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Pentadecapeptide BPC 157 and anaphylactoid reaction in rats and mice after intravenous dextran and white egg administration



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ABSTRACT

Anesthetized mice or rats received intravenously 6%, 10%, 20%, 40%, 60%, 80%, and 90% dextran and/or white egg (1 ml/rat or 0.15 ml/mouse) into their tails. Medication (/kg b.w., 5 ml/kg) was given intraperitoneally (BPC 157 10 µg, 1 µg, 10 ng, and 10 pg/kg, chloropyramine 20 mg/kg, and cimetidine 10 mg/kg intraperitoneally, alone or in combination while controls received an equivolume of saline), immediately after challenge or, alternatively, at 5 min after or 24 or 48 h before challenge. The effect was assessed at 5, 10, 20 and 30 min after dextran and/or white egg challenge. We commonly noted prominent edema involving the face, upper and lower lip, snout, paws and scrotum (presented with extreme cyanosis), poor respiration and the number of fatalities after dextran and/or white egg application. Contrary, BPC 157 regimens (10 µg, 1 µg, 10 ng, and 10 pg/kg) effectively, may both prevent anaphylactoid reactions that may arise from dextran and/or white egg application and furthermore, rescue already advanced reactions when given after the challenge. Chloropyramine and cimetidine given alone were only moderately effective. When given together with BPC 157, the observed effect correlates with the strong effect of BPC 157 given alone.

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1. Introduction

Anaphylactoid reactions have been recognized as infrequent but life-threatening responses to intravenous clinical dextran therapy since the 1960s (Disa et al., 2003; Hedin et al., 1980; Kohen et al., 1970; Ljungstrom, 2006; Michelson, 1968; Zinderman et al., 2006). Severe dextran-induced anaphylactoid reactions (DIARs) are characterized by bronchospasm, severe hypotension, cardiorespiratory arrest, and/or death (Hedin et al., 1976, 1980; Ljungstrom, 2006; Paull, 1987).

Likewise, they share the same characteristic presentation with ovalbumin (white egg) application in rats and mice (characteristic subcutaneous edema and hyperemia of the face, tongue, genitals and paws while vascular collapse when given intravenously (Halpern, 1956)). In this, we focused on the stable gastric pentadecapeptide BPC

157 (GEPPPGKPADDAGLV, M.W. 1419, PL-10, PLD-116, and PL 14736 in trials for inflammatory bowel disease, wound treatment, no toxicity reported, effective alone without carrier) (for review see, Sikiric et al., 2010) commonly shown to have a marked anti-inflammatory effect in various inflammatory models (Sikiric et al., 1997a, 1997b, 1993) while its effect on dextran and/or white egg-induced anaphylactoid reaction (Halpern, 1956) when given intravenously in rats and mice was not tested.

2. Materials and methods

Male Wistar Albino rats (200 g b.w.) or NMRI-mice (20 animals per each experimental group) randomly assigned were used in all experiments approved by Local Ethical Committee.

2.1. Drugs

Pentadecapeptide BPC 157 (GEPPPGKPADDAGLV, M.W. 1419), (Diagen, Ljubljana, Slovenia) dissolved in saline, was used in all experiments. The peptide BPC 157 is part of the sequence of

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human gastric juice protein BPC, and is freely soluble in water at pH 7.0 and saline. It was prepared as described previously (Sikiric et al., 2010) with 99% high pressure liquid chromatography (HPLC) purity, expressing 1-des-Gly peptide as an impurity. Chloropyramine (Sigma, USA) and cimetidine (Sigma, USA) were accordingly used.

2.2. Experimental protocol

All of the experiments were carried out in anesthetized rats and mice which received intravenously 6%, 10%, 20%, 40%, 60%, 80%, and 90% dextran and/or white egg (1 ml/rat or 0.15 ml/mouse) into their tails. Medication (/kg b.w., 5 ml/kg) was given intraperitoneally (BPC 157 10 µg, 1 µg, 10 ng, and 10 pg/kg, chloropyramine 10 mg/kg, and cimetidine 10 mg/kg intraperitoneally, alone or in combination while controls received an equivolume of saline), immediately after challenge or, alternatively, at 5 min after or at 24 or 48 h before challenge. The effect was assessed at 5, 10, 20 and 30 min after dextran and/or white egg challenge as follows: score 0 – normal presentation; score 1 – small suborbital edema; score 2 – prominent edema involving face, upper and lower lip, snout; score 3 – prominent edema involving face, upper and lower lip, snout, paws and scrotum; score 4 – prominent edema involving face, upper and lower lip, snout, paws and scrotum presented with apparent cyanosis; score 5 – prominent edema involving face, upper and lower lip, snout, paws and

scrotum presented with extreme cyanosis and poor respiration. Also, the number of fatalities was calculated.

2.3. Statistical analyses

Statistical analysis was performed by a non-parametric Kruskal–Wallis ANOVA and the subsequent Mann–Whitney *U*-test to compare groups. The Fisher-exact probability test was used for mortality analysis. Values of *P* < 0.05 were considered statistically significant.

3. Results

Considering the beneficial effect, particularly BPC 157 and chloropyramine and cimetidine, we commonly noted in controls prominent edema involving the face, upper and lower lip, snout, paws and scrotum (presented with extreme cyanosis) and poor respiration and the number of fatalities after dextran and/or white egg application, no difference considering injection time (Tables 1–3). Specifically, BPC 157 regimens (10 µg, 1 µg, 10 ng, and 10 pg/kg) effectively may both prevent anaphylactoid reactions that may arise from dextran and/or white egg application and rescue already advanced reactions when given after the challenge. Chloropyramine 10 mg/kg and cimetidine 10 mg/kg given alone were only moderately effective. When given together with BPC 157, the observed effect (chloropyramine+BPC 157;

Table 1
Anaphylactoid reaction induced in mice by 6%, 10%, 20%, 40%, 60%, 80%, and 90% dextran and/or white egg (1 ml/rat or 0.15 ml/mouse) into their tails, Minimum/Median/Maximum (Min/Med/Max). Medication (/kg b.w., 5 ml/kg) was given intraperitoneally (BPC 157 10 µg, 1 µg, 10 ng, and 10 pg/kg, intraperitoneally, while controls received an equivolume of saline), immediately after challenge or, alternatively, at 5 min after or 24 or 48 h before challenge. The effect was assessed at 5, 10, 20 and 30 min after dextran and/or white egg challenge.

Application time				Assessment time				Mortality 20 mice/group (%)	
– 48 h	– 24 h	0	Immediately after	5 min Min/ Med/Max	10 min Min/Med/Max	20 min Min/ Med/Max	30 min Min/Med/ Max		
Saline 5 ml/ kg ip BPC 157 10 µg/kg ip		Dextran 6%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	2/2/3*	1/2/3*	1/1/2*	0/1/1*	0*	
		Dextran 20%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	2/2/3*	2/2/3*	1/1/2*	0/1/1*	0*	
		Dextran 40%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	2/2/3*	1/2/3*	1/1/2*	0/1/1*	0*	
		Dextran 80%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	2/2/3*	1/2/2*	1/1/2*	0/1/1*	0*	
		Dextran 90%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	2/2/3*	1/2/3*	1/1/2*	1/1/1*	0*	
		Dextran 90%	Saline 5 ml/ kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	5/5/5	1/1/2*	1/1/3*	1/1/2*	0*	
		Dextran 90%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	2/3/3*	1/2/3*	1/1/2*	0/1/1*	0*	
		Dextran 90%	Saline 5 ml/ kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	1/2/3*	1/2/3*	1/1/1*	0/1/1*	0*	
		Dextran 90%+ ovalbumin	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	2/2/3*	1/2/3*	1/1/2*	0/1/1*	0*	
		Dextran 90%+ ovalbumin	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	20	
			BPC 157 10 µg/kg ip	5/5/5	2/2/3*	1/2/3*	1/1/2*	0*	

* *P* < 0.05 vs. control at least.

Table 2

Anaphylactoid reaction induced in rats by 6%, 10%, 20%, 40%, 60%, 80%, and 90% dextran and/or white egg (1 ml/rat or 0.15 ml/mouse) into their tails, Minimum/Median/Maximum (Min/Med/Max). Medication (/kg b.w., 5 ml/kg) was given intraperitoneally (BPC 157 10 µg, 1 µg, 10 ng, and 10 pg/kg, chloropyramine 200 mg and cimetidine 10 mg, alone and/or together, intraperitoneally, while controls received an equivolume of saline), immediately after challenge, at 5 min after challenge. The effect was assessed at 5, 10, 20 and 30 min after dextran and/or white egg challenge.

Application time		Assessment time				Mortality 20 rats/group (%)
0	Immediately after	5 min Min/Med/Max	10 min Min/Med/Max	20 min Min/Med/Max	30 min Min/Med/Max	
Dextran 6%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	30
	BPC 157 10 µg/kg ip	2/2/3*	1/2/3*	1/1/1*	0/1/1*	0*
	BPC 157 10 ng/kg ip	2/3/3*	1/2/3*	1/1/2*	0/1/1*	0*
Dextran 20%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	30
	BPC 157 10 µg/kg ip	2/2/3*	1/2/3*	1/1/2*	0/1/1*	0*
	BPC 157 10 ng/kg ip	2/2/3*	1/2/2*	1/2/2*	0/1/1*	0*
Dextran 40%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	30
	BPC 157 10 µg/kg ip	1/2/3*	1/2/2*	1/1/2*	0/1/1*	0*
	BPC 157 10 ng/kg ip	2/2/3*	1/2/2*	1/1/2*	0/1/1*	0*
Dextran 80%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	30
	BPC 157 10 µg/kg ip	2/2/3*	1/2/3*	0/1/2*	0/1/1*	0*
	BPC 157 10 ng/kg ip	2/2/3*	2/2/3*	1/1/2*	0/1/2*	0*
Dextran 90%	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	30
	BPC 157 10 µg/kg ip	1/2/3*	1/2/3*	1/1/2*	0/1/1*	0*
	BPC 157 10 ng/kg ip	2/2/3*	1/2/3*	1/1/2*	0/1/1*	0*
	BPC 157 10 pg/kg ip	2/3/4*	1/3/4*	2/3/3*	2/3/3*	10
	BPC 157 1 pg/kg ip	3/4/5*	3/4/5*	3/4/4*	2/4/4*	10
	BPC 157 10 fg/kg ip	4/5/5	5/5/5	5/5/5	5/5/5	30
	Chloropyramine 20 mg/kg ip	4/4/4*	4/4/4*	4/4/4*	4/4/4*	30
	Chloropyramine 20 mg/kg ip+BPC 157 10 µg/kg ip	2/3/4*	2/2/3*	1/1/3*	1/1/2*	0*
	Cimetidine 10 mg/kg ip	4/4/4*	4/4/4*	4/4/4*	3/4/4*	30
	Cimetidine 10 mg/kg ip+BPC 157 10 µg/kg ip	2/3/4*	1/2/3*	1/1/2*	1/1/1*	0*
Ovallbumin	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	50%
	BPC 157 10 µg/kg ip	2/3/3*	2/3/3*	1/2/3*	1/2/3*	0*
	BPC 157 10 ng/kg ip	2/3/3*	2/3/3*	1/2/3*	1/2/2*	10*
	BPC 157 10 pg/kg ip	2/3/4*	2/3/3*	2/3/3*	1/3/3*	10*
	BPC 157 1 pg/kg ip	2/4/4*	3/4/4*	3/4/4*	3/4/4*	20
	BPC 157 10 fg/kg ip	4/5/5	4/5/5	4/5/5	4/5/5	50
Ovallbumin +90% dextran	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	5/5/5	70
	BPC 157 10 µg/kg ip	2/3/3*	1/3/3*	2/3/3*	2/3/3*	0*
	BPC 157 10 ng/kg ip	2/3/3*	2/3/3*	2/3/3*	2/3/3*	10*
	BPC 157 10 pg/kg ip	2/4/5*	3/4/4*	2/3/4*	2/3/4*	10*

* $P < 0.05$ vs. control at least.

cimetidine+BPC 157) correlates with the effect of BPC 157 given alone (Table 3).

4. Discussion

In general, considering the consistent beneficial effect of BPC 157 in relation to dextran/white egg application, we should reemphasize the intravenous application that may produce the most severe disturbances, the short time period before symptom onset with intravenous bolus application (Disa et al., 2003; Hedin et al., 1980; Kohen et al., 1970; Ljungstrom, 2006; Michelson, 1968; Zinderman et al., 2006), and thereby, the injurious course severity providing that only a small dose of clinical dextran is enough to incite a reaction (Abir et al., 2004). Since the Selye's description; the fresh white egg-peculiar syndrome of anaphylactoid reaction in rats (edema of the paws and of the nose) was commonly coined with that of dextran (Halpern, 1956), it seems that BPC 157 (either given before or after challenge) may rapidly counteract the complete presentation of this syndrome and of its mechanisms, including an amplification when given together.

However severe, DIAR is an immune-complex-mediated (type III) anaphylactoid reaction (that occurs when infused dextran molecules bind to endogenous dextran-reactive immunoglobulin (Ig) G antibodies) involving an over-release histamine or 5-HT and further capillary system failure (Disa et al., 2003; Halpern, 1956; Hedin et al., 1980; Kohen et al., 1970; Ljungstrom, 2006; Michelson, 1968; Zinderman et al., 2006). Considering the results,

it is rational to suggest that BPC 157 may fully counteract all of these events and is effective when given at 48 h or 24 h before challenge, immediately after challenge and finally, at 5 min after challenge. Therefore, its application is valuable when all animals express generalized pruritus, are already edematous, prostrated, cyanosed and dysphonic to the point where their condition aggravates rapidly and fatality occurs within a short period. Thus, BPC 157 may prevent dextran molecules binding to endogenous dextran-reactive immunoglobulin and/or mastocytes degranulation. In this, BPC 157 may have a longstanding sustained preventing beneficial effect (i.e., BPC 157 elicits its beneficial effect given at 1 or 2 days before challenge) that may be promptly initiated (i.e., BPC 157's beneficial effect given immediately after challenge). However, it is important to mention that BPC 157 produces the same beneficial effect later when the toxicity becomes even more severe. Histamine release occurs very rapidly (Disa et al., 2003; Halpern, 1956; Hedin et al., 1980; Kohen et al., 1970; Ljungstrom, 2006; Michelson, 1968; Zinderman et al., 2006), and thereafter, pentadecapeptide BPC 157 may (given at 5 min after 90% dextran) effectively rescue the most severe course of dextran (90%). Therefore, it may be more likely that BPC 157 particularly counteracts the effects of dextran/white egg-application such as capillary system failure. Besides, the antagonistic effect of histamine only being moderately effective when given alone (Berstad, 1982; Guo et al., 2001), may be markedly increased with BPC 157 co-administration. Namely, by blocking the effects of histamine, the drug inhibits the vasodilatation, increased vascular permeability, and tissue edema associated with histamine release in the tissue.

Table 3
Anaphylactoid reaction induced in rats, comparison between the injection time, and BPC 157 and chloropyramine and cimetidine effects. Minimum/Median/Maximum (Min/Med/Max).

Time	Groups	Assessment time (min)			Mortality	
		10	20	30		
– 48 h	BPC 157 10 µg/kg ip	1/2/3	1/1/1	0/1/1	0	
+ 5 min	BPC 157 10 µg/kg ip	2/2/3	1/1/2	0/1/1	0	
<i>P</i> -level		NS	NS	NS	NS	
– 48 h	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	20%	
+ 5 min	Saline 5 ml/kg ip	5/5/5	5/5/5	5/5/5	20%	
<i>P</i> -level		NS	NS	NS	NS	
Dextran 90%						
Application time		Assessment time				Mortality 20 rats/group
0 min	Immediately after	5 min Min/ Med/Max	10 min Min/ Med/Max	20 min Min/ Med/Max	30 min Min/ Med/Max	
Dextran 90%	BPC 157 10 µg/kg ip	1/2/3	1/2/3	1/1/2	0/1/1	0
	Chloropyramine 20 mg/kg ip+BPC 157 10 µg/kg ip	2/3/4	2/2/3	1/1/3	1/1/2	0
	<i>P</i> -level	NS	NS	NS	NS	NS
	BPC 157 10 ng/kg ip	2/2/3	1/2/3	1/1/2	0/1/1	0
	Chloropyramine 20 mg/kg ip+BPC 157 10 µg/kg ip	2/3/4	2/2/3	1/1/3	1/1/2	0
	<i>P</i> -level	NS	NS	NS	NS	NS
	BPC 157 10 pg/kg ip	2/3/4	1/3/4	2/3/3	2/3/3	10
	Chloropyramine 20 mg/kg ip+BPC 157 10 µg/kg ip	2/3/4	2/2/3	1/1/3	1/1/2	0
	<i>P</i> -level	NS	< 0.05	< 0.05	< 0.05	< 0.05
	BPC 157 1 pg/kg ip	3/4/5	3/4/5	3/4/4	2/4/4	10
	Chloropyramine 20 mg/kg ip+BPC 157 10 µg/kg ip	2/3/4	2/2/3	1/1/3	1/1/2	0
	<i>P</i> -level	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05
	BPC 157 10 fg/kg ip	4/5/5	5/5/5	5/5/5	5/5/5	30%
	Chloropyramine 20 mg/kg ip+BPC 157 10 µg/kg ip	2/3/4	2/2/3	1/1/3	1/1/2	0
<i>P</i> -level	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	

Furthermore, anti-histamines do not actually prevent mediator release, and mediators other than histamine are of equal biological importance (Brown, 1995).

This likely suggests that BPC 157 may have additional effects over the effect of histamine receptor antagonists. Consequently, important for this particular BPC 157 effect, similar effects have already been shown in different models of inflammation (both acute and chronic, and thereby distinctive from that of the standard agents) for example; pentadecapeptide BPC 157's beneficial effect on both the wound and mucosa healing reduces the number of inflammatory cells (Sikiric et al., 2010) and levels of leukotriene B₄ (LTB₄), thromboxane B2 (TXB2), and myeloperoxidase (MPO) in both the serum and inflamed tissues (Krivic et al., 2008; Veljaca et al., 1995) and furthermore, has been found to counteract the effect of compound 48/80 (Veljaca et al., 1995) which promotes both histamine release and mast cell degranulation (Rotschild, 1970). In support, BPC 157 may accordingly particularly protect the endothelium and interact with the NO-system, counteracting the effects of both NOS-blockers and NO-precursors, in different models and species (Balenovic et al., 2009; Boban-Blagaic et al., 2006; Grabarevic et al., 1997; Kliceck et al., 2008; Sikiric et al., 1997a, 1997b).

Finally, providing the de novo synthesis of the transcription factor Egr1 required for the full responsiveness of mast cells in the production of cytokines in response to IgE stimulation (Li et al., 2006; Yang et al., 2009), and Egr1 to initiate both activation and inhibition signals, this clearly corresponds to the prominently stimulated expression of Egr-1 gene, which induces cytokine and growth factor generation and early extracellular matrix (collagen) formation, and furthermore its repressor nab2 presented with the application of the pentadecapeptide BPC 157 (Tkalcic et al., 2007) in wound healing studies.

As a final point, when BPC 157 was used previously LD1 could not be achieved, limit tests were negative, no side effects were found in trials, and no complications were observed (Sikiric et al.,

1997a, 1997b, 2010). And, although probably not indicative, pharmacokinetics in the rat after single intravenous administration (Istituto di Ricerche Biomediche “A. Marxer”, RBM, May 03, 1996) revealed a plasma concentration of radioactivity of 1.88 ± 0.47 µg eq./ml at the last sampling time (168 h). The half-life of elimination of radioactivity was 77 h. The area under the plasma concentration versus time curve extrapolated to infinity (AUC) was 878 h µg eq./ml. Thereby, BPC 157 may be usefully applied in anaphylactoid reactions therapy.

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