SOME CARDIOVASCULAR ACTIONS OF SODIUM TAUROGLYCOCHOLATE

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Summary: Sodium tauroglycocholate reduced the response of the frog's isolated heart to acetylcholine and vagal stimulation. It increased the acetylcholine action on the rat blood pressure in low doses, and blocked it in higher doses. The response to low dose of sodium tauroglycocholate was blocked by atropine and potentiated by physostigmine. Irregular effects were observed on dog blood pressure. It produed bradycardia on direct application to sinio-auricular node in the dog.

Key words: sodium tauroglycocholate cholinergic responses heart

Bradycarida, hypotension and pruritus usually accompany jaundice. An intravenous injection of bile salt produces marked fall in blood pressure and bradycardia (3). The slowing of the heart is thought to be due to stimulation of the vagal centre. Larger doses depress the heart directly. The bile salts have also been reported to produce reversible inhibition of acetylcholine-induced stimulation of autonomic ganglia (4). Thus the effect of bile salts on the autonomic nervous system is not quite clear The present study was undertaken to investigate the effects of bile salts on the parasympathetic control of cardiovascular system of experimental animals.

MATERIALS AND METHODS

Sodium tauroglycocholate (Ward Blenkinsop and Co. Ltd., London) was the bile salt used in all the experiments.

The isolated frog heart (frogs weighing about 150—200 *g*) was perfused with frog Ringer Locke solution through the sinus venosus (1) and the vagus nerve was stimulated (square wave pulses; 5 to 10 volts; 1 msec; 30 Hz; total duration, 15 sec).

Carotid blood pressure of the rats (male and female albino rats weighing about 250 *g*) was recorded with Candon's manometer and the effect of acetylcholine was recorded before and after the administration of various doses of sodium tauroglycocholate. The effect of physostigmine and atropine on the response to acetylcholine and to sodium tauroglycocholate was also studied.

The systemic blood pressure of dogs weighing 8-10 *kg* was recorded from the carotid artery. Sodium tauroglycocholate was injected in doses of 5, 10, 20 or 40 *mg/kg*. In some experients, contractions of the auricle and the ventricle were recorded in an open-chest preparation. The right vagus nerve was stimulated with square wave pulses of different strengths (1 *msec*; 30 Hz; for 15 sec.). In other experiments, the sinoauricular node was perfused with blood taken from femoral

artery (2). This preparation was used for studying the effect of sodium tauroglycocholate directly on the sinoauricular node.

Drugs: Acetylcholine chloride, atropine sulphate, physostigmine salicylate, (-) - adrenaline hydrochloride (-) noradrenaline hydrochloride, isoprenaline sulphate and sodium tauroglycocholate.

RESULTS

Frog heart: In 15 experiments, sodium tauroglycocholate was added to the perfusion fluid in graded concentrations of 10, 25, 50 and 75 $\mu g/ml$. The effect of stimulation of the right vagus was noted before and after the addition of sodium tauroglycocholate. The results were similar in all experiments. Stimulation of the vagus produced missing of a few beats. In the presence of sodium tauroglycocholate, the inhibitor effect was converted to stimulation. Recovery of the inhibitor effect on switching back to perfusion with normal Ringer solution (Fig. 1) was seen in eight experiments.

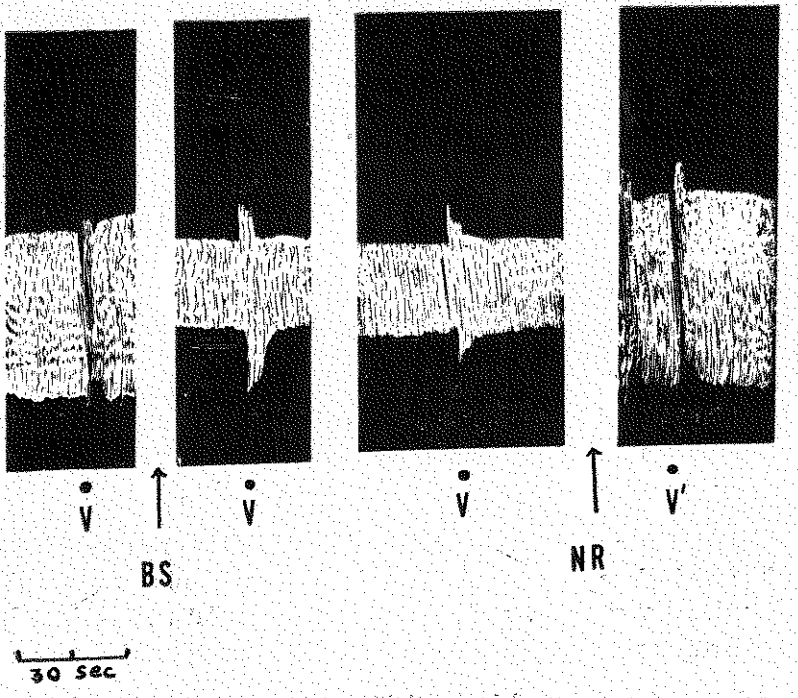

Fig. 1: Effect of sodium tauroglycocholate on the responses of isolated frog heart to vagal stimulation (V-6 volts for 15 sec., V'-10 volts for 15 sec.). NR-Normal Ringer Locke solution. Note a reversal of the effect of vagal stimulation by sod. tauroglycocholate (BS 70 $\mu g/ml$).

The effect of adrenaline (1-3 μg), nor-adrenaline (1-3 μg) and isoprenaline (1-3 μg) injected into the cannula through the rubber tubing was not influenced by the presence of

sodium tauroglycocholate in the perfusion fluid. The effect of acetylcholine (2 μg) injected similarly was very much reduced in the presence of sodium tauroglycocholate (n=6, Fig. 2). There was a partial recovery on switching back to normal Ringer Locke solution.

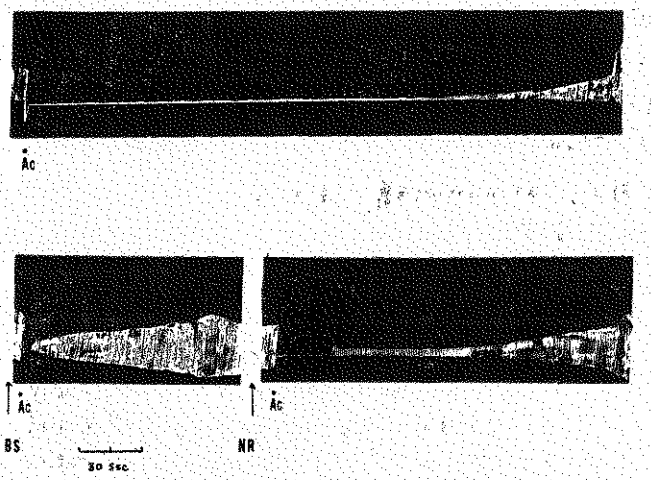

Fig. 2: Effect of sodium tauroglycocholate (BS 50 $\mu g/ml$) on the response of isolated frog heart to acetylcholine (AC, 2 μg). NR—normal Ringer Locke Solution.

Note blockade of acetylcholine effect.

Rat blood pressure: The effect of sodium tauroglycocholate on rat blood pressure was variable. In a dose range of 2-4 *mg/kg*, there was a slight pressor effect in two experiments and no effect whatsoever in another. Sodium tauroglycocholate (2 *mg/kg*) increased the duration of action of acetylcholine (0.5 μg total dose) from 6—10 sec to 2—10 mins. However, after a very high dose (16 *mg/kg*) of sodium tauroglycocholate, the action of acetylcholine became irregular and was ultimately completely blocked (n=4). In six experiments, sodium tauroglycocholate produced a purely depressor response (20±4 mm Hg) in a dose of 200 $\mu g/kg$. This response was potentiated (25±5%) after the administration of physostigmine (0.5 *mg/kg*) and blocked by atropine (2 *mg/kg*).

Experiments in dogs: Sodium tauroglycocholate did not produce any effect on the blood pressure of dog in doses upto 10 *mg/kg*. The influence of the bile salt on the response to acetylcholine (0.5—1 $\mu g/kg$) or stimulation of the vagus was not always uniform. When used in a dose of 10 *mg/kg*, sodium tauroglycocholate did not produce any effect on the acetylcholine response but it slightly reduced the depressor effect produced by vagal stimulation, which became biphasic in three experiments. However, when used in the same dosage, there was a potentiation (15 to 20%) of vagal stimulation in three other experiments.

The effect of sodium tauroglycocholate on the responses of auricles and ventricles to vagal stimulation was studied in eight experiments. Again, the results were not uniform. In one experiment, sodium tauroglycocholate failed to alter the response to acetylcholine (0.5—2.0 $\mu g/kg$) or stimulation of vagus nerve when used in graded doses upto 40 *mg/kg*. In a dose of 10 *mg/kg*, the effect of vagal stimulation was potentiated (20—25%) in three experiments, slightly reduced (5—10%) in three experiments and completely blocked in one.

The effect of sodium tauroglycocholate on the pseudocholinesterase of plasma was also studied. Acetylcholine (50 μg) was incubated at 37°C for 15 mins with 5.0 *ml* of plasma (obtained from the same animal prior to the experiment). Sodium tauroglycocholate (0.5 *mg*) did not effect the rate of hydrolysis of acetylcholine which was assayed biologically on frog rectus abdominis muscle pretreated with physostigmine.

The effect of sodium tauroglycocholate on the sino-auricular node of the dog was studied in eleven experiments. In all cases, direct application of 100 μg and 250 μg in 1 *ml* of normal saline to S.A. node produced bradycardia (30±6%) which was maximal in 3 min and lasted for 8—10 min.

DISCUSSION

The effect of sodium tauroglycocholate on living tissue seems to be very complex. A study of the physiological and pharmacological properties of bile salts specially with reference to drug interactions will be of interest in understanding of its role in obstructive juandice. Injections of sodium tauroglycocholate as such, unless given in very high dose, did not seem to produce any demonstrable action on the blood pressure of the dog but the responses to acetylcholine and also to vagal stimulation were altered. The present study was mainly concerned with exploration of the influence of sodium tauroglycocholate on vagal mechanisms, but even in this limited context the results have been bizarre. In the rat, the effect of sodium tauroglycocholate itself was variable, it produced an increase in acetylcholine response in low doses and a blockade with higher dose. The depressor response to sodium tauroglycocholate was potentiated by physostigmine and blocked by atropine. In the dog, again no consistent responses were obtainable, on the blood pressure. The irregular effects may have been due to intravascular haemolysis, produced by large doses of the bile salt.

Consistent results were obtained only in the frog, where acetylcholine action and the efiect of vagal stimulation were reduced in the presence of the bile salt. This does not explain the bradycardia seen in obstructive jaundice. The results on the S.A. node of the dog were also uniform and the bradycardia thus produced may well explain some of the clinical features seen in obstructive jaudice. The maechnaism of action of bile salt on the S.A. node is currently under investigation.

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