg | *4* | *3* | *5* | *4* | *3* | *5* | 4 | 3 | 5 | 5 | 4 | 5 | 5 | 3 | 5 |
| | 10 ng | *4* | *3* | *5* | *4* | *3* | *5* | 4 | 3 | 5 | 5 | 3 | 5 | 5 | 3 | 5 |
| 100.0 | **control** | **2** | **0** | **3** | **2** | **0** | **3** | **4** | **3** | **5** | **5** | **3** | **5** | **4** | **3** | **5** |
| | 10 μg | *3* | *2* | *4* | *3* | *2* | *4* | 4 | 3 | 5 | 5 | 3 | 5 | 5 | 3 | 5 |
| | 10 ng | *3* | *2* | *4* | *2* | *2* | *3* | 4 | 3 | 5 | 4 | 4 | 5 | 4 | 4 | 5 |

in challenged rats. Pentadecapeptide BPC 157 application in the dose of 10 μg or 10 ng/kg b.w. apparently attenuated the otherwise consistent catalepsy course in haloperidol-challenged rats (Fig. 2). Given at the lower dose regimens, BPC 157 could inhibit the haloperidol-induced gastric lesions (see below), but not the haloperidol-induced catalepsy.

*3.3.2. Haloperidol gastric lesions*

The gastric lesions appeared regularly in haloperidol-treated rats (i.e., 18 of 20 control rats), in analogy with results of our previous studies (Sikiric et al., 1986, 1988). Therefore, this mucosal injury in haloperidol rats may also be characteristic of haloperidol activity like the known haloperidol-induced catalepsy. Support for this suggestion is that they were obtained with the same haloperidol regimen. Coadministration of pentadecapeptide BPC 157 with haloperidol completely inhibited lesion development. This beneficial effect was shared by the microgram and the nanogram regimens, as the rats were protected even with the lower-dose pentadecapeptide regimens (Fig. 3).

The microscopy data were in full agreement with macroscopic observations. Generally, macroscopically visible haloperidol lesions appeared as mucosal defects ranging from erosions (as seen from the present experiments for the 5.0 mg/kg b.w., i.p. dose), surrounded with edema of the lamina propria and submucosa with a mixed inflammatory reaction, to frank ulcers (as seen with the highest

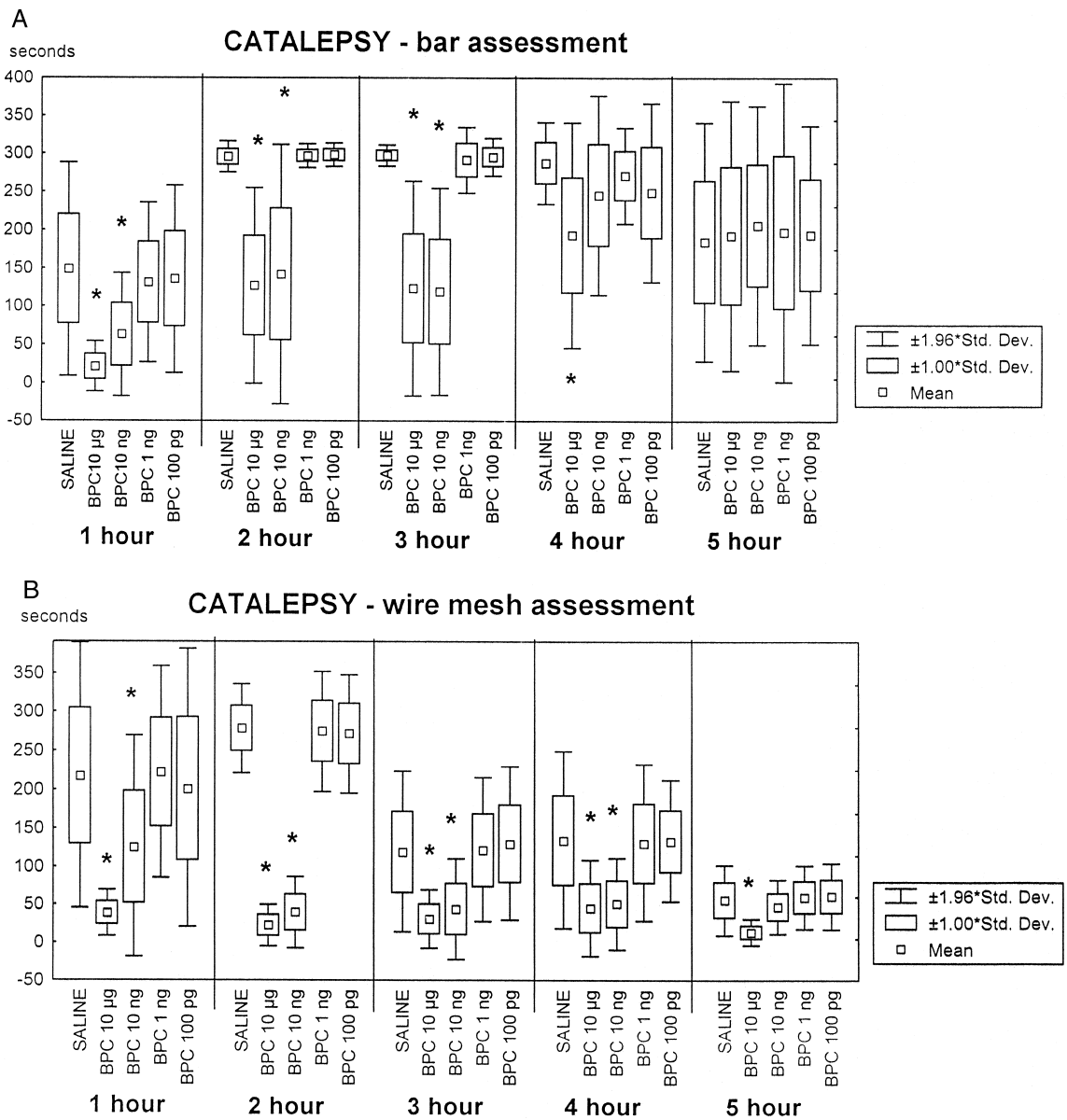


Fig. 2. Catalepsy induced by haloperidol (5 mg/kg, i.p.) when pentadecapeptide BPC 157 (10 μg, 10 ng, 1.0 ng or 100 pg/kg, i.p.) or saline (control, 0.5 ml/kg, i.p.) was given simultaneously with haloperidol. Catalepsy time (s) was assessed using a modified procedure, previously described by Barnes et al. (1990), for 5 min on the horizontal bar (bar catalepsy) (A) and inclined screen (wiremesh catalepsy) (B) at 60, 120, 180, 240 and 300 min post-injection. Total number, 20 rats per each group. $^{*}P < 0.01$, at least vs. control.

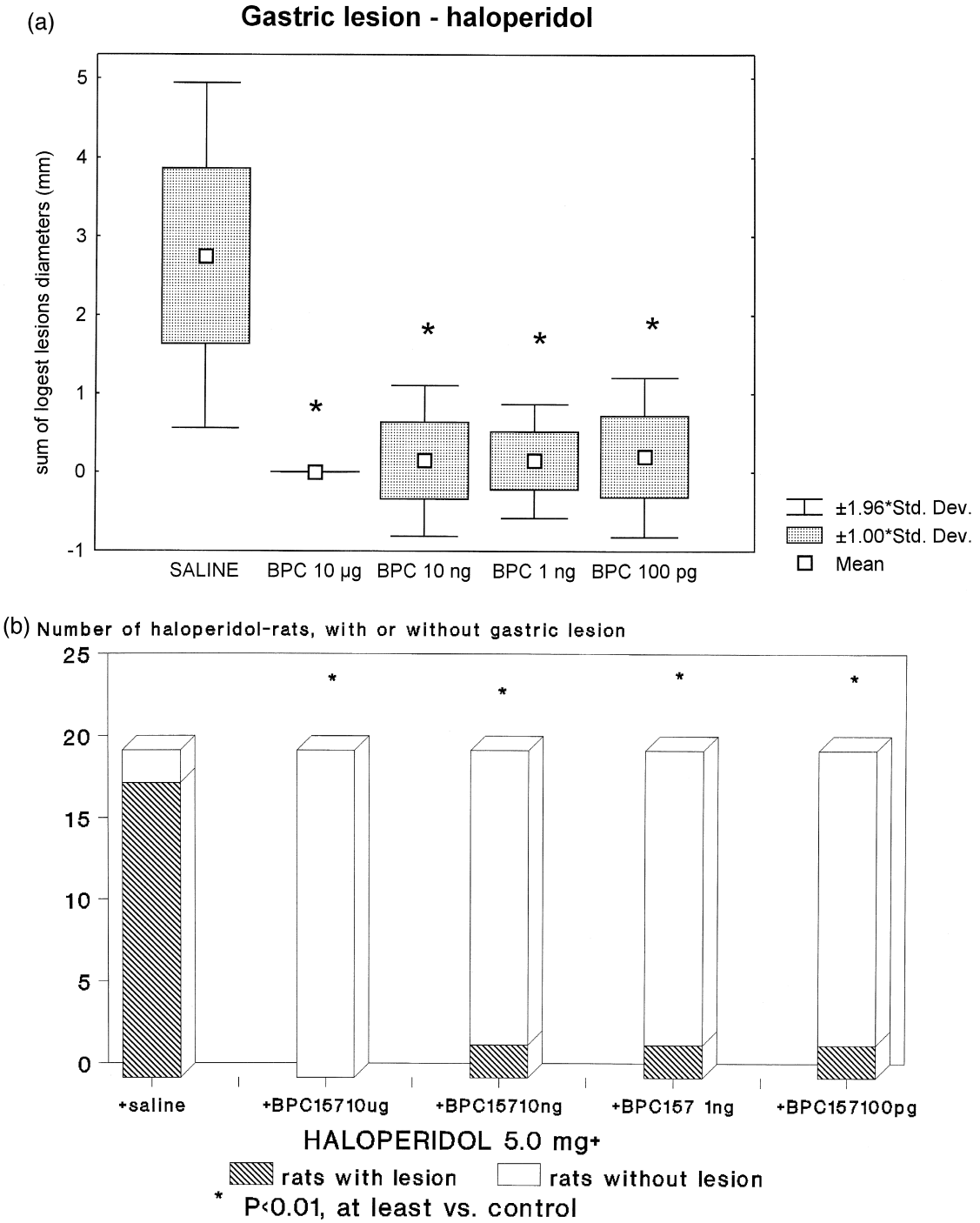


Fig. 3. Ulcerogenesis induced by haloperidol (5 mg/kg, i.p.) when pentadecapeptide BDP 157 (10 μg, 10 ng, 1.0 ng or 100 pg/kg, i.p.) or saline (control, 0.5 ml/kg, i.p.) was given simultaneously with haloperidol. Gastric lesions (sum of longest diameters of lesions, mm) (a), and lesion incidence (number of rats with and the number of rats without lesions) (b) 24 h after haloperidol administration. Total number, 20 rats per group. $^{*}P < 0.01$, at least vs. control.

dose of haloperidol, i.e., 25 mg/kg b.w., i.p.; Sikiric et al., 1986).

## 4. Discussion

Severe behavioral disturbances were produced in all animals treated with haloperidol or fluphenazine, e.g., marked catalepsy was seen in these animals. It is important that the dose regimen used for haloperidol and fluphenazine even exceeded the dosages applied in other studies (Barnes et al., 1990; Elliot et al., 1990; Fujiwara, 1992; Moore et al., 1993; Krish et al., 1994; Sebens et al., 1995; Bartoszyk et al., 1996). Thus, the catalepsy observed in these animals appears to fulfill all criteria for anticataleptic effects inves-

tigation. In general, the neuroleptic that induced catalepsy has dopamine $D_1/D_2$ receptor blocking activity (Fujiwara, 1992; Moore et al., 1993), particularly in the striatal system (Koffer et al., 1978). Thus, although the site of action of pentadecapeptide BPC 157 was not investigated in the present study, it would be expected that the anticataleptic effect of this pentadecapeptide is mediated through these receptors. However, other possibilities should not be neglected; for instance, atropine blocks catalepsy via muscarine receptor blockade, and a secondary cholinergic link may be activated in neuroleptic-induced catalepsy (Koffer et al., 1978).

In the sulpiride or clozapine groups, only somatosensory disorientation (more expressed in sulpiride-treated mice) was seen, without catalepsy, unlike in the case of haloperidol or fluphenazine mice. A number of other studies were unable to show catalepsy following sulpiride or clozapine administration (Fujiwara, 1992). Nevertheless, other unwanted side-effects were produced, e.g., excessive sedation (Gerlach, 1991; Krish et al., 1994). Sulpiride has been considered to have greater selectivity for dopamine $D_2$ receptors with a preferential action on the mesolimbic dopamine system (Fujiwara, 1992). Clozapine has been suggested to reflect the balance between serotonin 5-$HT_{2A}$ receptor antagonism and antidopaminomimetic properties (Kalkman et al., 1997). Although far less investigated than catalepsy, somatosensory disorientation is thought to be an indicative epiphenomenon related to a lesser extent of a dopamine $D_1/D_2$ receptor blockade (i.e., sulpiride, clozapine) that would otherwise lead to catalepsy (e.g., haloperidol, fluphenazine) (Moore et al., 1993). In support, the catalepsy was also antagonized by BPC 157 application. However, the mechanism of the noted anticataleptic effect of the pentadecapeptide remains to be further defined.

Taking these findings together with results of our previous dopamine receptor supersensitivity studies (Jelovac et al., 1998), a (temporary) lack of dopamine system function due to dopamine receptor blockade by neuroleptic(s) is commonly considered to be responsible for both neuroleptic-induced catalepsy and amphetamine/haloperidol-induced climbing behavior (Masuda et al., 1991; Fujiwara, 1992). In theory, the attenuation of both of these disturbances (i.e., in the case of pentadecapeptide BPC 157) could suggest two possibilities. Dopamine receptor blockade may have less extent than otherwise, so that the dopamine system can still function (i.e., catalepsy appearance was postponed in pentadecapeptide BPC 157-treated mice). Alternatively, as suggested above (Koffer et al., 1978), dopamine function may be at least partly replaced and functions that could otherwise be fully absent are partly restored towards a normal level. Consistently, the anticataleptogenic effect of the pentadecapeptide BPC 157 was particularly evident when all mice would otherwise have exhibited catalepsy, as was the case with the highest doses of haloperidol and fluphenazine. The findings in other pentadecapeptide BPC 157 studies, that the stereotypy induced by amphetamine was also prevented/reversed (Jelovac et al., 1998), could suggest an effect close to receptors that may modulate dopamine release/synthesis, by-passing/preventing, or at least interfering with early dopamine receptor blockade. Indeed, this anticataleptic effect was present in the early period at more prolonged intervals, and was also present, even when the highest doses of haloperidol or fluphenazine were given. Likewise, in both investigations, our previous report (Jelovac et al., 1998) and in the present study, the pentadecapeptide was applied simultaneously with a dopamine receptor antagonist. Thus, under both theoretical conditions, dopamine receptor blockade (e.g., Moore et al., 1993) and dopamine receptor supersensitivity development (Masuda et al., 1991), the counteracting effect of the pentadecapeptide tested is prompt and probably related to the same inherent mechanism of action of the pentadecapeptide, needing further consideration. In any event, later negative effects of dopamine receptor (ant)agonist(s) application would be prevented. Theoretically, such an ability to maintain the balance of the dopamine system could be very useful in various conditions related to disturbances of dopamine system functions. Also, it could explain why neither catalepsy nor somatosensory disorientation was seen when pentadecapeptide BPC 157 was applied alone in normal animals. Further, continued activity of constitutive NO synthase is necessary for normal body movement to occur (Starr and Starr, 1995), and the involvement of NO was suggested in both haloperidol-induced sensitization (Pudiak and Bozarth, 1997) and methamphetamine-induced dopaminergic neurotoxicity (Abekawa, 1997). Recently, the pentadecapeptide was shown to modulate NO-release and the activity of the NO agents, $N^G$-nitro-L-arginine methylester (L-NAME) a competitive inhibitor of endothelium NO generation, and the NO precursor, L-arginine (Grabarevic et al., 1997; Sikiric et al., 1997d).

Finally, whatever the mechanism of the central action of this pentadecapeptide after its i.p. application, behavioral effects of the peptides — given peripherally — are commonly thought to be an outward expression of specific cellular signals, most likely initiated at some visceral receptive relay of the central nervous system (Koob and Bloom, 1983). Besides, there are few regions in the brain where the blood–brain barrier does not exist, the so-called circumventricular organs, and here, some peptides act on specific peptide receptors to stimulate neuronal pathways within the brain (McKinley and Oldfield, 1998). Likewise, in keeping with the generally known presence of the gut peptides in both brain and gut (Thompson et al., 1987), the suggested presence of the pentadecapeptide BPC 157 not only in the stomach, but also in the brain, although not fully defined (Sikiric et al., 1993a), could possibly be responsible for the effect noted. Moreover, the antagonism effects of the pentadecapeptide BPC 157 described are not completely uncommon. Namely, the antagonism of both amphetamine stereotypy and neuroleptic catalepsy, in addi-

tion to that by pentadecapeptide BPC 157, is shared by some agents known as dopamine agonists, and some agents referred to as dopamine antagonists (Parkes, 1974; Bartoszyk et al., 1996; Kalkman et al., 1997). A seemingly paradoxical ability of the dopaminomimetic, amantadine, that antagonizes (not promotes) amphetamine stereotypy along with reducing neuroleptic catalepsy has been mentioned (Parkes, 1974). Likewise, clozapine, a potent neuroleptic, was shown to antagonize (not promote) catalepsy induced by other neuroleptics, besides reducing amphetamine stereotypy (Bartoszyk et al., 1996; Kalkman et al., 1997). Moreover, clozapine could improve the tremor in Parkinson's disease patients (Kalkman et al., 1997).

Thus, the salutary action of the pentadecapeptide tested should be viewed according to an approach different from the traditional view. As an additional link between the disturbances focused in the present study and the gastric origin of the pentadecapeptide studied (Sikiric et al., 1993a,b, 1994, 1996a,b, 1997a,b,c,d,e; Grabarevic et al., 1997; Seiwerth et al., 1997; Jelovac et al., 1998; Konjevoda et al., 1998), it should be noted that dopamine dysfunction is widely implicated not only in central nervous system disorders but in various gastrointestinal malfunctions (Szabo and Neumeyer, 1983). Dopamine agonists have a salutary effect in both experimental animals and patients (Szabo and Neumeyer, 1983; Sikiric et al., 1986, 1991). On the other hand, dopamine antagonists, including those used as neuroleptics (e.g., haloperidol), either induce gastric ulcers when given alone, or potentiate gastrointestinal ulcers provoked by other challengers (Szabo and Neumeyer, 1983; Sikiric et al., 1986). However, although this harmful activity had been noticed in the patients taking neuroleptics (e.g., haloperidol) (Szabo and Neumeyer, 1983), clear experimental demonstration of the relation between catalepsy and mucosal gastric lesions was still lacking. However, the connection of catalepsy and gastrointestinal damage was clearly demonstrated in haloperidol-treated rats in the present study. This relation was not entirely unexpected, since MPTP, a centrally acting dopamine neurotoxin, also induced gastrointestinal lesions (Neumeyer and Szabo, 1986). Emphasizing the possible common link, it was shown that pentadecapeptide BPC 157, given as a 10-μg or 10-ng regimen, completely inhibited the appearance of gastric lesions otherwise induced by haloperidol along with its antagonism of the catalepsy induced by haloperidol in rats. Given as the lower regimens, it could inhibit haloperidol gastric lesions, but not haloperidol catalepsy. This finding is fully consistent with the reported beneficial effects of this pentadecapeptide against other gastrointestinal lesions induced by various challengers (Sikiric et al., 1993a, 1994, 1996a,b, 1997b,c,d,e; Paré and Kluczynski, 1994; Veljaca et al., 1994a,b, 1995a,b; Sandor et al., 1996, 1997; Bodis et al., 1997; Grabarevic et al., 1997) and with its gastric origin and high stability in gastric juice (Sikiric et al., 1993c; Veljaca et al., 1995a). Importantly, this pentadecapeptide BPC 157 activity may provide a basis for both connection and separation between neuroleptic(s)-induced catalepsy and gastric lesions.

In summary, in favour of this catalepsy/gastrointestinal lesion connection and inherent cataleptogenic and ulcerogenic neuroleptic potential, is the fact that both disturbances were induced with the same dose of haloperidol and were prevented by the pentadecapeptide BPC 157, with an apparently similar high incidence (i.e., the mucosal lesions were regularly present in haloperidol-treated control animals, like the catalepsy). Together, these findings may show that pentadecapeptide BPC 157 interacts fully with the dopamine system, both centrally and peripherally. As an alternative possible analogy for a non-dopamine explanation, atropine blocks catalepsy via muscarine receptor blockade, and a secondary cholinergic link may be activated in neuroleptic-induced catalepsy (Koffer et al., 1978). The development of specific antagonists of pentadecapeptide BPC 157, the receptors for BPC 157, or its target enzyme will certainly throw light on this issue.

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