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PROTECTIVE EFFECT OF A PAF-ACETHER ANTAGONIST, BN 52021, IN TRICHOHECENE TOXICOSIS

(T-2 toxin; mycotoxin; PAF-acether; BN 52021; rat)

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SUMMARY

Trichothecenes are mycotoxins which produce lethal toxicosis in humans and animals, yet no adequate therapeutic regimen has been developed. This study provides evidence that the selective platelet activating factor (PAF) antagonist, BN 52021 (5–15 mg/kg i.v.) can prolong the survival of conscious rats exposed to a highly lethal T-2 toxicosis. These data also suggest that PAF is an important mediator of this unique toxicosis.

INTRODUCTION

Trichothecenes are a chemically related group of biologically active fungal metabolites. T-2 toxin, a trichothecene mycotoxin, is a natural contaminant of foods and animal feeds that may cause severe illness in animals and humans [1] through deranged cardiorespiratory functions [2]. Although T-2 toxicosis is a disorder that has been associated with epidemic outbreaks in many countries, no specific therapy has been established for humans or animals. Recently, murine monoclonal antibody against T-2 toxin successfully protected and reversed severe T-2 toxicosis in the rat [2]. However, such therapeutic approach cannot be easily

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Abbreviation: PAF, platelet activating factor.

extrapolated to humans since no human anti-T-2 antibody is available to date.

Recently, a potent and selective PAF-acether antagonist, BN 52021, (9*H*,7*a*-(epoxymethano)-1*H*,6*aH*-cyclopenta[*c*]furo[2,3-*b*]furo-[3',2',3,4]cyclopenta[1,2-*d*]furan-5,9,12-(4*H*)-trione, β -*tert*-butylhexahydro-4,-7*b*,-11 hydroxy-8 methyl) was shown to provide substantial protection in several models of shock including endotoxemia [3,4]. Since lipopolysaccharide endotoxemia shows hemodynamic, cellular and endocrine similarities with T-2 toxicosis [5], we postulated that a PAF-acether antagonist might have a beneficial effect on survival from severe T-2 toxicosis.

METHODS

Male Sprague-Dawley rats (250–300 g) were chronically implanted with a PE-50 catheter in the femoral vein as previously described [2]. Three different protocols were used in which rats were subjected to i.v. injection of 0.65 mg/kg of T-2 toxin (Sigma, St. Louis, MO) in 200 μ l of 10% ethanol in 0.9% saline (sterile, pyrogen-free). This dose of T-2 toxin was selected from dose-response curves constructed in the conscious rat [2]. Three different groups of rats were treated as follows: (1) BN 52021 (kindly provided by Dr. P. Braquet, IHB, France) 15 mg/kg, 3 h after T-2 administration; (2) BN 52021, 15 mg/kg, 30 min prior to and 8 h after T-2 administration; (3) BN 52021, 5 mg/kg, 30 min and 6 h after T-2 administration. BN 52021 was injected in 150–400 μ l of 5% DMSO in 0.9% NaCl. Control rats received the vehicle injections of the T-2 and BN 52021 solvents. The vehicles used were shown to have absolutely no untoward effects in the rat. The rats were kept in single cages with food and water ad libitum for the complete duration of the experiment.

Statistics

Fisher's exact probability test was used to evaluate the difference in survival ratio between the control and BN 52021-treated groups.

RESULTS

In each group of rats treated with BN 52021, a substantial increase in survival rate was clearly demonstrated (Fig. 1). Most remarkably, a single dose of BN 52021 quadrupled the ultimate survival rate of the rats (Fig. 1, middle panel).

DISCUSSION

Although PAF-acether has not been demonstrated in T-2 toxicosis as yet, our data infer a role for PAF-acether also in the pathophysiology of T-2 toxicosis. This conclusion is based on previous studies showing that BN 52021 is a potent and selective PAF-acether antagonist [6]. Nevertheless, the substantial protective effect of

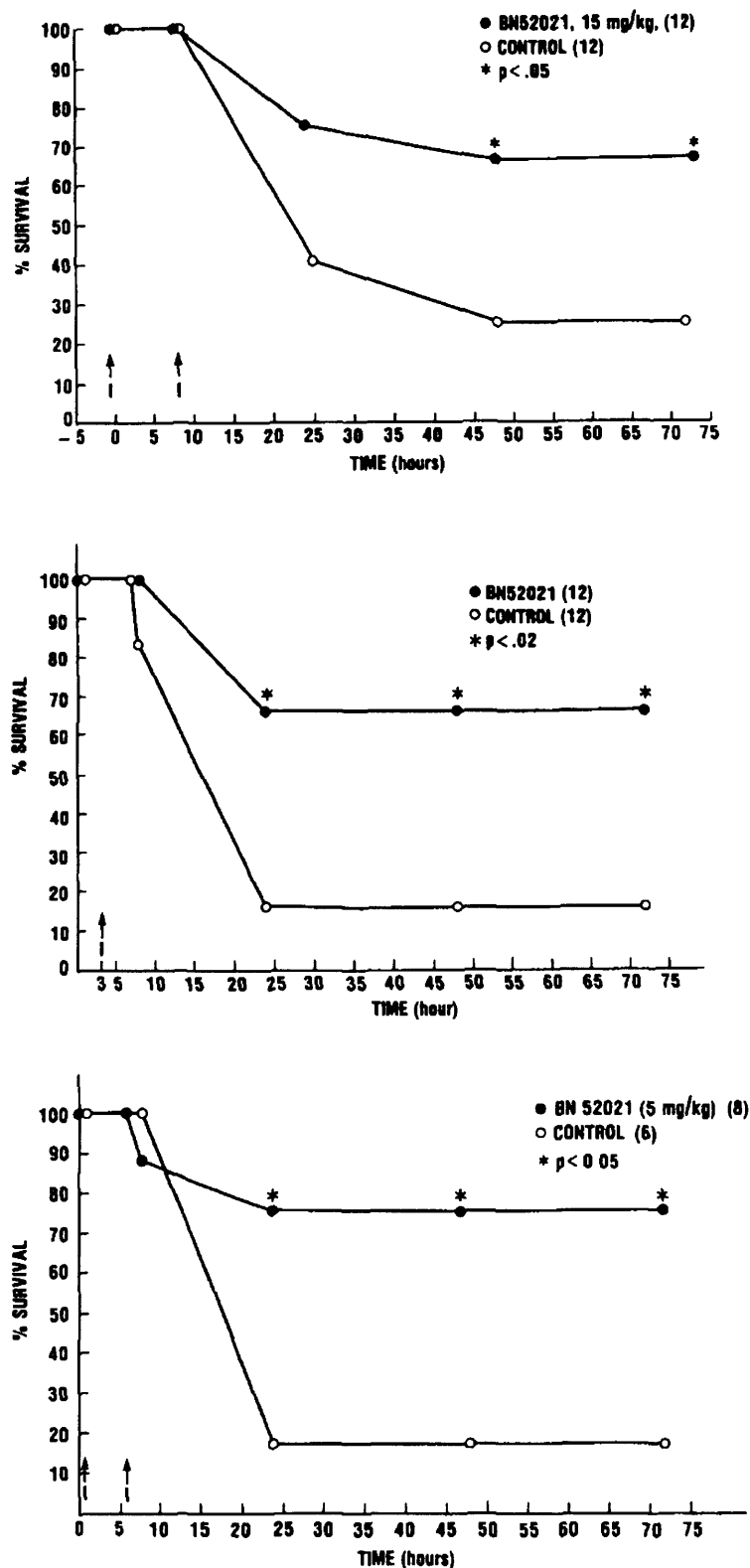


Fig. 1. Effect of BN 52021 on survival of rats exposed to T-2 toxin. Open circles represent vehicle-treated rats; closed circles represent BN 52021-treated rats. Time of BN 52021 injection is denoted by \uparrow . T-2 toxin was injected always at 0 time. Numbers of rats in each group are given in parentheses for each panel. Asterisks denote statistical significance at $P < 0.05$ for the upper and lower panels and $P < 0.02$ for the middle panel.

BN 52021 in this highly lethal mycotoxicosis might prove to be of beneficial effect in protecting livestock and humans exposed to trichothecene mycotoxins.

Since T-2 toxicosis is associated with widespread metabolic, hematologic, respiratory and cardiovascular derangements it is difficult to assess at this point the exact contribution of PAF in these pathophysiological processes. Further studies will be needed to identify PAF in T-2 toxicosis and to identify its primary target organs and systems.

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