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Differential effects of endogenous lithium on neurobehavioural functioning: A study on auditory evoked potentials

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ABSTRACT

Lithium occurs naturally in food and water. Low environmental concentrations in drinking water are associated with mental illnesses and behavioural offences, and at therapeutic dosages it is used to treat psychiatric (especially affective) disorders, partly by facilitating serotonergic (5-HT) neurotransmission. As little is known about the psychophysiological role of nutritional lithium in the general population, endogenous lithium concentrations were hypothesised to be associated with measurable effects on emotional liability and the loudness dependence (LD) that is proposed as one of the most valid indicators of 5-HT neurotransmission. Auditory evoked potentials of healthy volunteers [$N = 36$] with high (>2.5 μg/l) or low (<1.5 μg/l) lithium serum concentrations were recorded. Emotional liability was assessed using the Brief Symptom Inventory (BSI). Low-lithium levels correlated with *Somatisation* while correlations between lithium and LD were not significant. Still, LD correlated positively with *Paranoid Ideation*, negatively with *Anxiety* and, in the high-lithium group, inversely with further aspects of emotional liability (*Depression, Psychological Distress*). In conclusion, the effects of low levels of endogenous lithium are associated with emotional liability, and high levels with some protective effects, although findings remain inconclusive regarding LD. Potential benefits of endogenous lithium on neurobehavioural functioning, especially in high-risk individuals, would have public health implications.

1. Introduction

Lithium (Li) has been successfully used in psychiatric treatment for more than 50 years now (Cade, 1949). Therapeutic dosages of lithium are effective not only in acute mania, bipolar depression, as well as for prophylaxis, suicide prevention and augmentation of affective disorders (Goodwin et al., 1969; Stokes et al., 1971; De Montigny et al., 1985; Cipriani et al., 2005), but also in other conditions such as aggression, impulsiveness, attention deficit/hyperactivity and non-affective psychosis (Sheard, 1971; Kingsbury and Garver, 1998, Dorrego et al., 2002), and there is evidence that lithium inhibits deterioration in Alzheimer's disease (Nunes et al., 2007). Some studies showed heterogenous findings when lithium was given in therapeutic dosages to healthy volunteers, i.e., either a decrease of mood variability or no effect (Calil et al., 1990; Barton et al., 1993). By contrast, little attention has been paid to the physiological role of endogenous lithium for neurobehavioural states in the normal population, as already shown for other environmental agents (Kunert et al., 2004).

Nevertheless, first epidemiological studies showed inverse rates between lithium concentrations in the drinking water and urine and the occurrence of mental disorders and hospital admissions or homicide/suicide rates (Dawson et al., 1970, 1972) while other studies showed weaker or contradictory results (Voors, 1972; Pokorny et al., 1972; Oliver et al., 1976). Schrauzer and Shrestha (1990) and Schrauzer et al. (1992) also detected fewer admissions to mental hospitals and fewer behavioural offences in regions with high-lithium water levels >70 μg/l. It was proposed that high-risk populations would profit from elevated nutritional lithium concentrations.

Lithium is the lightest, most solid and least reactive of all alkaline metals, occurring widely in soils and mineral springs (Kabata-Pendias and Pendias, 2001). The primary sources of nutritional lithium intake include drinking water, grains and vegetables. Lithium is easily absorbed from the intestinal tract, evenly distributed in the body fluids and is excreted through the kidneys (Fyrö and Sedvall, 1975). Endogenous serum levels in humans as well as their daily intake were found to highly vary (from 1.1 to 59.7 μg/l, or 104.1 μg/day to 1596–2568 μg/day respectively), greatly depending on the environmental

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occurrence of lithium and on dietary habits (Lehmann, 1994). Schrauzer (2002) proposed a provisional recommended dietary allowance of 1 mg Li per day for a 70-kg adult. However, these data allow no inferences about the lithium in the body, particularly the central nervous system. Suggestions that lithium may be a biological trace element essential for mammals, and possibly humans, too, are primarily based on animal depletion studies: It was shown that nutritional lithium is required for normal health and life expectancy, growth, weight and reproduction (Anke et al., 1983; Pickett and O'Dell, 1992; Schrauzer, 2002; Schäfer, 2004). Lithium depletion in rats led to neurobehavioural alterations, including motor activity, response to handling, avoidance behaviour and social aggression (Ono and Wada, 1989; Klemfuss and Schrauzer, 1995), while lithium treatment reversed depression-like behaviour of learned helplessness (Faria and Teixeira, 1993) or in forced swim tests (Nixon et al., 1994).

However, mechanisms of action of lithium are not fully understood yet. As one mode of action in the brain, therapeutic lithium concentrations affect intracellular transduction of interneuronal signals and several neurotransmitters. Lithium reduces the activity in the dopaminergic and noradrenergic systems, but at the same time primarily functions as a serotonin (5-HT) agonist (e.g. Brunello, 2004). Facilitating effects on other 5-HT antidepressants are known as co-treatment with lithium augments 5-HT levels and functions in animals (De Montigny et al., 1983; Wegener et al., 2003) and in humans (De Montigny et al., 1985; Cowen et al., 1991). Taken together, lithium is thought to restore equilibrium in the various signalling pathways in the brain (Brunello, 2004). The clinical relevance of 5-HT receptor sensitisation by lithium becomes apparent since a dysfunctional 5-HT system is associated with several psychic disorders, including depression, impulsive aggression, suicidal behaviour and anxiety (Apter et al., 1990; Maes and Meltzer, 1995).

Obtaining a biologically non-invasive but valid measure of 5-HT neurotransmission, auditory evoked potentials (AEPs) were measured in this study. The primary auditory cortex, which has been identified as the electrical source generator of the large negative AEP component, N1, is highly innervated by 5-HT fibres from the raphe nuclei (Azmitia and Gannon, 1986). Hegerl and Juckel (1993) proposed that a steeper N1/P2 slope with increasing auditory stimulus intensity is associated with low 5-HT neurotransmission and vice versa. The particular relationship between this loudness dependence (LD) of the AEP with the primary but not the secondary auditory cortex was confirmed in cats (Juckel et al., 1997). In fact, electrophysiological observations of intra-individual stability of an augmenting/reducing (A/R) characteristic of the N1 and P2 amplitudes in response to stimuli of varying intensities in event-related potentials (ERPs) go back to the earlier 1970s (Buchsbaum and Silverman, 1968; Buchsbaum et al., 1971). Clinically, an LD increase was found in neuropsychiatric disorders such as migraine (Wang et al., 1996), major depression (Gallinat et al., 2000), chronic ecstasy abuse (Tuchtenhagen et al., 2000), borderline personality disorder (Norra et al., 2003) as well as histrionic disorder (Wang et al., 2006), which are all characterised by 5-HT dysfunction. By contrast, a weaker LD as a function of enhanced 5-HT activity was seen in the serotonin syndrome (Hegerl et al., 1998), post-traumatic stress disorder (Paige et al., 1990), generalised anxiety disorder (Senkowski et al., 2003) and schizophrenia (Juckel et al., 2003). Psychopharmacological studies suggest that LD is a predictive marker for the clinical response to antidepressive 5-HT agents (Gallinat et al., 2000) and, in particular, prophylactic lithium has repeatedly been shown to induce a positive clinical response in patients with uni- or bipolar depression and a strong LD (Hegerl et al., 1987, 1992; Brocke et al., 2000; Juckel et al., 2004), respectively, an augmenting pattern in visual evoked potentials (e.g. Baron et al., 1975).

In order to understand the role of endogenous lithium in neurobiological functioning and emotional processing, the variability of serum lithium concentrations was hypothesised to be associated with measurable effects on LD (as a neurobiological indicator of overall 5-HT functioning) and emotional liability.

2. Methods

2.1. Subjects

Seventy six medical students who completed a course at the Unit of Environmental Medicine (UEM) of the Institute of Hygiene and Environmental Medicine (University Hospital Aachen, Germany) were screened using a semi-structured interview. Exclusion criteria were severe medical disorder, birth trauma, developmental, neurological or psychiatric disorders and a family history of neuropsychiatric disorder, regularly taking medication or substance abuse. After analysis of individual lithium serum concentrations and definition of extreme groups (see Section 2.2), a total of 40 students (20 per experimental group) could be identified according to the criteria and agreed to participate in the electroencephalogram (EEG) study. One showed an epileptic EEG recording and three others were excluded due to bad signal quality, so that the final study group consisted of 36. The study was approved by the local ethics committee and carried out according to the Declaration of Helsinki. All students gave written informed consent.

2.2. Analysis of lithium concentrations

All serum samples taken at the UEM were tested for lithium at the Institute of Hygiene and Environmental Medicine (University Hospital, Aachen, Germany) using inductively coupled plasma-mass spectrometry (ICP-MS). The analyses were done without knowledge of questionnaire outcomes.

Two experimental groups were defined using a numerical description (μg/l) of the distribution of all serum lithium concentrations consisting of the median as well as the values under the first and above the third quartiles. The interquartile range was assumed to cover the middle half of the data, which was expected to show the normal range of any distribution. Since this study was done on neurobehavioural differences due to pronounced serum lithium concentrations, all participants with measured values within the interquartile range were excluded (Moore and McCabe, 1998). The upper quartile of the sample distribution (Li > 2.5 μg/l) was defined as the high-lithium group, the lower quartile (Li < 1.5 μg/l) as the low-lithium group.

2.3. Auditory evoked potentials (AEP)

2.3.1. Stimuli and test session

A multi-channel EEG was recorded from 29 scalp sites according to the extended International 10/20 EEG electrode system with Ag^{+}/Cl^{-} electrodes. Cz was the reference electrode. Additionally, eye movements were monitored by a horizontal and vertical electro-oculogram (EOG). Impedances were kept at <5 kΩ. Subjects were tested in a sound-attenuated, electrically shielded room. They were seated in dim light, remaining relaxed while looking at the wall ahead and ignoring the auditory stimuli. Auditory stimuli (STIM, Neuroscan Inc.) were presented binaurally as pure sinus tones (1000 Hz, 100 ms, 10 ms rise and fall time) in a pseudorandomised order (interstimulus interval of 1800–2200 ms) with five different loudness levels (60, 70, 80, 90 and 100 dB sound pressure level). Each subject received 200 single trials of each loudness level. The EEG was recorded continuously (A/D rate 500 Hz; low pass 100 Hz, high pass 0.05 Hz) and then analysed offline.

2.3.2. Data processing

Further data analysis for each subject using brain electrical source analysis (BESA 5.1, MEGIS, Munich, Germany) included segmentation (200 ms pre- and 400 ms post-stimulus interval analysis time), digital filtering (low pass 30 Hz, 24 dB/oct slope; high pass 1 Hz, 24 dB/oct slope) and averaging per stimulus intensity. The A/D rate was 1000 Hz. In order to minimise eye movement artefacts, epochs with peaks >100 μV were rejected.

2.3.3. Analysis of loudness dependence (LD)

Peak-to-peak amplitudes (μV) and latencies (ms) of N1 and P2 potentials were measured manually for each subject in all five stimulus intensities (60–100 dB). Post-stimulus N1 and P2 latencies were considered to range between 64–122 ms and 140–220 ms, respectively. The measures for analysis of scalp potentials were taken at the frontal–central (FCz) and the temporal–basal electrodes (T7 and T8, inverse polarity) (Senkowski et al., 2003).

BESA, which relates equivalent intracranial dipole source activity to the recorded surface scalp potentials, was also done since it allows separating overlapping electrical dipole components from the primary and secondary auditory cortex (Scherg and von Cramon, 1985). The tangential dipoles (1 and 3) represent activity in the superior temporal plane arising from the primary auditory cortex, whereas the radial dipoles (2 and 4) represent the lateral part of the superior temporal gyrus, corresponding to the secondary auditory areas [Fig. 1]. Here (Norra et al., 2003), one grand average representing the individual mean of all stimulus intensity levels was calculated for each subject and used for one global grand average to be imported for construction of a dipole source model for further fitting (Scherg and Picton, 1991). The grand averages of all different intensity levels were then individually adjusted to yield an individual dipole model. Dipole activity peaks were separately determined for all intensities