Viral Hepatitis in Mice and ADP-Ribose Metabolism

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Introduction

We have shown earlier that the toxicity of endotoxin can be prevented to a large extent by antagonists of ADP-ribose metabolism (1). On the other hand there are some indications that muramyldipeptide (MDP) interferes with the this metabolism also (2). It was reported in 1980 that MDP, in combination with trehalose dimycolate, could induce resistance against influenza virus infection (3). In this chapter we are dealing with the influence of muramyldipeptide and benzamide upon the mouse hepatitis virus type 3 (MHV3).

Results

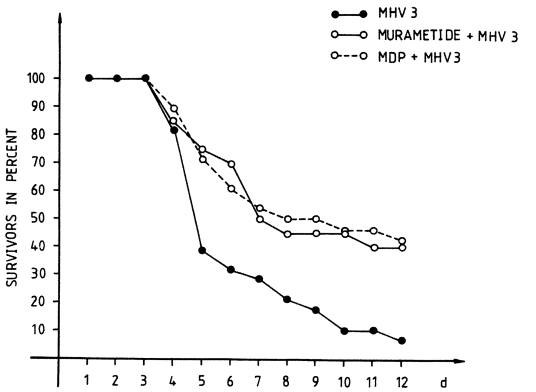

Fig. 1. Influence of muramyldipeptide and murametide upon the survival time of mice infected with MHV3 virus. Infection with MHV3 virus at time 0. Application of 1 mg (i.p.) each of MDP and murametide 1 hr, 24 hr, and 48 hr after MHV3 infection. Each group of 28 animals.

Determination of GOT and GPT were performed as described by Bergmeyer (4). The MHV3 virus belongs to the group of corona viruses. The procedure for the infection is described elsewhere (2). After the infection of mice with the virus MHV3 (2) there was a marked increase of GOT and GPT. In the animals given 1 mg of MDP or 1 mg of murametide 1 hr, 24 hr, and 48 hr after the MHV3 infection the increase of the GOT and GPT activity did not occur. Histopathological examination of the livers

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from mice infected with MHV3 revealed extensive necrotic lesions. In contrast, MDP treated animals showed a strong suppression of the hepatic necrosis. We measured the percent survival under this treatment and with MDP. With murametide as with MDP 40% of the animals survived (Fig. 1).

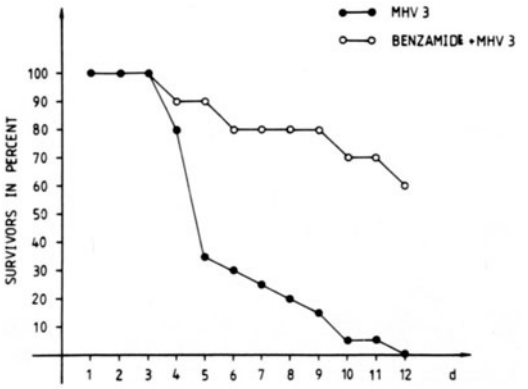

Fig. 2. Influence of benzamide upon the survival time of mice infected with MHV3 virus. Infection with MHV3 virus at time zero. Application of benzamide (i.p.): 25 mg/kg 1, 24, and 48 hr after infection. Each group of 10 animals.

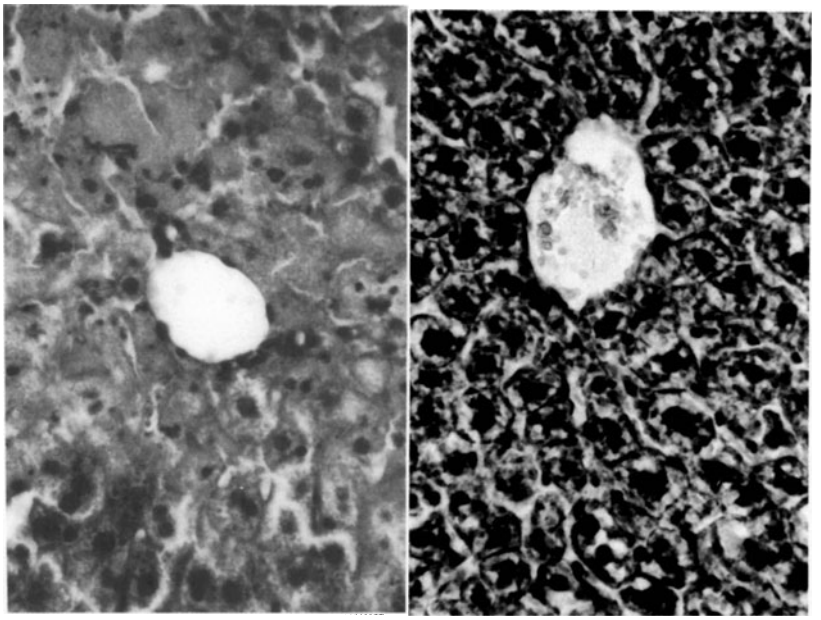

Fig. 3. Histopathological examination of the liver of mice. (Left) Injected with MHV3 (Right) Injected with MHV3 + benzamide (MDP). The same conditions as in Fig. 2 were used. Animals were killed at day 4 and liver was stained by haematoxilin eosin.

The acute toxicity of benzamide was tested by intraperitoneal injection. While 1.5 g/kg did not show any effect, a 2.0 g/kg injection resulted in the death of 75% of the animals. There was a marked reduction of the increase of GOT and GPT in mice infected with MHV3 virus and benzamide. Also therapeutic experiments were performed. With benzamide 60-80 % of the infected animals survived (Fig. 2). The histopathology of the liver showed that in mice infected with MHV3, necrotic lesions occured around the central artery on day 3 after infection (Fig. 3 left). This was completely inhibited by benzamide (Fig. 3 right).

Discussion

In earlier work we showed that the toxic effect of D-galactosamine on the liver can be inhibited by tryptophan and methionine (5). Furthermore, we found that D-galactosamine influences ADP-ribose metabolism (6). On the other hand it was reported that galactosamine enhances the effect of endotoxin (7). As already mentioned in the introduction, inhibitors of ADP-ribosylation reduce markedly the effect of endotoxin (1). These results stimulated us to study the effect of MDP on the ADP-ribose metabolism and we found indications for the interference of MDP with this metabolism (2). The induction of viral hepatitis by MHV3 in mice can be inhibited to a large extent by MDP and by benzamide. These are indications that the ADP-ribose metabolism plays a key role in the development of the hepatitis.

References

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Abbreviations:
GOT - Glutamic-oxalacetic transaminase
GPT - Glutamic-pyruvic transaminase
MDP - Muramyldipeptide
MHV3 - Mouse hepatitis virus type 3