

## BEHAVIOURAL, ELECTROCORTICAL AND SPECTRUM POWER EFFECTS AFTER INTRAVENTRICULAR INJECTION OF THALLIUM IN RATS

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**ABSTRACT** Marked behavioural, electrocortical and ECoG spectrum power changes were seen after microinjection of several doses of thallium sulfate into the 3rd cerebral ventricle in rats. Low doses produced behavioural sedation and/or sleep accompanied by larger amplitude slower frequency ECoG potentials whereas after higher doses an initial period of behavioral sedation was followed by an intense stimulatory symptomatology, stereotyped and abnormal movements, wild running crisis and epileptogenic ECoG discharges or electrocortical flattening according to the dose used. Significant changes occurred also in total as well as single bands of ECoG spectrum power. In conclusion, intraventricular injection of thallium produces a rich pattern of behavioural and electrocortical changes, the nature of which depends on the dose and which allow to explain the neurotoxicological profile in man. These results provide evidence for occurrence of epileptogenic disorders as well as for other ECoG abnormalities in thallotoxicosis.

**KEY WORDS** thallium sulfate; CNS; intraventricular injections; rats

The human toxicity of thallium has been recognized since the beginning of this century. The initial symptoms of acute intoxication include gastrointestinal, cardiovascular symp-

toms as well as peripheral and central nervous system (CNS) disorders<sup>(1)</sup>. As far as CNS effects are concerned these are characterized by extrapyramidal symptoms, headache, sleep disturbance, lethargy, psychotic behaviour, tremor and convulsions<sup>(1)</sup>. Cranial nerve involvement is also common in thallium poisoning, i. e. ptosis, nystagmus, deconjugation of eye movements, facial paralysis and optic neuritis. In addition, an abnormal EEG activity consisting in slow-wave potentials may be recorded<sup>(2)</sup>. Recovery from thallotoxicosis in man requires months and may not be complete; the common sequelae include neurological, EEG abnormalities and psychotic disturbances<sup>(1)</sup>.

The purpose of the present experiments was to characterize in rats behavioural and electrocortical effects of thallium after microinjection of several doses into the 3rd cerebral ventricle; the electrocortical activity was continuously quantitated and analyzed in single bands of frequency.

### METHODS

Adult Wistar-Morini rats ( $286 \pm 12$  g) were anesthetized with chloral hydrate. Cortical electrodes were chronically implanted<sup>(3)</sup>. The intraventricular injection of thallium was performed in awake rats by an Hamilton 10  $\mu$ l syringe at least 3 d after stereotaxic implantation of a cannula according to De Groot atlas<sup>(4)</sup>. The electrocortical activity was recorded by an 8-channel OTE EEG machine. The quantification of total voltage power and of single bands of frequencies was carried out by a

Received 1982 Nov 13 Revised 1983 Jun 9  
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Berg-Fourier analyzer (OTE Biomedica)<sup>(5)</sup>.

The spectrum power was plotted and the integrated energy signals were expressed as  $\mu V^2$ . In order to quantify changes of total voltage power induced by thallium, the area (expressed in  $mm^2$ ) under the curve corresponding to plotted total voltage values during 30-min periods after thallium was integrated by an IBM computer (370/115) according to the trapezoidal rule; then % changes of the integrated area in comparison to the same interval area during pretreatment period were easily calculated. The number of experiments is given in brackets (n).

## RESULTS

Thallium sulfate given into the 3rd cerebral ventricle produced marked and long-lasting behavioural, electrocortical and spectrum power changes.

In particular, a low dose ( $0.1 \mu mol$ ) of thallium sulfate (n 5) produced behavioural sedation and sleep lasting over 6 h; these effects become evident within the first 15 min after the injection. During this state the rats kept a posture with kyphosis. In comparison to control period, electrocortical activity after thallium was characterized by higher amplitude, slower frequency potentials (Fig 1).

The injection of higher doses ( $0.25$  and  $0.5 \mu mol$ ) of thallium (4 rats/dose) yielded marked behavioural effects which showed a

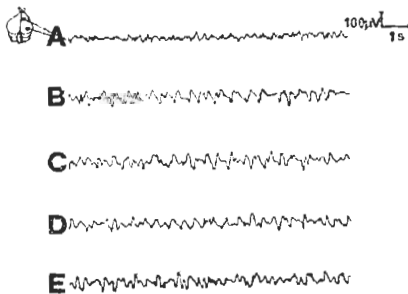


Fig 1. Electrocortical effects of an intraventricular injection of thallium ( $0.1 \mu mol$ ) in an adult rat. A) Control. B, C, D & E) 15, 60, 180 & 240 min from thallium infusion, showing slower frequency and higher amplitude potentials.

biphasic pattern. After an initial period of sedation lasting about 15 min a progressing increase in locomotor activity and an intense pattern of stereotyped movements (licking, grooming, sniffing, chewing, etc.) occurred in the rats; such excitatory symptomatology lasted over 4 h. Electrocortical activities both during the sedation state and during the excitatory phase were characterized by higher amplitude, slower frequency potentials (Fig 2) associated with an increase in total voltage power (Fig 3) and in the preselected bands of frequency (Fig 4). Occasionally after  $0.5 \mu mol$  higher voltage slow spikes or bursts of bilateral high-voltage spikes were recorded (Fig 2). The number of spikes and total voltage power increase after an intraventricular dose ( $0.5 \mu mol$ ) of thallium are given in Fig 3.

More dramatic behavioural and electrocortical effects were seen after the injection of  $0.75$

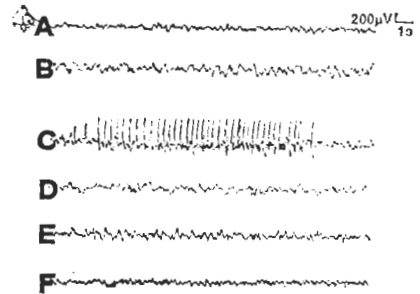


Fig 2. ECoG after an intraventricular injection of thallium  $0.5 \mu mol$  in an adult rat. A) Control. B, C, D, E & F) 1, 20, 45, 165 & 300 min after thallium. Slower frequency and higher amplitude potentials (B, D, E) and high-voltage spikes (C) were seen. F) Return to control ECoG.

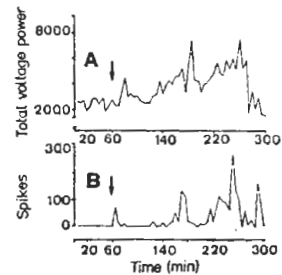
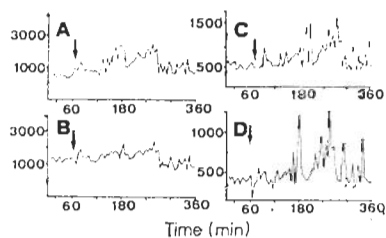
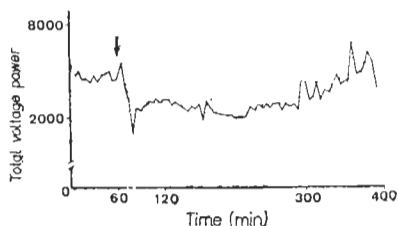


Fig 3. Total voltage power increase (A) and number of high-voltage electrocortical spikes (B) after an intraventricular injection of thallium sulfate  $0.5 \mu mol$  in an adult rat.

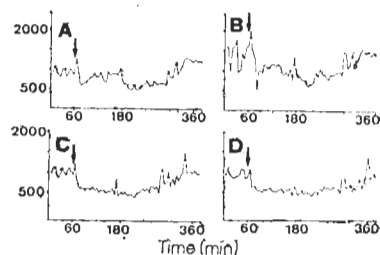


**Fig 4.** Effects of an intraventricular injection of thallium sulfate  $0.5 \mu\text{mol}$  on electrocortical power of 0-4 (A), 4-8 (B), 8-12 (C) and 12-16 (D) Hz frequency bands. The most prominent increase was seen in A, C & D.

and  $1 \mu\text{mol}$  ( $n$  6/dose). In particular, a complex behavioural syndrome was observed with alternating episodes of either increased locomotor activity culminating occasionally into wild running crisis or circling or reduced locomotor activity. In addition, a rich pattern of stereotyped movements (sniffing, grooming, licking) and other characteristic signs were noted, i. e. tail rigidity, postural changes, hunched back, hindlimb paresis and increased reactivity to sensory stimuli; moreover, the rats appeared tachypnoic and had ruffled hair. Such changes were gradual in onset, became progressively more intense and in 1/3 of the rats were followed by death; when the rats survived the effects were long-lasting (over 6 h). The above signs were accompanied by marked electrocortical changes consisting in flattening, disorganization of the normal pattern and occasionally in slowspikes or discharges of spikes of amplitude higher than that of ECoG recorded during the pretreatment period and by a significant fall in total ECoG voltage power (Fig 5) as well as in



**Fig 5.** Sustained decrease in total voltage power after an intraventricular injection of thallium sulfate  $1 \mu\text{mol}$  in an adult rat. Return to pretreatment values approximately 5 h afterwards.



**Fig 6.** Decrease in electrocortical power in all frequency bands: 0-4 (A), 4-8 (B), 8-12 (C) and 12-16 (D) Hz after an intraventricular injection of thallium sulfate  $1 \mu\text{mol}$  in an adult rat.

0-4, 4-8, 8-12 and 12-16 Hz frequency bands (Fig 6).

## DISCUSSION

The present experiments provide evidence to explain the CNS signs occurring in man after acute thallium intoxication. The symptomatology was dose-dependent, a sedation state occurring with the lower doses and an intense behavioural and locomotor stimulation with the highest. The pathophysiology of neurological disorders is unknown yet. It is speculated that a change in some neurotransmitters content or turnover in specific areas of the brain may occur or that behavioural and electrocortical disorders may be a consequence of an imbalance in ionic mechanism at the neuronal membrane level. In rats treated with thallium brain catecholamine metabolism does not seem to be altered<sup>(6)</sup>, although a subacute treatment with thallium produces a decrease in dopamine content in hypothalamus, limbic areas and striatum<sup>(7)</sup>. The decrease in dopamine content may be the consequence of an increased release of dopamine from nerve endings in striatum, limbic and cortical areas, thus explaining its extrapyramidal and psychotic effects in man.

After subacute thallium treatment in rats a decrease in serotonin content was revealed in striatum, brain stem and cerebellum<sup>(8)</sup>. In rat cerebellum thallium given for 7 d produced a significant increase in spontaneous discharge rate of cerebellar Purkinje neurons and this seemed to be due to a reduction in catecholaminergic input into central neurons<sup>(8)</sup>. The intense

behavioural and motor activity accompanied by ECoG disorganization and by epileptogenic discharges may be related to a decrease in GABAergic mechanisms, being GABA the main inhibitory transmitter in brain<sup>(8)</sup>. However, we have not found in several discrete areas of brain any change in GABA content, glutamate-decarboxylase activity, nor GABA-transaminase, the rate-limiting step enzyme in GABA synthesis and the main enzyme in GABA-breakdown, respectively<sup>(1)</sup>. The ability of thallium to interfere with K-dependent biological reactions seems to play a role in the toxicity. Thallous ions interacted with the cation transport mechanism across membranes of erythrocytes, kidney, muscle, brain, etc.<sup>(10)</sup> Thallium inhibited the ouabainsensitive K<sup>+</sup>-influx in human rbc in high Na<sup>+</sup>-medium<sup>(11)</sup> and replaced K in activation of Na<sup>+</sup>, K<sup>+</sup>-ATPase<sup>(12)</sup>. At high concentration thallium inhibited Na<sup>+</sup>, K<sup>+</sup>-ATPase as well as ouabainsensitive Na transport in human rbc<sup>(13)</sup> and in guinea pig myocardial cells<sup>(14)</sup>. It is conceivable that high doses of thallium given into cerebral ventricles produce electrophysiological and motor changes as a consequence of a decrease in intraneuronal K<sup>+</sup> concentration as occurs with digitalis glucosides<sup>(15)</sup>.

In conclusion, marked behavioural, electrocortical and spectrum power changes occur after intraventricular injection of thallium. These disorders are dose-dependent and provide evidences to explain epileptogenic, extrapyramidal effects and other ECoG abnormalities in man after acute thallium intoxication.

**ACKNOWLEDGMENTS** Thanks to the

Italian National Researches Commission (CNR) and Ministry of Public Education for their financial contributions.

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