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Some effects of resibufogenin: an aglycone of animal origin

Current textbooks of pharmacology still carry references to the importance of a hydroxyl group at C-14 in cardioactive glycosides such as digitalis (Goodman & Gilman, 1965; Bowman, Rand & West, 1968). This may be because the glycosides and aglycones which have received most attention have been those of plant origin.

The aglycones of animal origin are less thoroughly documented in Western pharmacology although they figure prominently in traditional Eastern medicine. One such biologically active compound, resibufogenin, can be obtained from the skin gland venom (Ch'an Su) of the Chinese toad, and has been widely used in clinical medicine in Japan (Kawashima & Furuhashi, 1963; Iwatsuki, Yusa & others, 1965). In structure, it resembles digitoxigenin but has an epoxide link between C-14 and C-15 with an unsaturated 6-membered lactone at C-17 (Meyer, 1952; Theissen, 1958). Unlike digitalis, resibufogenin has a respiratory stimulant action (Drs. M. F. Tyrell & J. M. Leigh, personal communication). We now report cardiotonic activity of resibufogenin in hypotensive dogs made hypotensive (50–70 mm Hg) in two ways.

Anaesthesia was induced with sodium thiopentone, 15 mg/kg, followed by intubation of the trachea. Maintenance was by nitrous oxide - oxygen (2 : 1) with supplementation by halothane (0·5–1·5%). Mean arterial blood pressure was measured intravascularly with a strain gauge transducer; pulse rate was counted from an electrocardiograph trace; and the cardiac output was determined by the dye dilution technique using indo-cyanine green.

Two groups of 7 dogs were used. The 7 normotensive dogs of Group A were given resibufogenin, allowed to recover and then became Group B animals. Group B were rendered hypotensive by bleeding 20–30% of estimated blood volume and Group C were made hypotensive by pentolinium tartrate. Resibufogenin in 50% propylene glycol was given intravenously at a rate of 0·017 mg/kg min^{-1}, the total dose being between 0·5 and 6·0 mg/animal.

In Group A animals, resibufogenin, like digitalis, had no apparent cardiac action, but unlike digitalis, it did have a respiratory stimulating action. Both hypotensive groups, i.e. Group B with reflexes intact and Group C with autonomic ganglionic traffic modified, showed significant rises in mean systemic arterial pressure following the administration of resibufogenin due to increases in cardiac output without a significant change in pulse rate, i.e. a largely inotropic action. The peak rise in arterial pressure was seen at 1 min and lasted between 3 and 5 min. The respiratory effects considerably out-lasted the cardiovascular effects.

It is of interest that cardiotonic activity has been demonstrated despite the absence of the C-14 hydroxyl group. It may be that the stereo-configuration of the C and D ring is of more importance to cardiotonic activity than possession of the hydroxyl

group at C-14 although epimerization of this latter group was previously considered to destroy such activity.

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Cobalt ion action on the vascular permeability and mast cells of the rat

The action of cobalt ion has been reported to be similar to that of histamine (Niebroj, 1958). Recent evidence suggested that only the second phase of cobalt-induced diphasic change in the vascular permeability of the guinea-pig skin was accompanied by local necrosis (Steele & Wilhelm, 1967). The present report supplies additional evidence on the mechanism of action of the metal on the vascular permeability and on the mast cells.

Male Wistar rats anaesthetized with urethane (600 mg/kg intraperitoneally) were used. $CoCl_2.6H_2O$ (AR) and histamine phosphate solutions were made up with saline (0·85%). The water used for solutions was previously deionized. Intradermal injections of 0·005, 0·01 and 0·02 M of cobalt chloride (pH 6·0) and 4·0 and 8·0 μg of histamine were made and control intradermal injections with 0·1 ml saline. The conventional technique for study of the vascular permeability using a 1% azovan (Merck) blue solution was used (Rocha e Silva & Dragstedt, 1941; Miles & Miles, 1952). In some of the animals promethazine hydrochloride (1 mg/kg) was previously injected intravenously. The cobalt ion effect on the morphology of the mast cells of the mesentery was assessed using a technique described to us by I. Mota (unpublished). This procedure allows microscopic observation of the mast cells of the mesentery *in situ* fixed and stained. 1 ml of a 0·02 M cobalt chloride solution was intraperitoneally injected. After 20, 40, 60 and 80 min, and under light ether anaesthesia, 10 ml of a 0·5% acetic acid, 10% formalin and 0·5% toluidine blue solution was intraperitoneally injected. After 2 h, small fragments of the mesentery were collected, washed in distilled water, attached to a slide and dried at ambiental temperature.

At the concentrations used, cobalt ion induced an immediate increase in the vascular permeability of the rat skin similar to that provoked by histamine. The strongest colour intensity provoked by the metal was always weaker than that elicited by histamine. Promethazine hydrochloride completely prevented the effect of histamine but not that of the cation. The microscopic examination of the mesentery showed that the morphological aspects of the mast cells were not altered by the cation.