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Comparison of the effect of acute LiCl intoxication on rat and mouse brain

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Morphological changes in the rat and mouse brain following acute lithium administration were studied using silver-copper impregnation for neurodegeneration. Vacuolization was observed in all the studied brain regions – cerebral cortex, cerebellar cortex and medulla oblongata of lithium-treated animals. Loss of Purkinje cells was seen in the cerebellum. Impregnated nerve fibres were observed to show a substantial damage of neuronal processes. No differences were noticed in the pattern of brain morphological changes between both species. Thus, rat and mouse models can be equally successful for the study of lithium salts effects on the brain.

Key words: lithium intoxication, rat, mouse, brain morphology, silver-copper impregnation

Introduction

Lithium is extensively used in psychiatric practice for the prevention and treatment of manic-depressive disorders. However, neurotoxicity of lithium salts within therapeutic dose has been reported in patients manifested by transient or persistent neurological deficits. Animal models are not sufficiently exploited for the study of lithium-affected brain morphology which restricts the possibility to follow up the pathological changes at an early stage. Cerebellar spongiform degeneration has been documented in a rat model of acute lithium intoxication [4] and these data correlate well with findings in humans [1]. Experimental data for the neurotoxic effect of lithium salts in mice are scarce.

The aim of the present study is to follow up the morphological changes in the rat and mouse brain provoked by acute lithium intoxication and to compare the effect of LiCl between both species.

Materials and Methods

Mature Wistar rats (four-month-old) and Balb/c mice (three-month-old) were subjected to acute lithium intoxication by a single dose of lithium chloride (250 mg/kg body

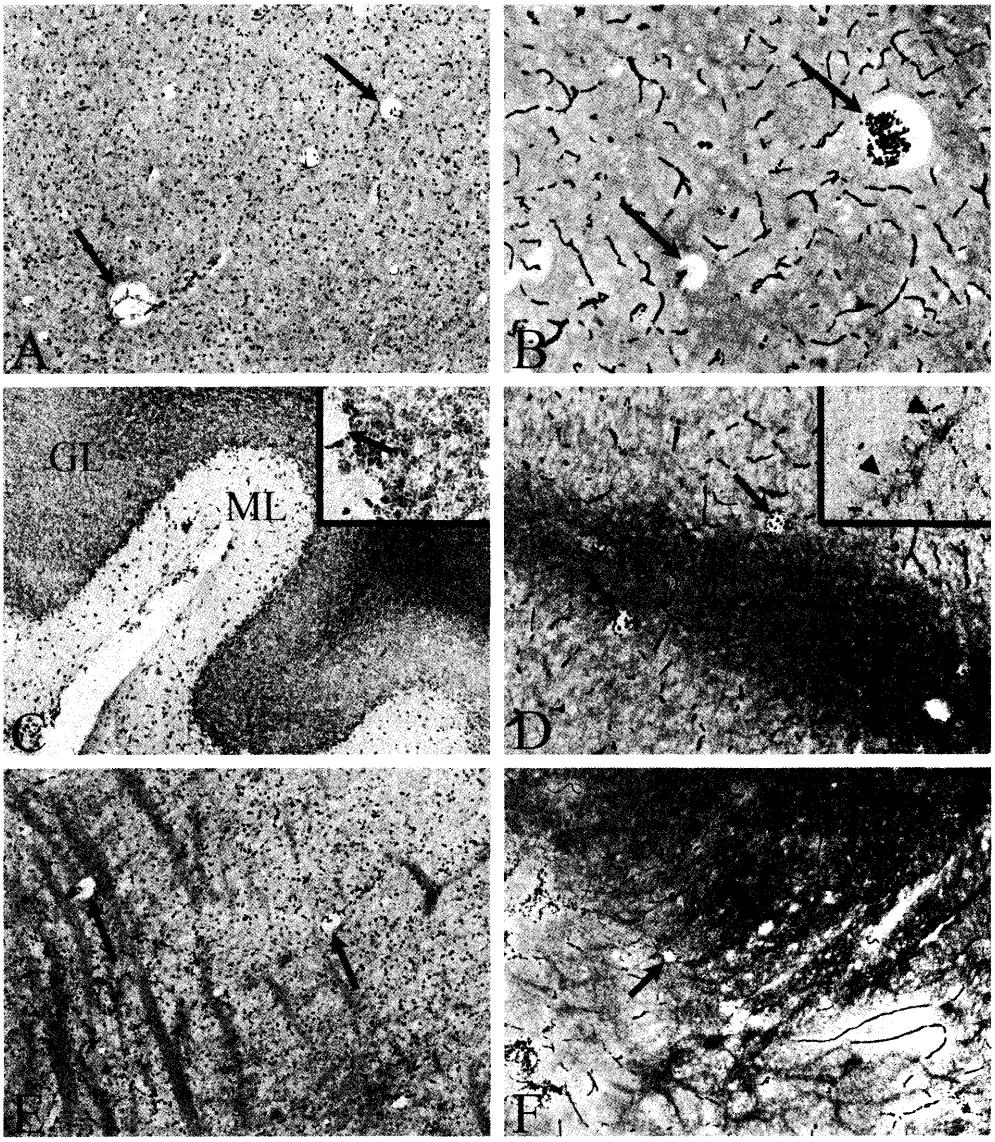

Fig.1. Morphological changes in different regions of mouse and rat brain following acute LiCl intoxication as detected by silver-copper staining. Similar vacuolization in the mouse (A) and rat (B) cerebral cortex (arrows). Preserved granular (GR) and molecular (ML) layers in the mouse cerebellar cortex (C). but empty spaces (arrow) of missing Purkinje cells (inclusion in C). Vacuoles of different size (arrows) in deeper zones of the granular layer of rat cerebellar cortex (D) and empty spaces (arrows) of lost Purkinje cells (inclusion in D). Sparsely located small vacuoles (arrows) in the mouse (E) and rat (F) medulla oblongata. A, B, D, E, F 200 X; C 100 X; inclusions 400 X.

weight, 0.2 ml dosing volume in saline, i.p.). Treated animals were sacrificed 24 hours following the administration under light anesthesia.

Different regions of the CNS were studied histologically – cerebral cortex, cerebellum and medulla oblongata using silver-copper staining for neurodegeneration. The silver impregnation was carried out exactly as described by De Olmos and Ingram [3]. All the sections were studied under Leica DM50008 (New York, USA) microscope.

Results and Discussion

Acute lithium intoxication in patients might be due to accidental (or deliberate) overdose of lithium-based drugs. In such cases, neuropathological changes found at autopsy prove to be similar to those in animal models of lithium toxicity. On the other hand, animal models allow following up the earliest histopathological signs of the intoxication. Our present investigation is prompted by the scanty morphological studies in experimental models of lithium-induced neurotoxicity. Most of the available data emphasize on biochemical, physiological, and behavioral effects of lithium, while brain histopathological changes are poorly investigated. Recently, we developed experimental rat and mouse models of lithium intoxication based on acute lithium administration. The silver-copper impregnation technique of de Olmos and Ingram [3] proved to allow precise localization of the morphological changes in the animal CNS and their topographic distribution in the brain.

Similar changes were observed in the mouse and rat cerebral cortex (Fig. 1 A, B). This brain region proved to be the most affected by the acute lithium intoxication. Vacuoles of different size (5-50 μm) were observed both in the outer and deeper cortical layers in the two species studied. Cell debris was visible inside the vacuoles. Significant loss of Purkinje cells was found in the cerebellar cortex of both species (Fig. 1 inclusions in C and D). However, in the mouse cerebellum no signs of vacuolization were observed (Fig. 1 C). In contrast, vacuoles of different size were detected in the deeper zones of rat cerebellar granular layer (Fig. 1 D). Data about the effect of lithium salts on the cerebellum morphology are rather controversial. Thus, no structural changes in the rat cerebellum have been reported by Licht et al. [5], whereas a widespread vacuolization was detected by Dethy et al. [4]. Much less pronounced vacuolization was registered in the medulla oblongata both in mouse and rat (Fig. 1 E, F). The formation of vacuoles in all brain regions is considered a common manifestation of brain neurodegeneration both in pathological conditions and during normal brain aging [2, 6].

In conclusion, acute lithium intoxication provokes similar pattern of changes but of different intensity in the rat and mouse brain. Therefore, rat and mouse models can be equally successful for studying the effects of lithium salts on the brain. Animal models of adverse brain impacts would be beneficial for the clinical trials because of the opportunity of detecting the early pathological signs.

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