Distribution of lithium in the rat brain after a single administration known to elicit aversive effects

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In order to get insight into the brain areas involved in the initial unpleasant effects resulting from the administration of lithium (Li⁺), its distribution was mapped in the rat brain using the ⁶Li(n,α)H nuclear reaction after a single injection of ⁶LiSO₄ at doses and latencies corresponding to the elicitation of such unpleasant effects. An improved method for visualization and measurement of local Li⁺ concentrations was used consisting in diffracting light along the tracks left by α particles in a dielectric detector. The distribution of Li⁺ was found less homogeneous than when Li⁺ was administered chronically. Periaqueductal and periventricular structures were the brain areas containing the highest concentrations of Li⁺.

The successful use of lithium (Li⁺) in the treatment of manic-depressive pathology has inspired an increasing number of studies attempting to elucidate its mechanism of action. Thus, studies on Li⁺ distribution in the brain concerned chronic Li⁺ treatment. Humans treated with Li⁺ report unpleasant feelings as soon as after its first administration [9]. This is consistent with the induction of aversion in animals attested by robust taste or place aversion through associating a novel taste or place with a single administration of Li⁺ [3, 7, 12]. Periventricular and periaqueductal neurons are responsive to Li⁺ treatment as attested by c-fos immunostaining studies [8, 23]. These brain areas might be the target site of action for Li⁺ simply because Li⁺ would accumulate there shortly after its administration. To verify this hypothesis mapping Li⁺ distribution in the brain shortly after a single administration is required. Mapping Li⁺ is fairly difficult since there is no radioisotope with a convenient half-life. Nevertheless, the feasibility of using the specific ⁶Li(n,α)H nuclear reaction in the presence of a dielectric particle track detector is well documented [17, 21].

Twelve rats (Long Evans, 300–350 g) were injected intraperitoneally with ⁶LiSO₄ purchased from the CEA, Saclay, France (1.2–3.6 mEq/kg). Care to these animals was in accordance to the guidelines of the french ministry of agriculture. Six rats were injected only once. Six others received one intraperitoneal injection daily for 10 days. One hour after the single or last injection, each rat was killed by an overdose of pentobarbital (120 mg). Its brain was perfused with cold saline (4°C) injected into its aorta. The brain was removed within less than 5 min, frozen by immersion into isopentane (−50°C), and sliced (50 μm thickness) using a freezing microtome. The slices were collected on plastic slides and dried under a stream of dry N₂. A pile of such slides alternated with dielectric detectors (CR39, Pershore Moulding LTD) were irradiated using thermal neutrons (5 × 10¹⁵ neutrons/m²) from the nuclear reactor of the Université Louis Pasteur, Strasbourg, France. After irradiation, the detectors were etched for 90 min in a 25% NaOH solution (80°C). A specially designed dark-field illuminator allowed us to evaluate the density of the α tracks by use of an image analyzer and to take photographs (Fig. 1). The periventricular structures were found to contain the highest concentrations of Li⁺ – the periventricular and, the periaqueductal gray and the lateral septum – together with the hippocampus. Ideally, for quantitative evaluation of the Li⁺ concentration, the number of tracks in the detector has to be counted using a microscope [17]. Here, an alternative method was used. It rests upon the principle that the quantity of light diffracted by each etched track sums up with a number of neighboring ones at lower magnification of the microscope. Therefore, the resulting local brightness should be proportional to the track density.
the latter being proportional to the number of $^6\text{Li}^+$ ions in our experimental conditions. This assumption was confirmed on brain standards containing known and homogeneous amounts of $^6\text{Li}^+$ (Fig. 2). The quantitative analysis confirmed the qualitative observations, namely that, after an acute administration of $^6\text{Li}^+$, its concentration was high around the ventricles and aqueduct, the highest being found in the gray matter below the IVth ventricle coextensive with the rostral area postrema (AP). After repeated administration, other structures further accumulate $^6\text{Li}^+$ (mainly the cerebral and the cerebellar cortex as well as the striatum and thalamus), thus decreasing the overall contrast. The distribution of $^6\text{Li}^+$ after chronic treatment was similar to that reported by others [13]. A two-way analysis of variance for mixed design experiments was used. Concentration of lithium in each of seven selected brain structures, namely cortex, lateral septum, rostral area postrema, reticular formation, periaqueductal gray, medial hypothalamus and hippocampus, was the within factor and the kind of treatment, acute versus chronic, was the grouping factor. It showed a significant difference for the treatment ($F_{60}^a = 5.26, P < 0.05$) and for the brain structure ($F_{60}^b = 26.31, P < 0.001$).

Taken together, these results show that, when administered once at a dose eliciting aversion [14], $^6\text{Li}^+$ shows high concentrations in areas that have been incriminated in the generation of aversion in animals as well as in humans [10, 15, 19]. Secretion of the cerebrospinal fluid may contribute to the high level of $^6\text{Li}^+$ in structures that surround the ventricles and aqueduct as the concentration of $^6\text{Li}^+$ was reported to reach its highest level in the cerebrospinal fluid much earlier than in the brain [22]. Furthermore, it has already been suggested that these circumventricular structures may be areas where some substances that hardly cross the blood–brain barrier gain access to the brain [11]. Once having penetrated into the periaqueductal and periventricular structures, $^6\text{Li}^+$ may excite neurons as the presence of extracellular $^6\text{Li}^+$ – at concentrations equivalent to those obtained by $^6\text{Li}^+$ treatment – was reported to cause cell depolarization [1]. Furthermore, periventricular and periaqueductal neurons produced c-fos after a single $^6\text{Li}^+$ administration [8, 23].

Such an activation would result in unpleasant effects as do other excitatory agents when injected into these brain areas [4]. Although the excitation of various periventricular or periaqueductal areas may contribute to the aversive effects of the administration of $^6\text{Li}^+$, the area postrema satisfies best the requirements for being implicated in the genesis of taste aversion as electrical stimulation of the area postrema elicits conditioned taste aversion [6] and as its ablation prevents it [18]. Another structure showing high $^6\text{Li}^+$ content, the periaqueductal gray, seems less implicated in taste aversion as its removal did not empeach taste aversion in our laboratory but more in the genesis of anxiety [20]. As the penetration of $^6\text{Li}^+$ into cells is slow [5] and as the intracellular action of $^6\text{Li}^+$ results in functional alterations in second messenger pathways (for more information, see ref. 16), it is finally suggested that chronic administration of $^6\text{Li}^+$ fa-
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