α-Amanitin uptake into hepatocytes. Identification of hepatic membrane transport systems used by amatoxins

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Hepatic transport studies with amatoxins, toxic bicyclic octapeptides from poisonous mushrooms of the genus Amanita were performed, using [(6'-O,1'-N-di[3H]methyl)trp4]-alpha-amanitin and [(6'-O,1'-N-di-methyl)trp4]-[4-[3H]desmethyl)hyi3]-gamma-ama nitin. Uptake into hepatocytes from rat liver was inhibited by taurocholate and antamanide. Photoaffinity labeling studies with isolated hepatocytes and basolateral plasma membranes, using the sodium salt of (7,7-azo-3 alpha, 12 alpha-dihydroxy-5 beta-[3 beta-3H]cholan-24-oyl)-2- aminoethanesulfonic acid demonstrated that the presence of alpha-amanitin decreased the labeling of the two sinusoidal bile salt-binding membrane polypeptides with the apparent molecular weights of 54,000 and 48,000. In basolateral plasma membrane vesicles amanitin uptake was temperature-dependent and could be stimulated 1.5 to 2-fold by an out to in Na+ gradient as compared to a K+ gradient or sucrose and 2 to 2.5-fold as compared to amanitin equilibration (overshoot). Kinetic studies proved saturability of amanitin uptake in the presence and absence of a Na+ gradient. Membrane transport could be inhibited by taurocholate, antamanide, phalloidin, prednisolone, and silybin, but not by penicillin G or thioctic acid. Hepatic uptake of amatoxins is mediated by the sinusoidal bile salt-transport systems which are also involved in the uptake of antamanide and phalloidin. This supports the concept of a multispecificity of hepatic transport systems for a wide variety of amphipathic molecules.

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