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Characteristics and Mechanisms of the Hypersensitivity Reactions Caused by Nanodrugs in Mice

ERIK ŐRFI[1]; TAMÁS MÉSZÁROS[2]; LÁSZLÓ HRICISÁK[1]; LÁSZLÓ DÉZSI[1,2]; PÉTER HAMAR[1]; LÁSZLÓ ROSIVALL[1,2]; ZOLTÁN BENYÓ[1]; JÁNOS SZEBENI[1,2]; GÁBOR SZÉNÁSI[1,2]

[1]*Institute of Translational Medicine, Semmelweis University, H-1094 Budapest, Hungary*
[2]*SeroScience Ltd., H-1089 Budapest, Hungary/Cambridge, MA 02138, USA*

Correspondence: rickrster@gmail.com

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1. Introduction

A new promising direction in pharmacotherapy and diagnosis is the use of nanodrugs for controlled, targeted drug delivery or for administration of diagnostic materials (1). However, an unsolved problem is that nanomaterials can cause IgE-independent hypersensitivity reactions (also known as pseudoallergy or anaphylactoid reaction). Previous studies showed variable contributions of complement (C) activation and C-independent immune stimulatory processes in pseudoallergy (2). We aimed to characterize the symptoms and basic mechanisms of pseudoallergy caused by intravenous injection of amphotericin B containing liposomes (AmBisome, 300 mg/kg; Abelcet, 30 mg/kg), polystyrene nanoparticles (PolyBeads, 500 nm, 26 mg/kg), and, for comparison, direct C activators, zymosan (ZY, 30 mg/kg) and cobra venom factor (CVF, 100 U/kg) in mice.

2. Materials and methods

The carotid artery and jugular vein were cannulated in anesthetized (pentobarbital, 90 mg/kg i.p.) male NMRI mice (n=5-7/group), and also in wild type (WT), thromboxane prostanoid receptor deficient (TP KO) mice on C57Bl/6 background, and blood pressure (BP) was recorded. Blood was collected from other groups of NMRI mice at 3-5 min after treatments, and plasma complement fragment C3a and thromboxane B2 (TXB2) concentrations were assayed using ELISA. Blood cell counting was carried out in Abacus vet5 hematology analyzer.

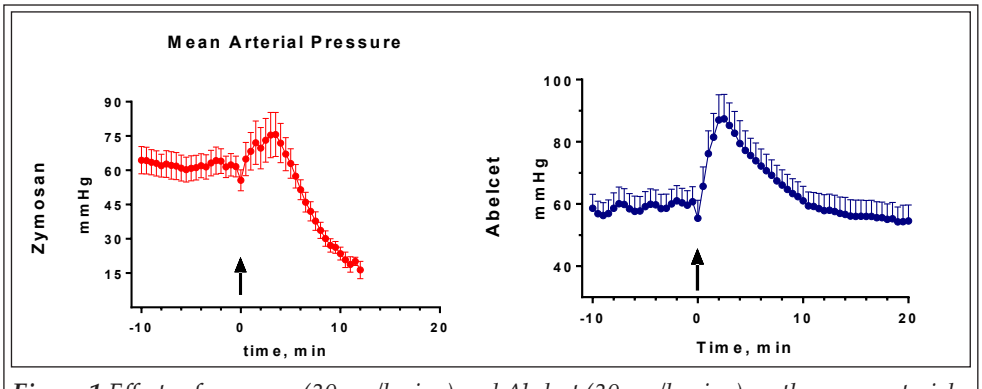

Figure 1 *Effects of zymosan (30 mg/kg i.v.) and Abelcet (30 mg/kg, i.v.) on the mean arterial blood pressure in anaesthetized mice.*

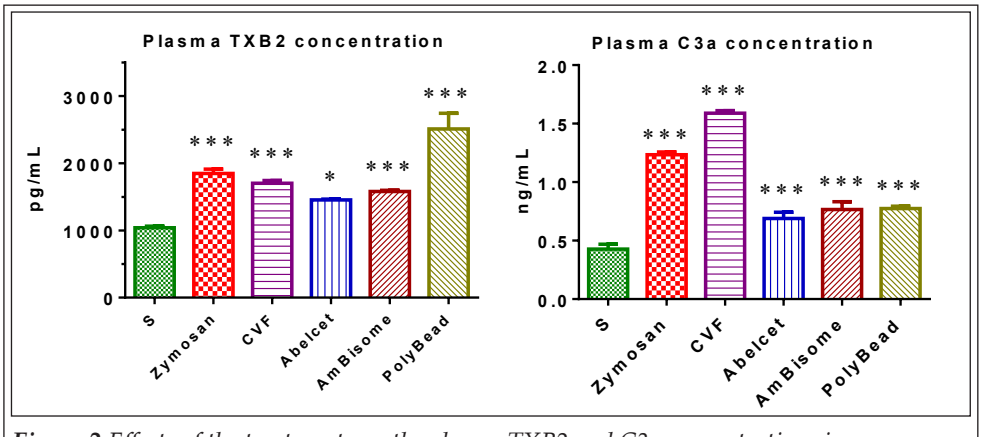

Figure 2 *Effects of the treatments on the plasma TXB2 and C3a concentrations in anaesthetized mice.*

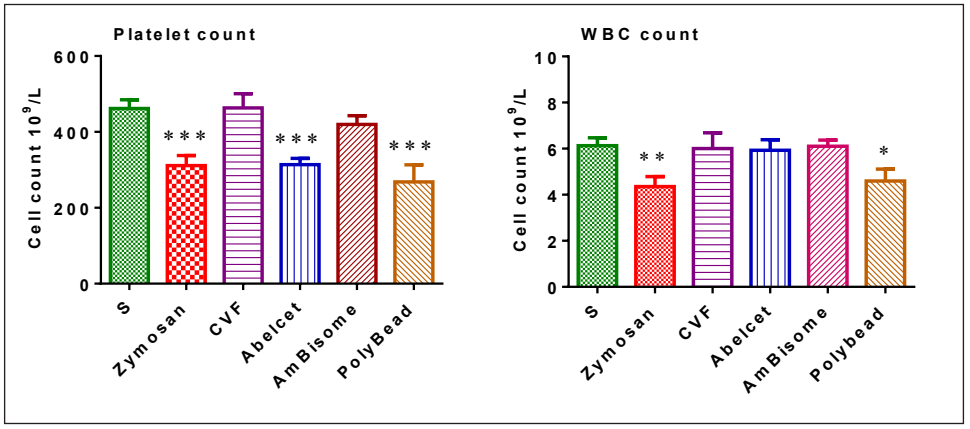

Figure 3 *Effects of the treatments on the platelet and white blood cell (WBC) count in mice.*

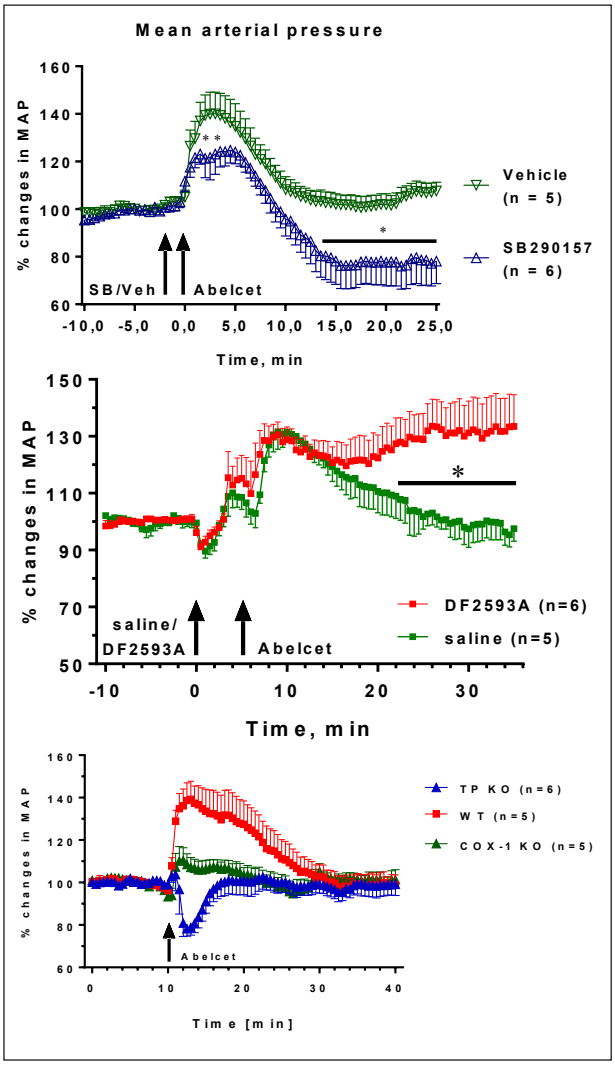

Figure 4 *Effects of pretreatment with SB290157 or DF2593A on the blood pressure effect of Abelcet (lef and middle panels, respectively) and the effects of Abelcet on the mean arterial blood pressure in thromboxan prostanoid receptor (TPKO) and cyclooxygenase 1 (COX-1) deficient anesthetized mice on C57Bl6N background.*

3. Results

3.1. Symptoms of pseudoallergy

All treatments caused an initial hypertension lasting for 3-10 min, while BP returned to baseline, decreased or progressed to hypotensive shock after administration of liposomes, PolyBeads and direct C activators, respectively. The effects of Abelcet and zymosan are shown as representative examples (***Figure 1***). All treatments increased plasma TXB2 and C3a concentrations. While plasma TXB2 concentration was increased most by PolyBeads, the direct complement activators zymosan and CVF increased plasma C3a concentration much more than any other treatments (***Figure 2***).

Zymosan, Abelcet and PolyBead reduced thrombocyte count while only zymosan and PolyBeads decreased white blood cell count (***Figure 3***).

3.2. Mechanisms of pseudoallergy

Pretreatment of mice with the complement C3a receptor (C3aR) antagonist, SB290157, decreased the initial hypertensive effect of Abelcet, and also caused delayed hypotension (***Figure 4***). On the other hand, the C5aR antagonist, DF2593A, lengthened the hypertensive effect of Abelcet that did not decrease up to 30 min. Finally, the blood pressure effect of Abelcet was abolished in COX-1 KO mice and the initial hypertension was turned to hypotension in TPR KO mice (***Figure 4***).

4. Conclusions

As shown in our previously published results (3), the main symptoms of pseudoallergy are changes in blood pressure, thrombocytopenia and leukocytosis in mice. However, the latter two changes seem to depend on the characteristics of the nanomedicines or direct C activator used.

The hypertensive effect of C activators and the amphotericin B-containing liposomal drugs, Abelcet and AmBisome, was associated with a rise of plasma thromboxane B_2 (TXB_2), a stable metabo-

lite of TXA_2. The present data showing significant reduction of Abelcet-induced hypertension in COX-1 KO mice is consistent with the causal role of TXA_2 in these reactions.

Our results with the anaphylatoxin receptor blockers also suggest that C activation contributes to the blood pressure changes in two phases; C3a promotes hypertension to a small extent, while C5a contributes later to the reversal of the initial hypertensive reaction in the second phase by a hypotensive effect. However, complement activation does not seem to have a major role in the blood pressure effect since the C3aR and the C5aR antagonist were only partially protective. The relationship between C activation and thromboxane release remains to be elucidated.

5. Acknowledgements

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References

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