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Pharmacologically induced reticuloendothelial blockade and the possibility of its application

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To investigate the physiological and pathophysiological roles of the reticuloendothelial system (RES), the depression or blockade of the granulopectic activity of this system has attracted considerable attention. Among substances effectively depressing reticuloendothelial (RE) activity are found materials with different physicochemical properties, for example, various colloids, steroids such as cortisone, esters of fatty acids such as methyl palmitate, carrageenan, silica. Different theories have been suggested to explain the mechanism of action of these materials.

Our earlier experiments [4] demonstrated that rare earth metal salts, among them gadolinium chloride ($GdCl_3$), depress RE activity and inhibit or completely abolish the effects of some RE stimulants. Our light- and electron-microscopic studies [3] show that the RE blockade induced by $GdCl_3$ is primarily due to depression of phagocytic activity of Kupffer cells. In the present paper we sumarize the functional aspects of the $GdCl_3$-induced RE blockade.

According to our studies [7, 8] with ^{51}Cr-labelled foreign red blood cells or bacterial endotoxin demonstrate that the $GdCl_3$-induced RE blockade greatly alters the distribution of the particulate matters among the organs of RES. As a consequence of the reduction in the hepatic component of clearance, the uptake in the extrahepatic RE organs (speen, lung, bone marrow) greatly increases. Since, macrophages localized in different tissues display special functions, the alteration in the distribution of particulate matter in the organism may have functional consequences.

Our studies [7] show that the RE blockade induced by $GdCl_3$ or sodium polyanetholsulphonate augments the humoral immune response to sheep red blood cell (SRBC), which is primarily due to the altered antigen distribution.

The spillover of the antigenic materials from liver to extrahepatic organs is of clinical significance [2]. The influence of macrophage defects induced by $GdCl_3$ on the hyperfibrinogenaemic response to bacterial endotoxin was analysed in an earlier study [5]. It was found that $GdCl_3$,

while depressing the liver RES function and the hepatic uptake of endotoxin, greatly reduced the hyperfibrinogenaemic response to endotoxin, which may be explained by the spillover of endotoxin from the liver, where the synthesis of fibrinogen takes place.

The potential usefulness of liposomes as carriers of therapeutic agents has been investigated extensively during recent years. Macrophages belonging to the RES are predominantly responsible for uptake of liposomes from the blood. Our studies [9] show that by treatment with $GdCl_3$, not only a shift of liposome uptake from liver to spleen can be effected but also, within the liver, a shift from Kupffer cells to liver parenchymal cells and even within the Kupffer cell population, from large cells to small cells. These findings offer a new possibility for targeting of liposomes in the organism.

It is suggested that in severe injuries, such as septic shock, the gradual activation of liver macrophages and the excessive release of macrophage destructive and immunosuppressive products may contribute to multiple organ failure [1]. Our observations support this hypothesis. According to our investigations [6], Kupffer cell phagocytosis blockade induced by $GdCl_3$ improves the survival rate in septic peritonitis and septic shock induced in rats by coecal ligation and perforation. Our results also support the involvement of the RE function in anaphylaxis. Gadolinium chloride injected 24 or 48 hours prior to the challenge of anaphylaxis to mice sensitized to ovalbumin, greatly reduced the symptoms of anaphylaxis, including the elevation in 5-hydroxytryptamine levels in the liver and lung, and also anaphylactic death [7].

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