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EFFECTS OF THALLIUM SULFATE ON CARDIOVASCULAR AND RESPIRATORY SYSTEMS OF VARIOUS ANIMALS

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ABSTRACT Thallium sulfate po or iv depressed cardiovascular and respiratory systems of dogs, cats, rats, rabbits, kids and pigeons. These effects were partially direct and partially, due to a participation of higher vasomotor and respiratory centers, indirect, but mostly dependent on a decrease of the vasomotor reactivity evaluated by stimulation of nervous pathways and baroreceptor areas. Experiments *in vitro* also documented a depression of spontaneous tonic and phasic activity as wellas a depression of the contraction by various mediators (ACh, histamine, 5-HT, norepinephrine, bradykinin, $PGF_{2\alpha}$).

KEY WORDS thallium; cardiovascular system; respiratory system; vasomotor reactivity; hypotension; bradycardia

Thallium is an extremely toxic ion capable to accumulate in the organism. Its toxic effects have heen noted since its discovery in 1861. Now thallium salts (especially sulfate) are used as rodenticides and insecticides. Thallium poisonings are associated with cardiovascular changes (hypo-hypertension arrhythmias) which are, particularly in chronic intoxications, due to deterioration of autonomic nervous system[1-3]. The mechanism has not yet adequately been defined. The present study was conducted *in vivo* and *in vitro* using thallium sulfate.

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METHODS

Adult, or old, ♂ and ♀ (but not pregnant) NOS white rats (210±13 g), cats (3.2 ±0.6 kg), dogs (8.2±0.2 kg), rabbits (2.7 ±0.4 kg), kids (6.5±0.4 kg), guinea pigs (460±21 g), pigeons (395±18 g) and frogs (26±2 g) were fasted (with free access to water) 12 h before experiment.

Thallium sulfate (Merck), *l*-norepinephrine bitartrate and *dl*-isoprenaline sulfate (C H-Boehringer Ingelheim), acetylcholine-Cl and histamine-Cl (Hoffmann-La Roche), nicotine bitartrate (Simes), 5-hydroxytryptamine creatinine-sulfate (Sigma), synthetic bradykinin (Sandoz), and $PGF_{2\alpha}$ trometamine (Upjohn).

In vivo research: Rats, cats and rabbits were anesthetized with im ethyl-urethane 1 g/kg while dogs, kids and pigeons with iv pentobarbital-Na 25-30 mg/kg.

ECG was recorded by Epsilon or ETA electrocardiograph. In some cases the arterial blood pressure was recorded at left femoral artery by a mercury manometer or by a Hellige polygraph, the respiration by a cannula in trachea connected to a Marey tambour or to a Hellige polygraph, the venous BP at femoral vein by a Hellige polygraph. Thallium sulfate was administered in one single dose via oral route (by gavage), via gastric route (by a cannula into stomach through esophageal window), via intracerebroventricular route, via successive iv injections (femoral vein in dog, kid, and cat; axillary vein in pigeon), or via vertebral artery. The experiments lasted no longer than 6 h.

In vitro research. Auricles of guinea pigs were isolated and monitored on a Basile's Cardiotacograph, hearts of rats and guinea pigs on a Langendorff-Spadolini apparatus. The isolated organs were placed in a Ringer–Locke solution ($95\%O_2+5\%$ CO_2) at 37°C. Frog hearts were mounted on a Meneghetti's cannula and perfused with a Goethlin solution.

Statistical evaluation of the data used the formulas of Burn *et al*[4].

RESULTS

In vivo experiments

1. Thallium sulfate 20–40 mg/kg given via gastric route in rats slowed down the heart rates (c –30, –40 beats/min) of sinus rhythm (with increase of PQ and TP intervals and QRS voltage). At 25 mg/kg in dog and kid it caused a slow, moderate and transitory arterial hypotension (c –20, –30 mm Hg), associated with no significant modifications in ECG and respiration. A decrease (c –50, –60%) of the hypertensive response to the 30–s occlusion of the carotid arteries was also seen. In rabbit 35 mg/kg yielded a slow and progressive arterial hypotension (c –10, –30 mm Hg) with sinus bradycardia (c –60, –80 beats/min) characterized by a lengthening of PQ and TP intervals together with a reduction of respiratory amplitude without any marked changes of carotid sinus reflexivity (30–s occlusion of two common carotid arteries).

2. In dogs, kids, pigeons and cats, thallium sulfate was injected iv by successive injections (once in 2 min). Thallium sulfate 0.001–10 μg/kg did not cause any significant alterations of arterial BP, respiration, ECG and femoral artery plethysmogram; for doses starting from 0.1 mg/kg it brought about a moderate and dose-proportional sinus bradycardia (c –10, –30 beats/min) with lengthened PQ and TP intervals which were associated with modifications of ST intervals and voltage of T wave for 1–10 mg/kg.

3. In rats thallium sulfate iv by successive injections (once in 2 min) caused sinus bradycardia (c –10 beats/min) with heightened QRS voltage after 0.1 mg/kg, atrioventricular block after 1–10 mg/kg, and death after 10 mg/kg.

4. Thallium sulfate iv by successive injections (once in 2 min) starting from 1–10 μg/kg caused in dog, kid and cat a dose-proportional decrease (c –11, –31%) of hypertensive response to occlusion of both common carotid arteries and to nicotine and a decrease of hypotensive response to stimulation at the proximal end of the sectioned vagus nerve (c –9, –36%); in dog iv 0.001–10 mg/kg did not seem to affect the vasomotor responses to *l*–norepinephrine, ACh, *dl*–isoprenaline and to histamine.

5. In dog thallium sulfate injected in 5 s via vertebral artery in successive injections starting from 100 μg/kg caused sinus bradycardia (c –20, –30 beats/min) and for 1–10 mg/kg bradycardia was accompanied by an immediate and transitory hypotension followed by an intense and lasting (c 5–10 min) hypertension (c +10, +20 mm Hg) as well as remarkable changes of

respiration (bradypnea with increased amplitude and occurrence of Cheyne-Stokes respiration) followed by death.

6. In dog, single injections of 2 μl thallium sulfate 0.1–1–10 mg/kg into 3rd cerebral ventricle caused a very moderate reduction of BP (*c* –5, –15 mm Hg), a reduction of femoral venous pressure (*c* –4, –16 mm Hg), an increase of cardiac output, and very moderate decreases of respiratory amplitude and arterial blood flow (c +25, +75 ml/min).

7. In dog 0.1–1% thallium sulfate infiltrated (0.2 ml/sinus) at carotid sinus baroreceptor zones decreased the hypertensive response after occlusion of both common carotid arteries (*c* –11, –19%).

8. In dog thallium sulfate 0.1–1 mg/kg depressed the baroreceptor and chemoreceptor reactivity respectively of carotid sinus and glomus when rapidly injected in 5 s into common carotid artery with a denervated (or not) sinus.

9. Male white rats were anesthetized with im ethyl-urethane 1 g/kg and prepared for registration of gastrocnemius muscle contractions stimulated either directly or indirectly by faradic current[5]. Thallium sulfate injected iv 1–10 mg/kg in rats in successive injections (once in 2 min) decreased the contractions of gastrocnemius muscle evoked by direct or indirect (sciatic nerve) electro-stimulation, and, for doses of 0.001–1 mg/kg, moderately potentiated the curaric effect of both *d*-tubocurarine and of succinylcholine.

***In vitro* researches**

1. Thallium sulfate 10–1000 μg/ml produced a moderate inhibition of the sinus chronotropism of rat's and guinea pig's auricle and heart without any significant changes of inotropism. On frog's heart the sinus inotropism and chronotropism were temporarily decreased for concn of 10–100 mg/ml. The coronary blood flow of rat's and guinea pig's hearts was not altered even after 1 mg/ml. On frog's heart a 10-min perfusion with Goethlin soln medicated with thallium sulfate 10 pg –1 mg/ml decreased the inotropism and positive inotropic effect by isoprenaline 100 ng/ml.

2. Intestinal and uterine segments of white rats, kids and guinea pigs, antero-posterior longitudinal segments of gall-bladder and urinary bladder of guinea pigs, spleens of rabbits, vas deferens of rats and abdominal aorta of guinea pigs were isolated in an oxygenated Ringer-Locke soln at 37℃. Rectus abdominis muscle of frogs were put in a Ringer-Locke soln at room temp (22℃).

Thallium sulfate did not markedly modify the tonic and the phasic activities of duodenal musculature of rats and kids, the uteri of pregnant rats (at the end of gestation) and of quiescent she-kid's uteri for concns of 1–1000 ng/ml, caused moderate hypotonic and hypophasic effects for concns of 10–100 μg/ml, and brought forth an immediate hypertonic effect with a decrease of phasic activity of she-kid's uteri for concn of 1 mg/ml.

On some isolated organs the effects of a 5-min pretreatment with thallium sulfate 10-100 μg/ml *in vitro* on the contractile actions of various agonists were studied according to dose-response curves[6]. Thallium antagonized in a noncompetitive way the contractions evoked by ACh on rat's and guinea pig's ileum, virgin rat's uteri, guinea pig's gallbladder and frog's rectus abdominis muscle, by histamine on ileum, gallbladder and urinary bladder of guinea pigs, and uteri of virgin guinea pigs, by 5-HT on uteri of virgin rats and guinea pigs, by bradykinin on ileum of guinea pigs and uteri of virgin rats, by norepinephrine on spleen of rabbits, vas deferens of rats and abdominal aorta of guinea pigs, and by $PGF_{2\alpha}$ on ileum of guinea pig and

uterus of virgin rat.

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