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Short communication

The influence of gastric pentadecapeptide BPC 157 on acute and chronic ethanol administration in mice

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Abstract

The stable gastric pentadecapeptide BPC 157 (GEPPPGKPADDAGLV, M.W.1419), which was promising in inflammatory bowel disease (PL-10, PLD-116, PL-14736, Pliva) trials, protects against both acute and chronic alcohol-induced lesions in stomach and liver, but also, given peripherally, affects various centrally mediated disturbances. Now, in male NMRI mice BPC 157 (10 pg intraperitoneally, 10 ng and 10 μg, intraperitoneally or intragastrically) (i) strongly opposed acute alcohol (4 g/kg intraperitoneally) intoxication (i.e., quickly produced and sustained anesthesia, hypothermia, increased ethanol blood values, 25% fatality, 90-min assessment period) given before or after ethanol, and (ii) when given after abrupt cessation of ethanol (at 0 or 3 or 7 h withdrawal time), attenuated withdrawal (assessed through 24 hours) after 20%-alcohol drinking (7.6 g/kg) through 13 days, with provocation on the 14th day.

Keywords: Stable gastric pentadecapeptide BPC 157; Acute alcohol intoxication; Withdrawal/chronic alcohol consumption

1. Introduction

The stable gastric pentadecapeptide BPC 157 (GEPPPGKPADDAGALV, M.W.1419), which has a very safe clinical profile, is promising against inflammatory bowel disease (clinical phase II, PL-10, PLD-116, PL-14736, Pliva), (i.e., Sikiric et al., 1994, 1997, 1999; Veljaca et al., 2002). Previously, it was shown to counteract and reverse damage induced by acute and chronic alcohol ingestion in stomach and liver (including portal hypertension) (Sikiric et al., 1994, 1997; Prkacin et al., 2001a,b, 2002), and also, when given peripherally, to affect various disturbances supposed to be centrally mediated (Jelovac et al., 1998, 1999; Sikiric et al., 1999, 2000, 2001, 2002). We hypothesized that it may have a beneficial effect against acute alcohol intoxication or withdrawal following chronic consumption. We thus tested BPC 157 in dose regimens used previously (Jelovac et al., 1998, 1999; Sikiric et al., 1994, 1997, 1999, 2000, 2001, 2002; Prkacin et al., 2001a,b, 2002) and administered the drug intraperitoneally (i.p.) or intragastrically (i.g).

2. Materials and method

Male NMRI mice (25–30g, kept at 22 °C ±1–2 °C, 12-h light dark cycle, food and water ad libitum, randomly assigned for experiments, approved by local ethic committee, assessed by an observer blind about treatment) were subjected to either (i) acute alcohol (4 g/kg i.p.)) intoxication or (ii) 20%-alcohol drinking (7.6 g/kg) for 13 days, with withdrawal provocation on the 14th day. (i) We applied saline (5 ml/kg) or BPC 157 (manufactured by Diagen, d.o.o., Ljubljana, Slovenia) (10 pg i.p., 10 ng and 10 μg/kg, i.p. or i.g., dissolved in saline) at 5 min before (pre-treatment) or after (post-

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Table 1
Acute alcohol intoxication and pentadecapeptide BPC 157 in mice

Acute alcohol (4 g/kg i.p.) intoxication Male NMRI mice		Points of assessment (behaviour score (0–5) (median/minimum/maximum), temperature ratio (means±SD) (°C), ethanol level in blood (means±SD) (mg/l)), mortality (total number/fatal outcome for given regimen), number of animals in parentheses. Time 0 was either immediately before ethanol (pre-treatment regimen) or after medication (post-treatment regimen)). Thereafter, assessment at intervals of 10 min over period of 90 min.									
		0	10 min	20 min	30 min	40 min	50 min	60 min	70 min	80 min	90 min
Medication before ethanol (pre-treatment)											
0.9% NaCl	Behaviour (10)	5/5/5	0/0/3	0/0/3	0/0/3	0/0/3	0/0/4	0/0/5	1/0/5	2/0/5	2/0/5
5.0 ml/kg	Temperature	1.0±0.00	0.93±0.00	0.90±0.01	0.88±0.01	0.89±0.01	0.90±0.01	0.91±0.01	0.91±0.01	0.93±0.00	0.93±0.00
i.p. 77/18	ratio T_x/T_0 (10)										
	Ethanol level in blood (39)		4.03±0.17		3.98±0.09			3.93±0.04			3.91±0.04
BPC 157	Behaviour (10)	5/5/5	3/0/5	3.5/0/5*	3/0/5*	2.5/0/5	3/0/5	2.5/0/5	3/0/5	3/0/5	3/0/5
10 pg/kg	Temperature	1.0±0.01	0.92±0.01*	0.91±0.01	0.92±0.01*	0.94±0.01*	0.94±0.01*	0.94±0.01*	0.96±0.01*	0.96±0.01*	0.97±0.01*
i.p. 60/1*	ratio T_x/T_0 (10)										
	Ethanol level in blood (39)		3.63±0.12*		3.52±0.22*			3.66±0.08*			3.52±0.24*
BPC 157	Behaviour (10)	5/5/5	3/1/5*	3/1/5*	3/1/5*	3/1/5*	3/1/5*	3/1/5*	3.5/1/5*	3.5/1/5*	3.5/4/5*
10 ng/kg	Temperature	1.0±0.01	0.94±0.03	0.92±0.03	0.93±0.03*	0.94±0.03*	0.96±0.03*	0.96±0.03*	0.96±0.03*	0.97±0.02*	0.98±0.02*
i.p. 60/0*	ratio T_x/T_0 (10)										
	Ethanol level in blood (40)		3.00±0.26*		3.15±0.15*			3.45±0.32*			3.48±0.18*
BPC 157	Behaviour (10)	5/5/5	3.5/0/5*	3/0/5*	4/0/5*	3.5/0/5*	3.5/0/5*	4/2/5*	4/0/5*	4.5/2/5*	5/2/5*
10 μg/kg	Temperature	1.0±0.01	0.93±0.01	0.92±0.01*	0.93±0.02*	0.94±0.01*	0.95±0.01*	0.95±0.02*	0.97±0.02*	0.97±0.01*	0.98±0.01*
i.p. 60/0*	ratio T_x/T_0 (10)										
	Ethanol level in blood (40)		2.82±0.09*		2.80±0.09*			2.97±0.17*			2.92±0.25*
0.9% NaCl	Behaviour (10)	5/5/5	0/0/3	0/0/2	0/0/2	0/0/2	0.5/0/2	1/0/3	1.5/0/3	1.5/0/3	2/0/3
5.0 ml/kg	Temperature	1.0±0.01	0.93±0.01	0.91±0.02	0.88±0.01	0.89±0.01	0.90±0.02	0.91±0.00	0.91±0.01	0.92±0.02	0.93±0.01
i.g. 50/11	ratio T_x/T_0 (10)										
	Ethanol level in blood (19)		4.03±0.07						3.95±0.05		
BPC 157 *	Behaviour (10)	5/5/5	2/1/3*	2/1/3*	2/1/3*	2/1/3*	2/1/3*	2.5/1/3	2.5/1/3	3/1/3	3/1/4
10 ng/kg	Temperature	1.0±0.01	0.95±0.01*	0.93±0.01*	0.90±0.01*	0.89±0.01	0.90±0.02	0.90±0.01	0.90±0.02	0.91±0.02	0.91±0.01
i.g. 40/1	ratio T_x/T_0 (10)										
	Ethanol level in blood (19)		3.84±0.11*						3.69±0.04*		
BPC 157 *	Behaviour (10)	5/5/5	2.5/0/5*	2.5/1/5*	2.5/0/5*	2.5/0/5*	3/1/5*	3/2/5*	4/2/5*	4/2/5*	4/2/5*
10 μg/kg	Temperature	1.0±0.01	0.97±0.02*	0.95±0.02*	0.92±0.02*	0.92±0.02	0.93±0.03	0.93±0.03	0.92±0.04	0.92±0.04	0.93±0.04
i.g. 40/0	ratio T_x/T_0 (10)										
	Ethanol level in blood (20)		3.52±0.08*						3.22±0.05*		

Medication after ethanol (post-treatment)											
0.9% NaCl	Behaviour (10)	0/0/3	0/0/3	0/0/3	0/0/4	0/0/4	0/0/5	1/0/5	2/0/5	2/0/5	2/0/5
5.0 ml/kg	Temperature	0.94±0.01	0.90±0.01	0.88±0.01	0.88±0.01	0.89±0.02	0.89±0.03	0.90±0.03	0.90±0.03	0.91±0.03	0.91±0.03
i.p. 78/19	ratio T_x/T_0 (10)										
	Ethanol level in blood (39)		4.06±0.19		4.05±0.11			3.87±0.02			3.91±0.05
BPC 157	Behaviour (10)	0/0/3	2/0/4	2/0/3*	2/0/3	2/0/3	2/1/3	2/0/3	2/0/4	2/0/4	2/0/4
10 pg/kg	Temperature	0.94±0.01	0.90±0.01	0.90±0.01*	0.90±0.01*	0.91±0.01	0.92±0.01	0.93±0.01	0.93±0.01	0.93±0.01	0.94±0.01
i.p. 60/0*	ratio T_x/T_0 (10)										
	Ethanol level in blood (40)		3.71±0.19*		3.56±0.06*			3.58±0.11*			3.54±0.14*
BPC 157	Behaviour (10)	0/0/2	1/0/4	2/0/5*	3/1/5*	3/2/5*	3/2/5	3/2/5*	3/2/5*	3/2/5*	3/2/5*
10 ng/kg	Temperature	0.95±0.01	0.90±0.01	0.91±0.01*	0.92±0.01*	0.92±0.00*	0.93±0.00*	0.94±0.01*	0.94±0.01*	0.95±0.01*	0.95±0.01*
i.p. 60/0*	ratio T_x/T_0 (10)										
	Ethanol level in blood (40)		3.56±0.20*		3.45±0.13*			3.38±0.28*			3.38±0.10*
BPC 157	Behaviour (10)	1/0/2	2/1/3*	3/1/4*	4/1/5*	4/2/5*	3/2/5*	3/1/5*	3/1/5*	3/1/5*	3/1/5*
10 μg/kg	Temperature	0.95±0.01	0.92±0.01*	0.92±0.01*	0.93±0.01*	0.94±0.01*	0.95±0.01*	0.96±0.01*	0.96±0.01*	0.96±0.01*	0.97±0.01*
i.p. 60/0*	ratio T_x/T_0 (10)										
	Ethanol level in blood (40)		2.98±0.09*		2.93±0.04*			2.99±0.07*			2.93±0.15*
0.9% NaCl	Behaviour (10)	0/0/1	0/0/0	0/0/1	0/0/2	0/0/2	1/0/3	1.5/0/3	2/0/3	2/0/3	2/0/3
5.0 ml/kg	Temperature	0.93±0.01	0.90±0.01	0.89±0.00	0.89±0.02	0.88±0.01	0.89±0.01	0.91±0.02	0.90±0.03	0.91±0.02	0.91±0.01
i.g. 52/12*	ratio T_x/T_0 (10)										
	Ethanol level in blood (20)		4.04±0.06					3.99±0.05			
BPC 157 *	Behaviour (10)	0/0/2	0.5/0/2*	1/0/2*	2/1/2*	2/1/3*	2/1/3	2/1/4	2/2/4	2/2/5	2.5/2/5
10 ng/kg	Temperature	0.95±0.01	0.94±0.01*	0.92±0.02*	0.91±0.01*	0.91±0.01	0.90±0.02	0.90±0.03	0.91±0.03	0.91±0.03	0.93±0.03
i.g. 40/0	ratio T_x/T_0 (10)										
	Ethanol level in blood (20)		3.98±0.05					3.79±0.11*			
BPC 157 *	Behaviour (10)	0/0/1	1/1/2*	2/1/2*	2/1/3*	2.5/1/4*	3/1/4*	3/2/4*	3/2/4*	3/2/4*	3/2/4*
10 μg/kg	Temperature	0.95±0.01	0.95±0.01*	0.94±0.02*	0.94±0.04*	0.94±0.05	0.94±0.06	0.94±0.06	0.94±0.06	0.95±0.06	0.95±0.06
i.g. 40/0	ratio T_x/T_0 (10)										
	Ethanol level in blood (20)		3.59±0.06*					3.53±0.06*			

* P<0.05 Fisher exact probability (two-sided) test (mortality) as well as in Kruskal–Wallis test, and due to Bonferroni's correcion, P<0.008 for subsequent comparisons using Mann–Whitney test.

treatment) ethanol. (ii) BPC 157 (0, 10 pg, 10 ng and 10 μg i.p.-medication/kg) was given after 0, 3 or 7 h of withdrawal.

In acutely intoxicated mice, time 0 was either immediately before ethanol (pre-treatment regimen) or after medication (post-treatment regimen). Thereafter, mouse behaviour was observed for 10 s over period of 90 min, at intervals of 10 min. Reaction to external stimuli (constant pressure to mouse tail as described before in neuroleptic mice (Jelovac et al., 1999)) was scored: 0—mice lying down with motionless, righting reflex absent, no reaction to external stimuli; 1—mice lying down with slow and occasional motion of hind limbs, righting reflex absent, no reaction to external stimuli; 2—righting reflex still absent, slow crawling with moderate reaction to external stimuli (escaping, but biting and turning reaction absent); 3—righting reflex present, very slow wavering walking with limbs strongly abducted, tottering, mild reaction to external stimuli (whole body slowly turned in the direction stimulated, no biting); 4—righting reflex present, walking and running, with occasional tottering, slight abduction of hind limbs, non-disturbed reaction to external stimuli (turning and biting, or in addition to turning and biting weak vocalization, external stimuli (turning and biting, and vocalization), no leg abduction; 5—righting reflex present, walking and running, no leg abduction, non-disturbed reaction to external stimuli (turning and biting with strong vocalization). As described (Sikiric et al., 1999) the rectal temperature ratio T_x (every 10 to 90 min after procedure initiation (T_x))/T_0 (temperature at time 0 as defined above) was recorded (°C) (digital thermometer (BAT-12, Sensortek, USA) 2.0 cm rectally until the temperature reached a plateau) in separate mice. Mortality was estimated at the end of the 90-min experimental period. Mixed arterial and venous blood samples were collected into plastic tubes after decapitation at 10, 30, 60 and 90 min after ethanol (pre-treatment), or after pentadecapeptide BPC 157/saline-medication (post-treatment)(i.p.-regimens), or 10 and 60 min after ethanol (pre-treatment) or after BPC 157/saline-medication (post-treatment) (i.g.-regimen). The ethanol level in blood was determined with the colorimetric method of Vitros ALC Slides (Products Vitros Chemistry). A 10-μl blood sample was deposited on the slide and was evenly distributed by the spreading layer to the underlying layers. The concentration of ethanol in the sample was determined by measuring the increase in NADH concentration at 340 nm after a 5-minute incubation at 37 °C.

Physically dependent mice were picked up by the tail (at 2, 4, 5, 6, 7, 8, 10 and 24 h withdrawal time) and scored as described by Malinowska et al. (1999): 0—little or no reaction; 1—mild reaction (tremor and turning) with slight jerkiness upon handling; 2—initial jerkiness escalating into clonic–tonic seizure within 5 s; 3—spontaneous seizure or an instantaneous clonic–tonic seizure upon being handled; 4—death.

Significant were values of $P<0.05$ in Fisher exact probability (two-sided) test (mortality) as well as in Kruskal–Wallis test, and after Bonferroni's correction, values of $P<0.008$ were considered significant for subsequent comparisons using Mann–Whitney test.

3. Results

In mice that were either acutely intoxicated or physically dependent on alcohol, BPC 157 intraperitoneally or intragastrically strongly prevented the effects of acute intoxication (i.e., quickly produced and sustained anesthesia, hypothermia, increased ethanol blood values, 25% fatality, 90-min assessment period) when given before or after ethanol, and none of the mice died (Table 1). When given after abrupt cessation of chronic ethanol (at 0 or 3 h withdrawal time), it attenuated withdrawal and handling-induced withdrawal seizures (Table 2).

The pentadecapeptide BPC 157 had no effect of its own in healthy mice.

4. Discussion

The pharmacological effects of ethanol are non-selective, in as much as alcohol can affect membrane organization, the function of membrane-bound enzymes, enzymes and proteins involved in signal transduction, ion channels, receptor-coupled ionophores, carrier proteins and gene expression (Fadda and Rossetti, 1998). In contrast, its effects are specific in as much as ethanol interacts with discrete sites on particular proteins that are critical for protein function and for cell functioning (Fadda and Rossetti, 1998). Thus, potential therapy should deal with an inherent mechanism of action that involves multiple subcellular sites in the CNS, thereby influencing the function of most, if not all, neuronal systems at molecular, cellular and system levels. Regardless whether this action is a direct or an indirect one, for a peptide given peripherally to exert a central effect, it must act at some visceral repetitive relay of the central nervous system (Koob and Bloom, 1983) or through circumventricular organs, one of the few regions in the brain where the blood–brain barrier does not exist (McKinley and Olfield, 1998), as already pointed out in our studies (Jelovac et al., 1998, 1999). In this respect (Egli, 2003), the pentadecapeptide BPC 157 is novel and interesting because there are few pharmacological agents (for review see i.e., Fadda and Rossetti, 1998) that consistently act as ethanol antagonists, and thereby consistently provide benefit for the otherwise opposite events elicited by acute or chronic alcohol disturbances. BPC 157 inhibits acute and chronic alcohol-induced stomach, endothelium (long recognized as the first target, provoking gastric lesion; Szabo et al., 1985), or liver lesions (including the complex chain of events leading to portal hypertension) (Sikiric et al., 1994,

Table 2
Physically alcohol-dependent mice (20%-alcohol drinking (7.6 g/kg) for 13 days, with withdrawal provocation at 14th day) and pentadecapeptide BPC 157

Male NMRI mice. 20%-alcohol drinking (7.6 g/kg) for 13 days, with withdrawal provocation at 14th day. Scoring (0–4) (median/minimum/maximum), number of animals per each group in parentheses

Time of medication application		Time of assessment							
		2 h withdrawal time	4 h withdrawal time	5 h withdrawal time	6 h withdrawal time	7 h withdrawal time	8 h withdrawal time	10 h withdrawal time	24 h withdrawal time
0.9% NaCl 5.0 ml/kg i.p.	0 h withdrawal time (10)	2/2/3	3/2/3	3/2/3	3/2/3	3/2/3	2.5/2/3	2/1/3	1.5/1/2
	3 h withdrawal time (10)	2/1/3	3/2/3	3/3/3	3/2/3	3/2/3	2/2/3	2/1/3	2/1/2
	7 h withdrawal time (10)	2/2/3	3/2/3	3/2/3	3/2/3	2.5/2/3	2.5/2/3	2/1/2	1/1/2
BPC 157 10 pg/kg i.p.	0 h withdrawal time (10)	1/1/3	2/1/3	3/2/3	3/2/3	3/2/3	2/1/3	2/1/3	2/1/2
	3 h withdrawal time (10)	2/1/3	2/1/2	2/1/3	2/2/3	2/1/3	2/1/2	1/1/2	1/1/2
	7 h withdrawal time (10)	3/1/3	3/2/3	3/2/32	3/3/3	2/2/3	2/1/3	1/1/3	2/1/2
BPC 157 10 ng/kg i.p.	0 h withdrawal time (10)	2/1/2	1/1/2*	2/2/3	2/2/3	2/1/3	2/1/3	2/1/2	2/1/2
	3 h withdrawal time (10)	2/2/3	2/1/2	2/2/2	2/1/3	2/2/2	1/1/3	1/1/2	1/1/2
	7 h withdrawal time (10)	2/1/3	3/2/3	2/2/3	3/3/3	3/2/3	2/1/3	2/1/3	2/1/2
BPC 157 10 μg/kg i.p.	2 h withdrawal time (10)	1/1/2*	2/1/2*	2/2/3	2/2/3	2/1/3	2/1/2	2/1/2	1/1/2
	2 h withdrawal time (10)	3/2/3	2/1/2*	2/1/2*	2/1/3	2/1/2	2/1/2	1/1/2	1/1/2
	2 h withdrawal time (10)	2/1/3	2/2/3	3/2/3	2/2/3	3/2/3	1/1/3	1/1/3	1/1/2

* $P<0.05$ Kruskal–Wallis test, and after Bonferroni's correction, $P<0.008$ for subsequent comparisons using Mann–Whitney test.

1997; Prkacin et al., 2001a,b, 2002) and interacts with the NO system (Sikiric et al., 1997), which is essential for alcohol-induced disturbances of other systems (Fadda and Rossetti, 1998). Consistently, it counteracts endothelin overexpression in rat chronic heart failure (Lovric-Bencic et al., 2004), and likely increases endothelial stimulation to release endothelin in alcohol-induced disturbances (Grogan and Kochar, 1994). More importantly, when given peripherally, it affects various disturbances thought to be centrally mediated (Jelovac et al., 1998, 1999; Sikiric et al., 1999, 2001, 2002) by systems (i.e., dopaminergic, GABA-ergic) involved in alcohol-induced disturbances (for review, see i.e., Fadda and Rossetti, 1998). In the same dose range, along with reducing blood levels of ethanol, the peptide also inhibits the toxic, overt behavioural and hypothermic effects of a large dose of ethanol. Antagonism of ethanol-induced hypothermia (involving various central structures, commonly related to disruption of the thermoregulatory systems (i.e., Fadda and Rossetti, 1998) to keep the body temperature constant is consistent with its antagonism of reserpine-induced hypothermia (Sikiric et al., 1999). Furthermore, the peptide reduces the severity of ethanol withdrawal after chronic treatment. Considering the presumably very low alcohol concentration at that time (as emphasized in studies of NO-related agents (Adams and Cicero, 1998)), and the effects mentioned before, this could be hardly related to the pharmacokinetics of alcohol. Finally, the higher mortality is likely due to known experimental variation (i.e., NMRI-mice have an increased vulnerability) but was successfully antagonized by application of the BPC 157.

In summary, BPC 157 is effective when given either intraperitoneally or intragastrically (and is stable in human gastric juice; Veljaca et al., 1995), when given either prophylactically or in already advanced disturbances (acute intoxication or withdrawal), and has a prompt action and a good safety profile. It has proven promising in inflammatory bowel disease trials (Veljaca et al., 2002) and may be a suitable candidate for the treatment of alcohol-induced disturbances. Further studies are in progress regarding its relation with the NO system (Sikiric et al., 1997).

References

Adams, M.L., Cicero, T.J., 1998. Alcohol intoxication and withdrawal: the role of nitric oxide. Alcohol 16, 153–158.

Egli, M., 2003. Peptides: their role in excess alcohol drinking and their promise as therapeutic tool. Physiol. Behav. 79, 89–93.

Fadda, F., Rossetti, Z.I., 1998. Chronic ethanol consumption: from neuroadaptation to neurodegeneration. Prog. Neurobiol. 56, 385–431.

Grogan, J.R., Kochar, M.S., 1994. Alcohol and hypertension. Arch. Fam. Med. 3, 150–154.

Jelovac, N., Sikiric, P., Rucman, R., Petek, M., Perovic, D., Konjevoda, P., Marovic, A., Seiwerth, S., Grabarevic, Z., Sumajstorcic, J., Dodig, G., Peric, J., 1998. A novel pentadecapeptide, BPC 157, blocks the stereotypy produced acutely by amphetamine and the development of haloperidol-induced supersensitivity to amphetamine. Biol. Psychiatry 43, 511–519.

Jelovac, N., Sikiric, P., Rucman, R., Petek, M., Marovic, A., Perovic, D., Seiwerth, S., Mise, S., Turkovic, B., Dodig, G., Miklic, P., Buljat, G., Prkacin, I., 1999. Pentadecapeptide BPC 157 attenuates disturbances induced by neuroleptics: the effect on catalepsy and gastric ulcers in mice and rats. Eur. J. Pharmacol. 379, 19–31.

Koob, G., Bloom, F.E., 1983. Memory, learning and adaptive behaviours. In: Krieger, D.T., Browstein, M.J., Martin, J.B. (Eds.), Brain Peptides. Wiley, New York, pp. 369–388.

Lovric-Bencic, M., Sikiric, P., Separovic, J., Seiwerth, S., Rogic, D., Kusec, V., Aralica, G., Konjevoda, P., Batelja, L., Boban Blagaic, A., 2004. Doxorubicine congestive heart failure-increased big-endothelin 1 plasma concentration. Reversal by amlodipine, losartan and gastric pentadecapeptide BPC 157 in rat and mouse. J. Pharmacol. Sci. 95, 19–26.

Malinowska, B., Napiorkowska-Pawlak, D., Pawlak, R., Buczko, W., Gothert, M., 1999. Ifenprodil influences changes in mouse behavior related to acute and chronic ethanol administration. Eur. J. Pharmacol. 377, 13–19.

McKinley, J., Olfield, B.J., 1998. The brain as an endocrine target for peptide hormones. TEM 9, 349–353.

Prkacin, I., Aralica, G., Perovic, D., Separovic, J., Gjurasin, M., Lovric-Bencic, M., Stancic-Rokotov, D., Ziger, T., Anic, T., Sikiric, P., Seiwerth, S., Staresinic, M., Mise, S., Rotkvic, I., Jagic, V., Rucman, R., Petek, M., Turkovic, B., Marovic, A., Boban-Blagaic, A., Ivasovic, Z., 2001a. Chronic cytoprotection: pentadecapeptide BPC 157, ranitidine and propranolol prevent, attenuate and reverse the gastric lesions appearance in chronic alcohol drinking rats. J. Physiol. (Paris) 95, 295–301.

Prkacin, I., Separovic, J., Aralica, G., Perovic, D., Gjurasin, M., Lovric-Bencic, M., Stancic-Rokotov, D., Staresinic, M., Anic, T., Mikus, D., Sikiric, P., Seiwerth, S., Mise, S., Rotkvic, I., Jagic, V., Rucman, R., Petek, M., Turkovic, B., Marovic, A., Sebecic, B., Boban-Blagaic, A., Kokic, N., 2001b. Portal hypertension and liver lesions in chronically alcohol drinking rats prevented and reversed by stable gastric pentadecapeptide BPC 157 (PL-10, PLD-116), and propranolol, but not ranitidine. J. Physiol. (Paris) 95, 315–324.

Prkacin, I., Staresinic, M., Suknaic, S., Separovic, J., Stancic Rokotov, D., Aralica, G., Boban Blagaic, A., Perovic, D., Rucman, R., Petek, M., Anic, T., Seiwerth, S., Sikiric, P., 2002. Reduction of Doppler shift of otherwise increased blood flow velocity in v. cava inferior and v. portae of chronically alcohol drinking portal hypertensive rats by gastric pentadecapeptide BPC 157 (PL-10). Gastroenterology 122, 353.

Sikiric, P., Seiwerth, S., Grabarevic, Z., Petek, M., Rucman, R., Turkovic, B., Rotkvic, I., Jagic, V., Duvnjak, M., Mise, S., 1994. The beneficial effect of BPC 157, a 15 amino acid peptide BPC fragment, on gastric and duodenal lesion induced by restraint stress, cysteamine and 96% ethanol in rats. A comparative study with H2 receptor antagonists, dopamine promoters and gut peptides. Life Sci. 54, PL63–PL68.

Sikiric, P., Seiwerth, S., Grabarevic, Z., Rucman, R., Petek, M., Jagic, V., Turkovic, B., Rotkvic, I., Mise, S., Zoricic, I., Konjevoda, P., Perovic, D., Jurina, L., Separovic, J., Hanzevacki, M., Artukovic, B., Bratulic, M., Tisljar, M., Gjurasin, M., Miklic, P., Stancic-Rokotov, D., Slobodnjak, Z., Jelovac, N., Marovic, A., 1997. The influence of a novel pentadecapeptide BPC 157 on N^{G}-nitro-L-arginine methylester and L-arginine effect on stomach mucosal integrity and blood pressure. Eur. J. Pharmacol. 332, 23–33.

Sikiric, P., Marovic, A., Matoz, W., Anic, T., Buljat, G., Mikus, D., Stancic-Rokotov, D., Separovic, J., Seiwerth, S., Grabarevic, Z., Rucman, R., Petek, M., Ziger, T., Sebecic, B., Zoricic, I., Turkovic, B., Aralica, G., Perovic, D., Duplancic, B., Lovric-Bencic, M., Rotkvic, I., Mise, S., Jagic, V., Hahn, V., 1999. A behavioral study of the effect of pentadecapeptide BPC 157 in Parkinson's disease models in mice and gastric lesions induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropropyridine. J. Physiol. (Paris) 93, 505–512.

Sikiric, P., Jelovac, N., Jelovac Gjeldum, A., Dodig, G., Staresinic, M., Anic, T., Zoricic, I., Perovic, D., Aralica, G., Buljat, G., Prkacin, I., Lovric-Bencic, M., Separovic, J., Seiwerth, S., Rucman, R., Petek, M., Turkovic, B., Ziger, T., 2001. Anxiolytic effect of BPC 157, a gastric pentadecapeptide: shock probe/burying test and light/dark test. Acta Pharmacol. Sin. 22, 225–230.

Sikiric, P., Jelovac, N., Gjeldum, A., Dodig, G., Staresinic, M., Anic, T., Zoricic, I., Rak, D., Aralica, G., Buljat, G., Prkacin, I., Lovric-Bencic, M., Separovic, J., Seiwerth, S., Rucman, R., Petek, M., Turkovic, B., Ziger, T., Boban-Blagaic, A., Bedekovic, V., Tonkic, A., Babic, S., 2002. Pentadecapeptide BPC 157 attenuates chronic amphetamine-induced behavior disturbances. Acta Pharmacol. Sin. 23, 412–422.

Szabo, S., Trier, J.S., Brown, A., Schnoor, J., 1985. Early vascular injury and increased vascular permeability in gastric mucosal injury caused by ethanol in the rat. Gastroenterology 88, 228–236.

Veljaca, M., Chan, K., Guglietta, A., 1995. Digestion of h-EGF, h-TGF alpha and BPC-15 in human gastric juice. Gastroenterology 108, 761.

Veljaca, M., Krnic, Z., Brajsa, K., Mildner, B., Pavic-Sladojev, D., Seveljevic-Jaran, D., Kolega, M., Erceg, D., Krznaric, Z., 2002. The development of PL 14736 for treatment of inflammatory bowel disease. IUPHAR-GI Section Symposium, Honolulu, Hawaii, 13-15, O-32.