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Gastric pentadecapeptide BPC 157 effective against serotonin syndrome in rats

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Abstract

Serotonin syndrome commonly follows irreversible monoamine oxidase (MAO)-inhibition and subsequent serotonin (5-HT) substrate (in rats with fore paw treading, hind limbs abduction, wet dog shake, hypothermia followed by hyperthermia). A stable gastric pentadecapeptide BPC 157 with very safe profile (inflammatory bowel disease clinical phase II, PL-10, PLD-116, PL-14736, Pliva) reduced the duration of immobility to a greater extent than imipramine, and, given peripherally, has region specific influence on brain 5-HT synthesis (α-[^{14}C]methyl-L-tryptophan autoradiographic measurements) in rats, different from any other serotonergic drug. Thereby, we investigate this peptide (10 μg, 10 ng, 10 pg/kg i.p.) in (i) full serotonin syndrome in rat combining pargyline (irreversible MAO-inhibition; 75 mg/kg i.p.) and subsequent L-tryptophan (5-HT precursor; 100 mg/kg i.p.; BPC 157 as a co-treatment), or (ii, iii) using pargyline or L-tryptophan given separately, as a serotonin-substrate with (ii) pargyline (BPC 157 as a 15-min posttreatment) or as a potential serotonin syndrome inductor with (iii) L-tryptophan (BPC 157 as a 15 min-pretreatment). In all experiments, gastric pentadecapeptide BPC 157 contrasts with serotonin-syndrome either (i) presentation (i.e., particularly counteracted) or (ii) initiation (i.e., neither a serotonin substrate (counteraction of pargyline), nor an inductor for serotonin syndrome (no influence on L-tryptophan challenge)). Indicatively, severe serotonin syndrome in pargyline+L-tryptophan rats is considerably inhibited even by lower pentadecapeptide BPC 157 doses regimens (particularly disturbances such as hyperthermia and wet dog shake thought to be related to stimulation of 5-HT$_{2A}$ receptors), while the highest pentadecapeptide dose counteracts mild disturbances present in pargyline rats (mild hypothermia, feeble hind limbs abduction). Thereby, in severe serotonin syndrome, gastric pentadecapeptide BPC 157 (alone, no behavioral or temperature effect) has a beneficial activity, which is likely, particular, and mostly related to a rather specific counteraction of 5-HT$_{2A}$ receptors phenomena.

Keywords: Gastric pentadecapeptide BPC 157; Pargyline/L-tryptophan; Serotonin syndrome; 5-HT$_{2A}$ receptor antagonism; (Rats)

1. Introduction

This study focus serotonin (5-HT) syndrome, the most serious toxic interaction of antidepressants (i.e., Houlihan, 2004) and attempts to further clarify an intriguing effect of a peripheral peptide, gastric pentadecapeptide BPC 157, on brain 5-HT synthesis and release (Tohyama et al., 2004). Namely, it initially reduced the duration of immobility to a greater extent than imipramine, suggestive for involvement of the brain serotonergic and noradrenergic systems (Sikiric et al., 2000). Currently, gastric pentadecapeptide BPC 157 (GEPPPGKPADDAGLV, M.W.1419; i.e., Sikiric et al., 1994, 1997a,b, 1999, 2003; Jelovac et al., 1999; Bilic et al., 2001; Lovric-Bencic et al., 2004; Tohyama et al., 2004; Veljaca et al., 2002) is promising in inflammatory bowel disease clinical phase II (PL-10, PLD-116, PL-14736, Pliva). More importantly, besides reduced duration of

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immobility and particular effect on brain 5-HT synthesis (Tohyama et al., 2004; Sikiric et al., 2000), also given peripherally, it affects various disturbances supposed to be centrally mediated (Jelovac et al., 1998, 1999; Sikiric et al., 1999, 2001, 2002; Boban Blagaic et al., 2004)) by the systems (i.e., dopaminergic, GABA-ergic) (Nisijima et al., 2001, 2003) involved also in 5-HT disturbances.

As indicated, very recently, using α-[^{14}C]methyl-L-tryptophan autoradiographic measurements, gastric pentadecapeptide BPC 157, a gut peptide, given peripherally, has region specific influences on brain 5-HT synthesis in rats, different following acute and chronic treatments (Tohyama et al., 2004). The effects of BPC 157 reported (Tohyama et al., 2004) do not resemble the results obtained with any other serotonergic drug using this method (Diksic, 2001; Diksic and Young, 2001; Diksic et al., 1995; Tohyama et al., 2002). This may suggest that although BPC 157 has an effect on 5-HT synthesis in some brain structures in which 5-HT synthesis is affected by drugs acting on the brain serotonergic system (e.g., fluoxetine, paroxetine), the mechanism of the BPC 157 action probably differs greatly (Tohyama et al., 2004). Most likely, this peptide has a prompt and inherent action since it also reduces antidepressant-arrhythmias, and severe cardiotoxicity (Lovric et al., 2003; Lovric-Bencic et al., 2004). Its particular stability (i.e., no degradation in otherwise highly degradating condition (i.e., Sikiric et al., 1994, 1997a,b, 1999, 2003; Jelovac et al., 1999; Lovric et al., 2003; Lovric-Bencic et al., 2004; Boban Blagaic et al., 2004), non-degraded in human gastric juice (Veljaca et al., 1995), and non-toxicity (even limit test negative, no side effects in trials (Veljaca et al., 2002)) certainly both contribute. Together, these findings could be of both theoretical and practical importance for antidepressants therapy.

Thus, in present study, presenting with a beneficial effect mostly related to a counteraction of 5-HT$_{2A}$-receptor phenomena, pentadecapeptide BPC 157 (in doses previously used (Sikiric et al., 1993; Sikiric et al., 1994, 1997a,b, 1999, 2000, 2002, 2003; Jelovac et al., 1998, 1999; Lovric et al., 2003; Lovric-Bencic et al., 2004; Tohyama et al., 2004; Boban Blagaic et al., 2004) particularly counteracts a severe 5-HT syndrome otherwise induced with pargyline (irreversible monoamine oxidase (MAO)-inhibition)/L-tryptophan (5-HT precursor) application (i.e., rats presented with fore paw treading, hind limbs abduction, wet dog shake, hypothermia followed by hyperthermia).

2. Materials and methods

2.1. Animals

Male Wistar rats aged 35 days weighing 150 g were used in all of the experiments accordingly with study of Darmani and Ahmad (1999), randomly assigned. The rats where housed at a room temperature of 22 °C ± 1–2 °C with a 12-h light–dark cycle singly caged, for 14 days before the experiment. Food and water were available ad libitum. Local ethic committee approved all of the experiments.

2.2. Drugs

Pargyline HCl (Sigma, USA) and pentadecapeptide BPC 157 (GEPPPGKPADDAGLV, molecular weight 1419 Da, manufactured by Diagen, Slovenia; Sikiric et al., 1993; Sikiric et al., 1994, 1997a,b, 1999, 2000, 2002, 2003; Jelovac et al., 1998, 1999; Lovric et al., 2003; Lovric-Bencic et al., 2004; Tohyama et al., 2004; Boban Blagaic et al., 2004) were dissolved in saline; L-tryptophan (Merck, Germany) was suspended in saline containing 0.5% carboxymethil cellulose sodium (Abdel-Fattah et al., 1995, 1996, 1997). All drugs were freshly prepared before starting the experiments.

2.3. Experimental protocol

The agents, pargyline (75 mg/kg), L-tryptophan (100 mg/kg), gastric pentadecapeptide BPC 157 (10 μg, 10 ng, 10 pg/kg), or saline (5.0 ml/kg), were given intraperitoneally (i.p.; Sikiric et al., 1993; Sikiric et al., 1994, 1997a,b, 1999, 2000, 2002, 2003; Jelovac et al., 1998, 1999; Lovric et al., 2003; Lovric-Bencic et al., 2004; Tohyama et al., 2004; Boban Blagaic et al., 2004; Abdel-Fattah et al., 1995, 1996, 1997). As described, 5-HT syndrome was induced with pargyline (75 mg/kg i.p.) and subsequent L-tryptophan (100 mg/kg i.p.) application, given at 15 min thereafter. Pentadecapeptide BPC 157 was challenged alone, in rats treated with either L-tryptophan or pargyline, and finally in pargyline-pretreated rats challenged with L-tryptophan as follows: (i) To discriminate whether pentadecapeptide BPC 157 could provoke a temperature change or even a 5-HT syndrome, pentadecapeptide BPC 157 (or an equivolume of saline) was given at 15 min before L-tryptophan (or an equivolume of saline). To point out the possible influence on MAO-inhibition induced by pargyline, or whether pentadecapeptide BPC 157 could be a 5-HT-substrate as L-tryptophan, pentadecapeptide BPC 157 (or an equivolume of saline) was given at 15 min after pargyline. (ii) Considering the influence of pentadecapeptide BPC 157 on 5-HT syndrome presentation in pargyline pretreated rats challenged with L-tryptophan, pargyline was applied at 15 minutes before L-tryptophan co-administered with pentadecapeptide BPC 157 or saline.

2.4. Assessment

The procedure (Darmani and Ahmad, 1999) was generally adopted. The behavior assessment was just before first administration and every 15 min to 90 min, and thereafter, at 150 min, and at 210 min for 15 sec (fore paw treading, hind limbs abduction) or 5 min (wet dog shake). The behavioral disturbance severity was assessed as a score (0–3) of fore paw treading or hind limbs abduction (score 0—absent,

score 1—moderate, score 2—mild, score 3—prominent), frequency of wet dog shake (number of wet dog shake per rat). Rectal temperature (°C) was assessed in separate animals with a digital thermometer (BAT-12, Sensortek., USA). A probe (1.5 mm in diameter, 10 cm long) was inserted 3 cm into the rectum until the recorded temperature reached plateau. Rectal temperature of each animal was recorded just before first administration, as starting temperature, and every 15 min to 90 min, and thereafter, after 90 min to 210 min, the assessment was every 1 h as described before (Boban Blagaic et al., 2004; Sikiric et al., 1999).

2.5. Statistical analysis

Analysis was carried out with Kruskal–Wallis test, and due to Bonferroni's correction, values of $P<0.008$ for subsequent comparisons using Mann–Whitney test were considered significant.

3. Results

Consistently with 5-HT-syndrome induction (irreversible MAO-inhibition+5-HT precursor), pargyline before L-tryptophan, produce together a severe disorder, a full 5-HT syndrome in rats (fore paw treading, hind limbs abduction, wet dog shake, hypothermia followed by hyperthermia; Fig. 1 and Table 2). Given separately, L-tryptophan as a 5-HT precursor produces no change (Fig. 2), while pargyline, as an irreversible MAO-inhibitor, induces only mild disturbances, i.e., hypothermia and feeble hind limbs abduction (Fig. 3 and Table 1).

Pentadecapeptide BPC 157 alone does not produce any behavioral or temperature change (Fig. 4). Furthermore, we investigate this peptide in full 5-HT syndrome, combining pargyline and subsequent L-tryptophan, BPC 157 as a co-treatment (Fig. 1 and Table 2). In addition, using pargyline or L-tryptophan given separately, gastric pentadecapeptide BPC 157 is tested as a possible 5-HT-substrate with pargyline (BPC 157 as a 15-min posttreatment; Fig. 3 and

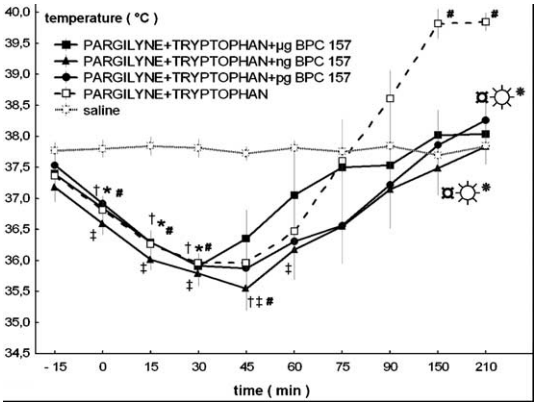

Fig. 1. Temperature change after pargyline, and subsequent L-tryptophan (serotonin syndrome), saline, or pentadecapepeptide BPC 157 application in pargyline-pretreated rats. 8–10 rats per each group. Rectal temperature (°C, Mean ± S.E.; temperature at indicated intervals till 210 min; starting temperature recorded just before saline or initial challenging medication (pargyline; −15), at 15 min before L-tryptophan alone, or co-administered with pentadecapeptide BPC 157 (BPC) or saline administration (0). Pargyline (75 mg/kg), L-tryptophan (100 mg/kg), gastric pentadecapeptide BPC 157 (10 µg, 10 ng, 10 pg/kg), or saline (5.0 ml/kg) given intraperitoneally. Kruskal–Wallis test, and due to Bonferroni's correction, $p<0.008$ for subsequent comparisons using Mann–Whitney test: vs. saline: #—pargyline+L-tryptophan+saline, †—pargyline+L-tryptophan+BPC 157 pg, ‡—pargyline+L-tryptophan+BPC 157 ng, *—pargyline+L-tryptophan+BPC 157 µg; vs. pargyline+L-tryptophan+saline: ¤—pargyline+L-tryptophan+BPC 157 pg, ☼—pargyline+L-tryptophan+BPC 157 ng, *—pargyline+L-tryptophan+BPC 157 µg.

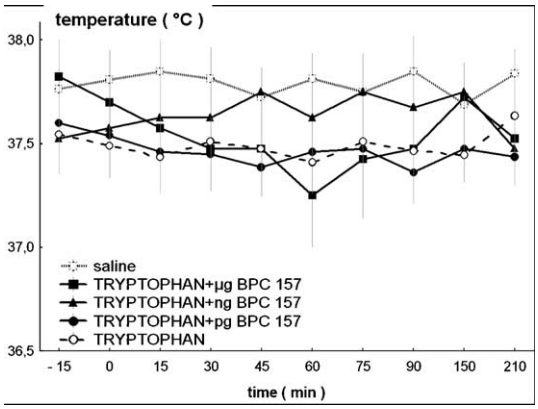

Fig. 2. The effect of pentadecapeptide BPC 157 given before L-tryptophan on rectal temperature (°C, Mean ± S.E.; temperature at indicated intervals till 210 min; starting temperature recorded just before saline or initial medication, pentadecapeptide BPC 157 (−15), at 15 min before L-tryptophan administration (0). Gastric pentadecapeptide BPC 157 (10 µg, 10 ng, 10 pg/kg) or saline (5.0 ml/kg) given intraperitoneally. 8–10 rats per each group. No significant change.

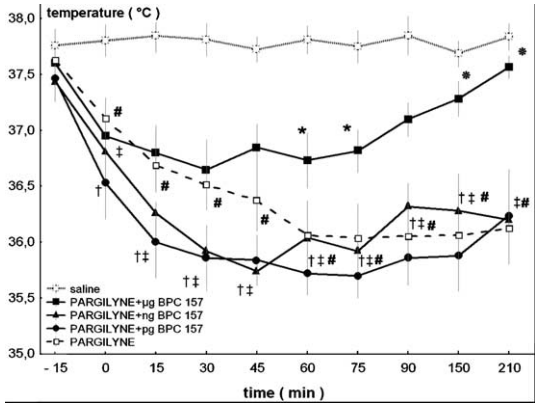

Fig. 3. Temperature change after pargyline, and subsequent pentadecapeptide BPC 157 or saline application in pargyline-pretreated rats. 8–10 rats per each group. Rectal temperature (°C, Mean ± S.E.; temperature at indicated intervals till 210 min; starting temperature recorded just before saline or initial challenging medication (pargyline; −15), at 15 min before (pentadecapeptide BPC 157) administration (0). Pargyline (75 mg/kg), gastric pentadecapeptide BPC 157 (10 µg, 10 ng, 10 pg/kg), or saline (5.0 ml/kg) given intraperitoneally. Kruskal–Wallis test, and due to Bonferroni's correction, $p<0.008$ for subsequent comparisons using Mann–Whitney test: vs. saline: #—pargyline+saline, †—pargyline+BPC 157 pg, ‡—pargyline+BPC 157 ng, *—pargyline+BPC 157 µg; vs. pargyline+saline: *—pargyline+BPC 157 µg.

Table 1
Behavioral disturbances after pargyline, and subsequent pentadecapeptide BPC 157 or saline application (at 15 min) in pargyline-pretreated rats

Treatment/kg i.p.	Time points of assessment (min; hind limb abduction, behaviour score (0–3) (minimum/median/maximum). Starting time (0) immediately before pargyline, and thereafter, assessment at indicated intervals over period of 210 min								
	0	15	30	45	60	75	90	150	210
Pargyline 75 mg+Saline (control)	0/0/0	0/1/1	1/1/1	2/2/2	2/2.5/3	2/3/3	2/2/3	1/1/2	1/1/1
Pargyline 75 mg+BPC 157 10 pg	0/0/0	0/0.5/1	1/1/2	1/2/3	2/2.5/3	2/2/3	2/2/2	1/1/2	1/1/1
Pargyline 75 mg+BPC 157 10 ng	0/0/0	0/0/1	1/1/1	1/1/2	1/2/2	0/1.5/2a	0/1/1a	0/0/1a	0/0/1
Pargyline 75 mg+BPC 157 10 μg	0/0/0	0/0/1	1/1/1	1/1/2	0/1/2a	0/1/2a	0/0/1a	0/0/0a	0/0/0a

8–10 rats per each group. a—vs. control, Kruskal–Wallis test, and due to Bonferroni's correction, $p < 0.008$ for subsequent comparisons using Mann–Whitney test.

Table 1) or as a potential 5-HT-syndrome inductor with L-tryptophane (BPC 157 as a 15-min pretreatment; Fig. 2). Gastric pentadecapeptide BPC 157 counteracts both temperature and behavioral changes in all these experiments, and obviously contrasts with 5-HT-syndrome either presentations (i.e., particularly counteracted (Fig. 1 and Table 2)) or initiation (i.e., neither a 5-HT-substrate (counteraction of pargyline (Fig. 3 and Table 1), nor an inductor for 5-HT-syndrome (no influence on L-tryptophan challenge (Fig. 2)).

Indicatively, severe 5-HT syndrome in pargyline+L-tryptophan rats is considerably inhibited even by lower pentadecapeptide BPC 157 doses regimens (particularly disturbances such as hyperthermia and wet dog shake thought to be related to stimulation of 5-HT_{2A} receptors), while the highest pentadecapeptide dose antagonizes mild disturbances present in pargyline rats (mild hypothermia, feeble hind limbs abduction).

4. Discussion

Gastric pentadecapeptide BPC 157 particularly counteracts 5-HT syndrome (i.e., otherwise induced by combining irreversible MAO-inhibition (pargyline) and 5-HT precursor

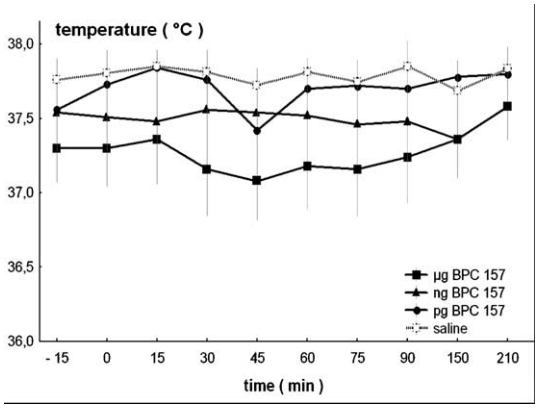

Fig. 4. The effect of pentadecapeptide BPC 157 or saline on rectal temperature (°C, Mean ± S.E.; temperature at indicated intervals till 210 min; starting temperature recorded just before initial medication (saline (control); − 15), at 15 min before pentadecapeptide BPC 157 administration (0). Gastric pentadecapeptide BPC 157 (10 μg, 10 ng, 10 pg/kg) or saline (5.0 ml/kg) given intraperitoneally. 8–10 rats per each group. No significant change.

(L-tryptophan; Darmani and Ahmad, 1999; Abdel-Fattah et al., 1997)). This emphasizes all of its effects reported: brain 5-HT synthesis and release (Tohyama et al., 2004), the duration of immobility reduced to a greater extent than imipramine (Sikiric et al., 2000) with other central effects (i.e., given in the same dose range (Jelovac et al., 1998, 1999; Sikiric et al., 1999, 2001, 2002; Boban Blagaic et al., 2004)) but not a 5-HT-substrate (i.e., pargyline effect not potentiated, but counteracted), nor a threatening inducer of 5-HT syndrome (i.e., presenting no influence on L-tryptophan alone). Furthermore, to a special gastric pentadecapeptide BPC 157–5-HT syndrome relation points an easier counteraction of more severe pargyline+L-tryptophan symptoms (also lower doses gastric pentadecapeptide BPC 157 regimens effective) than pargyline–mild hypothermia, feeble hind limbs abduction (i.e., the highest pentadecapeptide dose effective). This could be hardly explained unless specificity is considered. So far, no pharmacokinetic interaction for pentadecapeptide BPC 157 is known (Veljaca et al., 2002). Possibly, gastric pentadecapeptide BPC 157-pargyline+L-tryptophan symptoms relation is along with particularly high central 5-HT level (Abdel-Fattah et al., 1997) as a result of particular pargyline+L-tryptophan amplification, and pentadecapeptide BPC 157 region specific influence on brain 5-HT synthesis (Tohyama et al., 2004). Furthermore, just the phenomena (hyperthermia and wet dog shake (regardless they appeared at different time)) thought to be related to stimulation of 5-HT_{2A} receptors (Darmani and Ahmad, 1999; Abdel-Fattah et al., 1997) are consistently counteracted, but not 5-HT_{1A} receptor stimulation phenomena (i.e., fore paw treading, hind limbs abduction, hypothermia; Darmani and Ahmad, 1999). Thereby, in 5-HT syndrome, pentadecapeptide BPC 157 beneficial activity could be related to a rather specific and consistent counteraction of these 5-HT_{2A} receptors-related phenomena, while counteraction of pargyline effect (irreversible MAO-inhibition) is less important. Besides, the blockade of HT_{1A} receptor stimulates the appearance of the hyperthermic activity (Gudelsky et al., 1986) unlike strong counteraction of hyperthermia in pentadecapeptide BPC 157. Noteworthy, without inducing any temperature change in normal animal (Jelovac et al., 1998, 1999; Sikiric et al., 1999, 2000; Boban Blagaic et al., 2004), pentadecapeptide BPC 157 both prevents and reverses hypothermia induced

Table 2
Behavioral disturbances after pargyline, and subsequent L-tryptophan (serotonin syndrome), saline or pentadecapeptide BPC 157 application (at 15 min) in pargyline-pretreated rats

Treatment/kg i.p.	Assessed parameters	Time points of assessment (min) of hind limb abduction, fore paw treating, behaviour score (0–3), wed dog shake, frequency, number per rat (minimum/median/maximum). Starting time (0) immediately before pargyline, and thereafter, assessment at indicated intervals over period of 210 min								
		0	15	30	45	60	75	90	150	210
Pargyline 75 mg+	Hind limb abduction	0/0/1	0/0/2	2/2/3	2/3/3	3/3/3	3/3/3	2/3/3	2/2/3	1/2/2
Tryptophan 100 mg+	Fore paw treating	0/0/0	1/1/2	2/3/3	2/3/3	2/3/3	3/3/3	2/2/3	2/2/2	2/2/2
Saline (control)	Wed dog shakes	0/0/0	1/1/1	0/1/1	1/1/3	3/4/8	3/3/3	0/2/3	3/4/4	3/4/4
Pargyline 75 mg+	Hind limb abduction	0/0/1	0/0/1	2/2/2	2/2/3	3/3/3	3/3/3	2/3/3	1/2/2	1/2/2
Tryptophan 100 mg+	Fore paw treating	0/0/0	0/1/3	2/2/3	2/3/3	3/3/3	3/3/3	2/3/3	2/2/3	1/2/3
BPC 157 10 pg	Wed dog shakes	0/0/0	0/0/1	1/1/1	2/5/7	4/4/6	3/4/7	3/1/3	3/4/6	3/4/6
Pargyline 75 mg+	Hind limb abduction	0/0/0	0/1/2	2/2/3	2/3/3	2/3/3	2/2/3	2/2/3	2/2/2	1/1/2
Tryptophan 100 mg+	Fore paw treating	0/0/0	1/2/2	2/2/3	1/3/3	2/3/3	2/3/3	2/3/3	2/2/3	1/2/2
BPC 157 10 ng	Wed dog shakes	0/0/0	0/0/0a	0/0/1	0/7/8	0/3/6	1/1/1a	0/0/0a	0/0/0a	0/0/0a
Pargyline 75 mg+	Hind limb abduction	0/0/0	0/0/2	1/2/2	2/2/3	2/3/3	2/3/3	2/3/3	2/3/3	1/2/2
Tryptophan 100 mg+	Fore paw treating	0/0/0	1/1/2	2/2/3	1/2/3	2/3/3	2/3/3	2/3/3	1/3/3	1/2/3
BPC 157 10 μg	Wed dog shakes	0/0/0	0/0/0a	0/0/0	0/1/3	0/0/0a	0/0/0a	0/0/0a	0/0/0a	0/0/0a

8–10 rats per each group. a—vs. control, Kruskal–Wallis test, and due to Bonferroni's correction, $p < 0.008$ for subsequent comparisons using Mann–Whitney test.

by other disturbances, such as acute alcohol intoxication (Boban Blagaic et al., 2004) or reserpine application (Sikiric et al., 1999). Thereby, counteracting both hypothermia and hyperthermia, even with very low dose, pentadecapeptide BPC 157 by itself could have a particular role in temperature controlling as suggested before (Boban Blagaic et al., 2004; Sikiric et al., 1999).

Finally, pentadecapeptide BPC 157–5-HT syndrome relation is suggestive methodologically (i.e., auto radiographic method for regional 5-HT synthesis rate presents brain tissue traps α-[^{14}C]methyl-L-tryptophan in direct proportion to 5-HT-synthesis (Yamane et al., 2001; Tohyama et al., 2004)). Thereby, a peptide given peripherally (but supposed to influence a central function) is presenting with supporting region-specific influence on brain 5-HT synthesis (Tohyama et al., 2004). Peptide direct or indirect action (Jelovac et al., 1998, 1999; Tohyama et al., 2004; i.e., initiated also at some visceral repetitive relay of the central nervous system (Koob and Bloom, 1983) or through circumventricular organs, few regions in the brain where the blood–brain barrier does not exist (McKinley et al., 2003)) parallels brain 5-HT synthesis, increased in the medial anterior olfactory nucleus and substantia nigra reticulata, decreased in globus pallidus, dorsal and ventral hippocampus, dorsal thalamus, lateral geniculate body, and hypothalamus, given acutely (Tohyama et al., 2004). Particularly important could be the identification of the substantia nigra's (compacta and reticulata) structure–5-HT synthesis significantly increased, regardless an overall increase (pentadecapeptide BPC 157, acutely) or decrease (pentadecapeptide BPC 157, chronically) in brain 5-HT synthesis (Tohyama et al., 2004). This structure has a dense presence of dopaminergic neurons and receives dense projections of the serotonergic systems (Azmitia and Segal, 1978). Also, pentadecapeptide BPC 157 protects against a specific neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; Sikiric et al., 1999) (damages supposed to be related to lesions of dopamine substantia nigra cell bodies, and also 5-HT (Pankova et al., 2004)), consistently presenting a significant effect on the brain dopaminergic system (Jelovac et al., 1998, 1999; Sikiric et al., 1997a,b, 1999; Bilic et al., 2001). In support of this, pentadecapeptide BPC 157 prevents and reverses the consequence of dopamine system overstimulation, both acute and chronic (Jelovac et al., 1998; Sikiric et al., 2002). Therefore, the prominent improvement of otherwise severe 5-HT syndrome is within the framework of its beneficial effect, and obtained within the same dose range (Jelovac et al., 1998, 1999; Sikiric et al., 1997a,b, 1999; Bilic et al., 2001). Besides, this peptide has a peptidergic activity and stability of its own (i.e., non-degraded in human gastric juice) (Veljaca et al., 1995), and not need for peptide carrier or carrier's activities (Jelovac et al., 1998, 1999; Sikiric et al., 1993; Sikiric et al., 1994, 1997a,b, 1999, 2000, 2001, 2002; Bilic et al., 2001; Lovric-Bencic et al., 2004; Boban Blagaic et al., 2004), and no toxicity reported (Veljaca et al., 2002). Consequently, the evidenced amelioration could be unmistakably attributed to its own beneficial effect.

In summary, gastric pentadecapeptide BPC 157 could be a suitable alternative in pharmacotherapy presented with 5-HT syndrome induction, accordingly supported by a reduced duration of immobility to a greater extent than imipramine (Sikiric et al., 2000), region specific influences on brain 5-HT synthesis, different from any other serotonergic drug (Tohyama et al., 2004) along with influence on other interacting systems (i.e., given in the same dose range (Jelovac et al., 1998, 1999; Sikiric et al., 1999, 2001, 2002)), and finally 5-HT syndrome counteraction. This pentadecapeptide BPC 157 resistance is especial regardless other agents (i.e., diazepam) ameliorating 5-HT syndrome as well (Nisijima et al., 2000, 2001, 2003), and further studies to finally identify its relation to 5-HT$_{2A}$ receptor. Namely,

besides brain 5-HT synthesis (Tohyama et al., 2004) and anti-depressant activity (Sikiric et al., 2000), it presents no toxicity, particular effectiveness (Jelovac et al., 1998, 1999; Sikiric et al., 1993; Sikiric et al., 1994, 1997a,b, 1999, 2000, 2001, 2002; Bilic et al., 2001; Lovric et al., 2003; Lovric-Bencic et al., 2004; Boban Blagaic et al., 2004; Veljaca et al., 2002), even counteracting some antidepressant disturbances (Lovric et al., 2003; Lovric-Bencic et al., 2004).

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