Taipoxin, a presynaptically active neurotoxin, destroys mammalian skeletal muscle

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Taipoxin, isolated from the crude venom of the taipan *Oxyuranus scutellactus* has been defined as a presynaptically active neurotoxin (Kamenskaya & Thesleff, 1974). We have now demonstrated that taipoxin causes a necrotizing myopathy of mammalian skeletal muscle.

Taipoxin (2.0 μg in normal saline in a dose volume of 0.2 ml) was injected into one hind limb of female Wistar rats weighing 160–180 g. The injection was made so that the soleus muscle would be exposed to the toxin but not damaged by the insertion of the needle.

Within 1 h the wet weight of the intoxicated soleus muscles increased by 44% due to the accumulation of fluid within the interstitial spaces. The muscles remained oedematous for about 24 h after the injection of the toxin. During the period 3–10 days after injection, the muscles were wasted; the wet weight returned to normal by 21–28 days. The early increase in muscle wet weight was accompanied by the necrosis and phagocytosis of large numbers of superficial muscle fibres, the deeper fibres remaining undamaged. By 3 days, however small myotubes were present in the muscle. Immature muscle fibres were visible by 7 days and by 21 days the intoxicated muscles were virtually normal except for the persistence of centrally located nuclei.

The degeneration and regeneration of the muscles could be documented using physiological techniques. Thus by 6 h the mean resting membrane potential of the muscle fibres had fallen from a normal value of −76.9 mV (s.e. mean 0.31, $n=90$) to −15.6 mV (s.e. mean 2.1, $n=84$). By 3 days however, the mean resting membrane potential was −58 mV (s.e. mean 1.4, $n=70$) and was 'normal' by 7–14 days. During the period of 3–7 days after intoxication, fibrillation was common and in many fibres action potentials could be generated in the presence of tetrodotoxin (10^{-6} M).

The results demonstrate that taipoxin behaves both as a presynaptically active neurotoxin and as a myotoxin.

Reference

KAMENSKAYA, M.A. & THESLEFF, S.W. (1974). The neuromuscular blocking action of an isolated toxin from the Elapid *Oxyuranus scutellactus*. *Acta physiol. scand.*, **90**, 716–724.

The hepatotoxicity of lithocholic acid in male mice

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A few years ago it was thought that an important therapeutic advance had been made when it was found that oral administration of chenodeoxycholic acid (CDCA) to patients with cholesterol gallstones reduced the cholesterol saturation of bile and caused partial or complete dissolution of the gallstones (Danzinger, Hofmann, Thistle & Schoenfield, 1972). However optimism that this form of therapy would obviate the need for surgical treatment of gallstones in selected patients has declined, and clinical trials of CDCA treatment have been limited to certain centres in many countries (Dowling, Murphy & Iser, 1976). The major reason for caution in this form of therapy is that CDCA (3α,7α-dihydroxy-5β-cholanoic acid) is partially 7α-dehydroxylated by the intestinal microflora to yield the hepatotoxic secondary bile acid, lithocholic acid (3α-hydroxy-5β-cholanoic acid) (LA), some of which returns to the liver during enterohepatic circulation of bile acids. The large and prolonged doses of CDCA (about 1 g per day for many months) required for gallstone dissolution introduce the risk that the amounts of LA formed from the CDCA might cause liver damage in patients. Although LA causes intrahepatic cholestasis and early damage to the bile canaliculi in rodents, the mechanism by which LA produces these effects is not known.

As part of a programme on the effects of sex hormones on hepatobiliary function (Taylor, 1977) we have studied the effects of administering LA to male mice and monitoring the response by determining the cholesterol and bile acids of the gall-bladder bile and observing the development of lesions in the liver by standard histopathological techniques. Mature Balb/c mice were dosed with 8 mg of LA per day by gavage. Control animals received saline only. Ten animals from each group were killed at 0.5, 1.5, 2.5 and 3.5 days after the start of treatment. The gallbladder biles from each group were pooled. Cholesterol was determined colorimetrically, and bile acids (B.A.) by gas chromatography-mass spectrometry (Taylor, 1977). Samples of liver were taken for histological studies. Marked changes were observed only in the