

Chronic Lithium Administration to Rats Selectively Modifies 5-HT_{2A/2C} Receptor-Mediated Brain Signaling via Arachidonic Acid

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The effects of chronic lithium administration on regional brain incorporation coefficients k^* of arachidonic acid (AA), a marker of phospholipase A₂ (PLA₂) activation, were determined in unanesthetized rats administered i.p. saline or 1 mg/kg i.p. (±)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI), a 5-HT_{2A/2C} receptor agonist. After injecting [¹⁻¹⁴C]AA intravenously, k^* (brain radioactivity/integrated plasma radioactivity) was measured in each of 94 brain regions by quantitative autoradiography. Studies were performed in rats fed a LiCl or a control diet for 6 weeks. In the control diet rats, DOI significantly increased k^* in widespread brain areas containing 5-HT_{2A/2C} receptors. In the LiCl-fed rats, the significant positive k^* response to DOI did not differ from that in control diet rats in most brain regions, except in auditory and visual areas, where the response was absent. LiCl did not change the head turning response to DOI seen in control rats. In summary, LiCl feeding blocked PLA₂-mediated signal involving AA in response to DOI in visual and auditory regions, but not generally elsewhere. These selective effects may be related to lithium's therapeutic efficacy in patients with bipolar disorder, particularly its ability to ameliorate hallucinations in that disease.

Neuropsychopharmacology (2005) 30, 461–472, advance online publication, 24 November 2004; doi:10.1038/sj.npp.1300611

Keywords: lithium; serotonin; arachidonic acid; phospholipase A₂; DOI; bipolar disorder

INTRODUCTION

Lithium has been used to treat bipolar disorder for about 50 years, but its mechanism of action is not agreed on (Barchas *et al*, 1994; Cade, 1999). One suggestion is that it modifies neurotransmission imbalances that contribute to the disease (Bymaster and Felder, 2002; Janowsky and Overstreet, 1995). Evidence that cholinomimetics as well as drugs that inhibit dopaminergic transmission have an antimanic action in bipolar disorder suggest that the imbalances involve reduced cholinergic transmission and increased dopaminergic neurotransmission (Bunney and Garland-Bunney, 1987; Bymaster and Felder, 2002; Fisher *et al*, 1991; Janowsky and Overstreet, 1995; Peet and Peters, 1995; Post *et al*, 1980; Sultzer and Cummings, 1989). Additionally, reduced serotonergic (5-HT) transmission is suggested by observations that depressed or euthymic bipolar disorder patients have low brain concentrations of serotonin (5-HT) and its metabolites, and fewer brain 5-HT reuptake sites

(Mahmood and Silverstone, 2001). Clinical data also implicate disturbed glutamatergic transmission via NMDA receptors (Itokawa *et al*, 2003; Mundo *et al*, 2003; Scarr *et al*, 2003).

Some reported effects of lithium in rats are consistent with it ameliorating the suggested neurotransmission imbalances of bipolar disorder. Thus, lithium reduces the convulsant threshold to cholinomimetics (Evans *et al*, 1990; Joje, 1993; Lerer, 1985; Morrisett *et al*, 1987), consistent with it potentiating cholinergic neurotransmission. Lithium also appears to downregulate dopaminergic transmission, by reducing brain dopamine synthesis (Engel and Berggren, 1980) and altering the affinity of the presynaptic dopamine reuptake transporter for dopamine (Carli *et al*, 1997). Additionally, lithium feeding augments 5-HT_{2A/2C} agonist-induced locomotor activity, phosphoinositide-linked 5-HT-receptor stimulation, and 5-HT agonist induced Fos-like immunoreactivity throughout the cerebral cortex (Moorman and Leslie, 1998; Williams and Joje, 1994; Williams and Joje, 1995). It does not reduce the convulsant threshold to NMDA (Ormandy *et al*, 1991).

Agonist binding to certain neuroreceptors can activate phospholipase A₂ (PLA₂) to release the second messenger, arachidonic acid (AA, 20:4 n:6), from the stereospecifically numbered (*sn*)-2 position of membrane phospholipids (Axelrod, 1995). Receptors that are coupled to PLA₂ via G-proteins include muscarinic M_{1,3,5} receptors, dopaminergic

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Received 20 February 2004; revised 4 October 2004; accepted 7 October 2004

Online publication: 11 October 2004 at <http://www.acnp.org/citations/NPP101104040080/default.pdf>

D₂ receptors, and 5-HT_{2A/2C} receptors (Axelrod, 1995; Bayon *et al*, 1997; Felder *et al*, 1990; Vial and Piomelli, 1995), whereas NMDA receptors are coupled by allowing Ca²⁺ into the cell (Lazarewicz *et al*, 1990; Weichel *et al*, 1999). The released AA and its bioactive eicosanoid metabolites can influence many physiological processes, including membrane excitability, gene transcription, apoptosis, sleep, and behavior (Fitzpatrick and Soberman, 2001; Shimizu and Wolfe, 1990).

A fraction of the AA that is released by PLA₂ activation will be rapidly reincorporated into phospholipid, whereas the remainder will be lost by conversion to eicosanoids or other products, or by β -oxidation (Rapoport, 2001; Rapoport, 2003). Unesterified AA in plasma rapidly replaces the amount lost, as AA is nutritionally essential and cannot be synthesized *de novo* in vertebrate tissue (Holman, 1986). Replacement is proportional to PLA₂ activation and can be imaged *in vivo* by injecting radiolabeled AA intravenously, then measuring regional brain radioactivity by quantitative autoradiography. A regional AA incorporation coefficient k^* (regional brain radioactivity/integrated plasma radioactivity), calculated in this way, has been shown to be independent of changes in cerebral blood flow and to represent plasma-derived AA reincorporated in phospholipids (Basselin *et al*, 2003a; Chang *et al*, 1997; DeGeorge *et al*, 1991; Rapoport, 2001; Rapoport, 2003; Robinson *et al*, 1992).

To test the hypothesis that lithium acts in bipolar disorder by correcting its neurotransmission imbalances (see above), and to see if these imbalances might involve neuroreceptor-initiated signaling via AA, we first imaged the effect of LiCl feeding on k^* for AA in different brain regions of unanesthetized rats administered arecoline, an agonist of cholinergic muscarinic receptors that can be coupled to PLA₂ (Basselin *et al*, 2003b; Bayon *et al*, 1997; DeGeorge *et al*, 1991). Consistent with the hypothesis, the LiCl diet compared with control diet potentiated arecoline-induced increases in k^* for AA in 52 of 85 brain regions examined.

In this paper, we evaluated lithium's ability to modify k^* for AA in rats administered the 5-HT_{2A/2C} receptor agonist, (\pm)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI). DOI, a hallucinogen (Sadzot *et al*, 1989), has a high and equal affinity for 5-HT_{2A} and 5-HT_{2C} receptors (<http://kidb.cwru.edu/pdsp/php>, 2003), which can be coupled to PLA₂ (Bayon *et al*, 1997; Qu *et al*, 2003). We chose a DOI dose of 1 mg/kg i.p. rather than the 2.5 mg/kg that we used previously (Qu *et al*, 2003), since the latter dose produced large increments (about 60%) in k^* and we wished a more graded response to minimize any interactions between DOI and lower affinity non-5-HT_{2A/2C} receptors (Abi-Saab *et al*, 1999; Kuroki *et al*, 2003; Obata *et al*, 2003; Ramirez *et al*, 1997; Scruggs *et al*, 2000). Furthermore, 1 mg/kg DOI is reported to have significant central effects in rats (Bull *et al*, 2004; Ichikawa *et al*, 2002).

MATERIALS AND METHODS

Animals and Diets

Experiments were conducted following the 'Guide for the Care and Use of Laboratory Animals' (National Institute of

Health Publication No. 86-23) and were approved by the Animal Care and Use Committee of the National Institute of Child Health and Development (NICHD). Male Fischer CDF (F-344)/CrIBR rats (Charles River Laboratories, Wilmington, MA), 2-month old and weighing 180–200 g, were housed in an animal facility in which temperature, humidity, and light cycle were regulated. One group of rats was fed *ad libitum* Purina Rat Chow (Harlan Teklad, Madison, WI) containing 1.70 g LiCl/kg for 4 weeks, followed by a diet containing 2.55 g LiCl/kg for 2 weeks (Basselin *et al*, 2003b). This feeding regimen produces 'therapeutically equivalent' plasma and brain lithium levels of about 0.7 mM (Bosetti *et al*, 2002; Chang *et al*, 1996). Control rats were fed lithium-free Purina rat chow under parallel conditions. Water and NaCl solution (0.45 M) were available *ad libitum* to both groups.

Drugs

Unanesthetized rats received 0.3 ml i.p. 0.9% NaCl (saline) (Abbott Laboratories, North Chicago, IL) or 1 mg/kg i.p. DOI (RBI Signaling Innovation, Sigma-Aldrich, Natick, MA) in 0.3 ml saline. [¹⁴C]AA in ethanol (53 mCi/mmol; 99.4% pure, Moravsek Biomedicals, Brea, CA) was evaporated and suspended in 5 mM HEPES buffer, pH 7.4, which contained 50 mg/ml of bovine serum albumin (Sigma-Aldrich). Tracer purity, which exceeded 98%, was ascertained by gas-liquid chromatography after converting it to its methyl ester with 1% sulfuric acid in anhydrous methanol (Makrides *et al*, 1994).

Surgical Procedures and Tracer Infusion

After 6 weeks on a control or a LiCl diet, a rat was anesthetized with 2–3% halothane in O₂, and polyethylene catheters were inserted into the left femoral artery and vein, as described previously (Basselin *et al*, 2003b). The wound was closed and the rat was wrapped loosely, with its upper body remaining free, in a fast-setting plaster cast taped to a wooden block. It was allowed to recover from anesthesia for 3–4 h, while its body temperature was maintained at 37°C. Mean arterial blood pressure, heart rate and rectal temperature were monitored before and after injecting either saline or DOI. Head-turning behavior also was recorded.

Twenty min after an i.p. saline or DOI injection, the rat was infused for 5 min through the femoral vein with 2 ml [¹⁴C]AA (170 μ Ci/kg) at a rate of 400 μ l/min (Basselin *et al*, 2003b). Timed arterial blood samples were collected from the start of infusion to time of death at 20 min. The samples were centrifuged and plasma was removed to measure [¹⁴C]AA radioactivity. At 20 min, the rat was killed by an overdose (50 mg/kg i.v.) of sodium pentobarbital (Richmond Veterinary Supply, Richmond, VA) and decapitated. The brain was removed, frozen in 2-methylbutane at –40°C, and stored at –80°C for quantitative autoradiography.

Chemical Analysis

The arterial plasma samples (30 μ l) were extracted with 3 ml CHCl₃:MeOH (2:1, v/v) and 1.5 ml 0.1 M KCl (Folch *et al*, 1957). AA concentrations were determined in 100 μ l of the

lower organic phase by liquid scintillation counting. The percent efficiency for ^{14}C counting was 88%.

Quantitative Autoradiography

Frozen brains were cut in serial 20 μm thick sections on a cryostat, then placed for 6 weeks together with calibrated [^{14}C]methylmethacrylate standards on autoradiographic film in an X-ray cassette (Basselin *et al*, 2003b). A total of 94 brain regions were identified by comparing the autoradiographs with an atlas of the rat brain (Paxinos and Watson, 1987). Regional brain radioactivities, c_{brain}^* (20 min) nCi/g, were determined by densitometry using the NIH image analysis program (Version 6.5) created by Wayne Rasband (National Institutes of Health) (Basselin *et al*, 2003b). Regional incorporation coefficients k^* (ml/s/g brain) of AA were calculated as,

$$k^* = \frac{c_{\text{brain}}^* (20 \text{ min})}{\int_0^{20} c_{\text{plasma}}^* dt} \quad (1)$$

where c_{plasma}^* equals plasma radioactivity determined by scintillation counting (nCi/ml) and t equals time (min) after beginning of [^{14}C] AA infusion.

Statistical Analysis

A two-way Analysis of Variance (ANOVA), comparing Diet (LiCl vs control) with Drug (DOI vs saline), was performed for each brain region using SPSS 10.0 for Macintosh (SPSS Inc., Chicago, IL, and <http://www.spss.com>). At regions in which Diet \times Drug interactions were statistically insignificant, probabilities of main effects of Diet and of Drug were separately calculated (Tabachnick and Fidell, 2001). At regions in which interactions were statistically significant, these probabilities were not calculated because they cannot be interpreted with certainty. Instead, unpaired t -tests were used to test for individual significant differences between means. Data are reported as means \pm s.d., with statistical significance taken as $p \leq 0.05$.

RESULTS

Physiological Parameters

LiCl-fed rats had a 15% lower mean body weight compared with control diet-fed rats ($257 \pm 9 \text{ g}$ vs $303 \pm 10 \text{ g}$, $p < 0.0001$, $n = 17$). Such a reduction has been ascribed to uncompensated polyuria (Teixeira and Karniol, 1982). LiCl feeding did not significantly affect mean arterial blood pressure, heart rate, or body temperature (data not shown). DOI compared with saline increased mean blood pressure by 26% and decreased mean heart rate by 18% to the same extents in the LiCl and control diet groups ($p < 0.0001$, $n = 8-9$). These effects have been ascribed to stimulation of central and peripheral 5-HT₂ receptors (Chaouche-Teyara *et al*, 1993; Dedeoglu and Fisher, 1991; Freo *et al*, 1991; Rittenhouse *et al*, 1991). DOI also produced periods of ventral, dorsal, and lateral head movements, as previously reported (Kitamura *et al*, 2002). In the 20 min following DOI, the mean number of head-movement periods, each lasting about 30 s, did not differ significantly ($p > 0.05$) between the

LiCl and control diet rats (33 ± 4 ($n = 9$) in LiCl-fed rats and 39 ± 5 ($n = 8$) in control diet rats).

Regional Brain AA Incorporation Coefficients

Figure 1 illustrates color-coded values for k^* for AA, in autoradiographs of brain coronal sections from rats fed a control diet and administered saline (a) or DOI (b); or fed a LiCl diet and administered saline (c) or DOI (d). The mean values for k^* in each of 94 brain regions, collated from all autoradiographs, are presented in Table 1. Data for each region in the table were subjected to a two-way ANOVA. Probabilities for main effects were determined in regions in which Diet \times Drug interactions were statistically insignificant. In regions where interactions were significant, unpaired t -tests were used to compare diet and drug effects separately (asterisks and crosses in Table 1). In areas in which the increments were statistically significant (by t -tests) in control animals, DOI increased the means by 39% on average.

Insignificant Diet \times Drug Interactions

Of the 94 regions examined, 70 had a statistically insignificant Diet (LiCl diet vs control diet) \times Drug (DOI

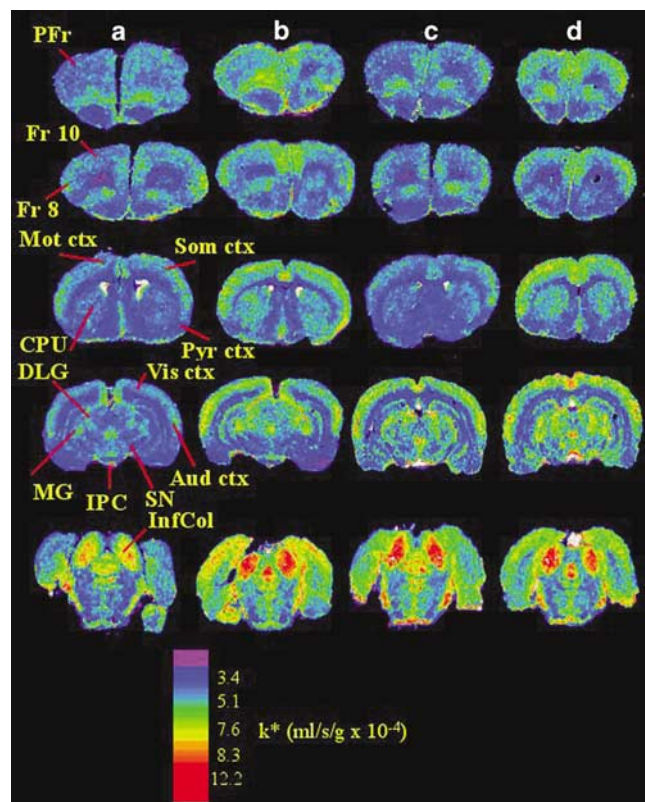


Figure 1 Effects of acute DOI administration and LiCl feeding on arachidonic acid incorporation coefficients k^* in 94 brain regions of unanesthetized rats. Abbreviations: Aud ctx, auditory cortex; CPU, caudate putamen; DLG, dorsal lateral geniculate; Fr, frontal cortex; InfCol, inferior colliculus; IPC, interpeduncular nucleus central; MG, geniculate medial; Mot ctx, motor cortex; PFr, prefrontal cortex; Pyr ctx, pyriform cortex; SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata; Som ctx, somatosensory cortex; Vis ctx, visual cortex.

Table 1 Arachidonic Acid Incorporation Coefficients $^1k^*$ in Control Diet-Fed and LiCl-Fed Rats, at Baseline (in Response to Saline) and in Response to DOI

| Brain region | Control diet | | LiCl diet | | LiCl diet \times DOI interaction | LiCl effect | DOI effect |
|-----------------------------|-----------------|---------------------|---------------------------------|---------------------|------------------------------------|-------------|------------|
| | Saline (n = 8) | DOI 1 mg/kg (n = 9) | Saline (n = 8) | DOI 1 mg/kg (n = 9) | P-value | P-value | P-value |
| Prefrontal cortex layer I | 6.58 \pm 1.36 | 7.41 \pm 0.59 | 5.58 \pm 0.47 | 7.73 \pm 1.34 | 0.049 | | |
| Prefrontal cortex layer IV | 6.27 \pm 1.19 | 8.04 \pm 0.82 | 5.49 \pm 0.44 | 7.92 \pm 1.26 | 0.269 | 0.156 | <0.001 |
| Primary olfactory cortex | 6.13 \pm 1.02 | 6.91 \pm 1.09 | 5.23 \pm 0.77 | 6.54 \pm 1.02 | 0.568 | 0.177 | 0.031 |
| <i>Frontal cortex (10)</i> | | | | | | | |
| Layer I | 6.19 \pm 1.19 | 8.10 \pm 0.52 | 5.94 \pm 0.46 | 8.11 \pm 0.87 | 0.649 | 0.661 | <0.001 |
| Layer IV | 6.00 \pm 1.04 | 8.99 \pm 1.20 | 5.94 \pm 0.70 | 8.17 \pm 0.96 | 0.269 | 0.208 | <0.001 |
| <i>Frontal cortex (8)</i> | | | | | | | |
| Layer I | 6.12 \pm 0.53 | 7.96 \pm 0.54 | 5.98 \pm 0.75 | 8.18 \pm 0.83 | 0.429 | 0.864 | <0.001 |
| Layer IV | 6.60 \pm 1.17 | 8.73 \pm 0.69 | 6.23 \pm 0.77 | 7.97 \pm 1.15 | 0.551 | 0.102 | <0.001 |
| Pyramidal cortex | 5.28 \pm 0.94 | 6.11 \pm 0.78 | 5.10 \pm 0.51 | 5.95 \pm 1.63 | 0.176 | 0.080 | 0.001 |
| Anterior cingulate cortex | 7.03 \pm 1.09 | 9.81 \pm 1.08 | 7.65 \pm 0.66 | 9.33 \pm 0.94 | 0.120 | 0.753 | <0.001 |
| <i>Motor cortex</i> | | | | | | | |
| Layer I | 6.33 \pm 0.78 | 7.68 \pm 0.76 | 6.01 \pm 0.91 | 8.46 \pm 1.16 | 0.165 | 0.699 | <0.001 |
| Layer II–III | 6.47 \pm 0.74 | 7.82 \pm 0.44 | 6.01 \pm 0.87 | 8.43 \pm 0.99 | 0.058 | 0.787 | <0.001 |
| Layer IV | 6.56 \pm 0.87 | 8.72 \pm 0.88 | 6.42 \pm 0.87 | 9.25 \pm 0.75 | 0.257 | 0.520 | <0.001 |
| Layer V | 5.26 \pm 0.57 | 6.29 \pm 0.67 | 5.10 \pm 0.79 | 6.66 \pm 1.01 | 0.345 | 0.706 | <0.001 |
| Layer VI | 5.09 \pm 0.51 | 6.12 \pm 0.48 | 4.94 \pm 0.78 | 6.59 \pm 1.08 | 0.247 | 0.539 | <0.001 |
| <i>Somatosensory cortex</i> | | | | | | | |
| Layer I | 6.40 \pm 0.76 | 8.34 \pm 1.06 | 5.98 \pm 0.86 | 8.38 \pm 0.77 | 0.493 | 0.567 | <0.001 |
| Layer II–III | 6.31 \pm 0.46 | 8.51 \pm 0.82 | 6.15 \pm 0.84 | 8.88 \pm 0.73 | 0.302 | 0.683 | <0.001 |
| Layer IV | 6.60 \pm 0.69 | 9.20 \pm 0.68 | 6.88 \pm 0.81 | 9.26 \pm 0.87 | 0.683 | 0.523 | <0.001 |
| Layer V | 6.20 \pm 0.59 | 7.56 \pm 0.61 | 5.96 \pm 0.69 | 8.03 \pm 1.38 | 0.260 | 0.696 | <0.001 |
| Layer VI | 6.30 \pm 0.75 | 7.33 \pm 0.56 | 5.74 \pm 0.68 | 7.72 \pm 1.57 | 0.174 | 0.795 | <0.001 |
| <i>Auditory cortex</i> | | | | | | | |
| Layer I | 6.73 \pm 0.83 | 7.79 \pm 0.76* | 10.32 \pm 1.07 ^{†††} | 9.62 \pm 1.02 | 0.010 | | |
| Layer IV | 7.27 \pm 0.93 | 8.83 \pm 1.23 | 11.62 \pm 1.53 | 11.48 \pm 1.16 | 0.053 | <0.001 | 0.107 |
| Layer VI | 7.08 \pm 0.53 | 7.51 \pm 0.56 | 9.88 \pm 1.83 | 9.53 \pm 1.10 | 0.321 | <0.001 | 0.929 |
| <i>Visual cortex</i> | | | | | | | |
| Layer I | 5.98 \pm 0.37 | 7.72 \pm 0.62*** | 9.62 \pm 1.54 ^{†††} | 9.09 \pm 1.20 | 0.003 | | |
| Layer IV | 6.37 \pm 0.44 | 8.60 \pm 0.92*** | 10.48 \pm 1.57 ^{†††} | 10.25 \pm 1.21 | 0.003 | | |
| Layer VI | 5.66 \pm 0.35 | 7.90 \pm 0.73*** | 9.93 \pm 1.25 ^{†††} | 9.63 \pm 0.89 | <0.001 | | |

Table 1 Continued

| Brain region | Control diet | | LiCl diet | | LiCl diet \times DOI interaction | LiCl effect | DOI effect |
|------------------------------|-----------------|---------------------|--------------------------------|---------------------|------------------------------------|-------------|------------|
| | Saline (n = 8) | DOI 1 mg/kg (n = 9) | Saline (n = 8) | DOI 1 mg/kg (n = 9) | P-value | P-value | P-value |
| Preoptic area (LPO/MPO) | 5.48 \pm 0.39 | 6.47 \pm 0.82 | 5.65 \pm 0.93 | 6.52 \pm 1.06 | 0.848 | 0.708 | 0.003 |
| Suprachiasmatic nu | 5.53 \pm 0.42 | 6.80 \pm 0.88 | 5.63 \pm 0.90 | 6.48 \pm 0.86 | 0.430 | 0.684 | <0.001 |
| Globus pallidus | 5.02 \pm 0.41 | 5.56 \pm 0.81 | 5.30 \pm 0.85 | 6.68 \pm 1.29 | 0.181 | 0.033 | 0.005 |
| Bed nu stria terminalis | 5.40 \pm 0.39 | 6.49 \pm 0.61 | 5.65 \pm 0.72 | 6.53 \pm 1.04 | 0.701 | 0.575 | 0.001 |
| Olfactory tubercle | 6.74 \pm 0.57 | 7.40 \pm 0.28 | 6.47 \pm 0.97 | 7.64 \pm 0.94 | 0.347 | 0.069 | <0.001 |
| Diagonal band dorsal | 6.53 \pm 0.89 | 6.91 \pm 0.88 | 5.74 \pm 1.10 | 7.36 \pm 1.53 | 0.122 | 0.669 | 0.016 |
| Diagonal band ventral | 5.43 \pm 0.47 | 6.59 \pm 1.40 | 4.88 \pm 0.77 | 6.64 \pm 1.49 | 0.458 | 0.545 | 0.001 |
| Amygdala basolat/med | 4.96 \pm 0.63 | 7.07 \pm 0.67 | 5.03 \pm 0.76 | 7.84 \pm 1.64 | 0.332 | 0.247 | <0.001 |
| <i>Hippocampus</i> | | | | | | | |
| CA1 | 4.46 \pm 0.79 | 6.24 \pm 0.69 | 4.94 \pm 0.67 | 7.30 \pm 1.18 | 0.339 | 0.014 | <0.001 |
| CA2 | 4.43 \pm 0.75 | 6.39 \pm 0.52 | 4.88 \pm 0.66 | 7.53 \pm 1.09 | 0.214 | 0.007 | <0.001 |
| CA3 | 4.79 \pm 0.70 | 6.67 \pm 0.55 | 4.87 \pm 0.66 | 7.72 \pm 1.23 | 0.100 | 0.059 | <0.001 |
| Dentate gyrus | 5.38 \pm 0.54 | 7.48 \pm 0.60 | 4.92 \pm 0.74 | 7.87 \pm 1.01 | 0.185 | 0.899 | <0.001 |
| Accumbens nucleus | 5.88 \pm 0.49 | 7.35 \pm 0.81 | 5.52 \pm 0.68 | 6.86 \pm 1.55 | 0.851 | 0.227 | <0.001 |
| Anterior commissure | 5.97 \pm 0.77 | 7.37 \pm 0.85 | 5.96 \pm 0.45 | 6.97 \pm 1.51 | 0.841 | 0.301 | <0.001 |
| <i>Caudate putamen</i> | | | | | | | |
| Dorsal | 5.86 \pm 0.56 | 7.56 \pm 0.84 | 5.35 \pm 0.48 | 7.96 \pm 0.95 | 0.087 | 0.823 | <0.001 |
| Ventral | 5.87 \pm 0.55 | 7.48 \pm 0.78 | 5.34 \pm 0.49 | 7.72 \pm 1.11 | 0.169 | 0.600 | <0.001 |
| Lateral | 5.96 \pm 0.26 | 7.44 \pm 0.66 | 5.43 \pm 0.48 | 7.76 \pm 1.08 | 0.217 | 0.431 | <0.001 |
| Medial | 5.98 \pm 0.38 | 7.51 \pm 0.81 | 5.36 \pm 0.46 | 7.82 \pm 1.03 | 0.060 | 0.461 | <0.001 |
| Septal nu lateral | 5.17 \pm 0.29 | 6.42 \pm 1.01 | 5.44 \pm 0.54 | 6.56 \pm 1.37 | 0.853 | 0.795 | <0.001 |
| Septal nu medial | 5.61 \pm 0.61 | 6.96 \pm 0.80 | 5.80 \pm 0.68 | 7.05 \pm 1.42 | 0.880 | 0.669 | <0.001 |
| Entopeduncular nu | 4.99 \pm 0.41 | 5.55 \pm 0.90 | 5.36 \pm 0.86 | 5.37 \pm 0.51 | 0.262 | 0.706 | 0.251 |
| <i>Diencephalon</i> | | | | | | | |
| Habenular nu lateral | 7.24 \pm 0.98 | 8.84 \pm 1.07 | 10.21 \pm 1.93 | 10.53 \pm 1.21 | 0.171 | <0.001 | 0.044 |
| Habenular nu medial | 7.72 \pm 0.97 | 8.76 \pm 1.02 | 10.11 \pm 1.46 | 10.32 \pm 0.88 | 0.278 | <0.001 | 0.108 |
| Lateral geniculate nu dorsal | 6.68 \pm 1.07 | 8.94 \pm 1.27** | 9.53 \pm 1.22 ^{†††} | 9.66 \pm 0.63 | 0.007 | | |
| Medial geniculate nu | 5.80 \pm 0.62 | 7.96 \pm 0.78*** | 9.83 \pm 1.59 ^{†††} | 9.45 \pm 0.78 | 0.001 | | |
| <i>Thalamus</i> | | | | | | | |
| Ventroposterior lat nu | 6.47 \pm 0.51 | 8.61 \pm 1.26 | 5.95 \pm 0.90 | 9.18 \pm 1.74 | 0.202 | 0.959 | <0.001 |
| Ventroposterior med nu | 6.55 \pm 0.65 | 8.61 \pm 1.24 | 6.19 \pm 0.63 | 9.36 \pm 0.87 | 0.080 | 0.529 | <0.001 |

Table 1 Continued

| Brain region | Control diet | | LiCl diet | | LiCl diet × DOI interaction | LiCl effect | DOI effect |
|---------------------------------|----------------|---------------------|-----------------------------|---------------------|-----------------------------|-------------|------------|
| | Saline (n = 8) | DOI 1 mg/kg (n = 9) | Saline (n = 8) | DOI 1 mg/kg (n = 9) | P-value | P-value | P-value |
| Paratenial nu | 6.47 ± 0.66 | 7.39 ± 0.95 | 6.70 ± 1.01 | 7.89 ± 1.39 | 0.703 | 0.315 | 0.006 |
| Anteroventral nu | 6.87 ± 0.90 | 10.62 ± 0.76*** | 9.41 ± 0.94 ^{†††} | 9.86 ± 1.73 | <0.001 | | |
| Anteromedial nu | 6.65 ± 1.35 | 7.69 ± 0.70 | 7.05 ± 0.70 | 7.83 ± 1.41 | 0.726 | 0.478 | 0.022 |
| Reticular nu | 7.82 ± 1.49 | 8.30 ± 0.69 | 6.57 ± 1.05 | 7.73 ± 1.85 | 0.475 | 0.059 | 0.086 |
| Paraventricular nu | 7.66 ± 1.78 | 7.75 ± 1.04 | 6.65 ± 1.08 | 7.45 ± 1.78 | 0.483 | 0.202 | 0.387 |
| Parafascicular nu | 6.63 ± 0.72 | 7.84 ± 0.59 | 8.26 ± 1.14 | 8.13 ± 1.33 | 0.059 | 0.008 | 0.125 |
| Subthalamic nu | 6.30 ± 0.35 | 8.35 ± 0.93*** | 8.88 ± 1.66 ^{†††} | 9.01 ± 1.35 | 0.024 | | |
| <i>Hypothalamus</i> | | | | | | | |
| Supraoptic nu | 5.89 ± 0.36 | 5.48 ± 1.36 | 6.14 ± 0.68 | 7.67 ± 1.98 | 0.037 | | |
| Lateral | 5.02 ± 0.49 | 5.81 ± 0.58 | 6.21 ± 0.77 | 7.00 ± 1.72 | 0.170 | 0.063 | 0.001 |
| Anterior | 5.30 ± 0.48 | 6.52 ± 0.95 | 6.13 ± 0.64 | 7.05 ± 1.78 | 0.704 | 0.085 | 0.009 |
| Periventricular | 4.36 ± 0.38 | 5.32 ± 0.87 | 5.14 ± 0.50 | 5.90 ± 1.38 | 0.759 | 0.036 | 0.009 |
| Arcuate | 5.63 ± 0.67 | 6.09 ± 1.07 | 6.23 ± 0.65 | 7.75 ± 1.72 | 0.342 | 0.019 | 0.041 |
| Ventromedial | 5.49 ± 0.67 | 6.17 ± 1.16 | 6.28 ± 0.66 | 7.44 ± 1.79 | 0.570 | 0.018 | 0.032 |
| Posterior | 6.42 ± 0.38 | 7.48 ± 0.37 | 6.45 ± 0.87 | 7.43 ± 1.38 | 0.891 | 0.989 | 0.002 |
| Mammillary nucleus | 7.31 ± 1.06 | 7.77 ± 1.28 | 6.72 ± 1.44 | 8.98 ± 1.86 | 0.078 | 0.531 | 0.010 |
| Medial forebrain bundle | 5.70 ± 0.68 | 6.33 ± 0.88 | 5.57 ± 0.74 | 6.94 ± 1.41 | 0.296 | 0.495 | 0.008 |
| <i>Mesencephalon</i> | | | | | | | |
| Interpeduncular nucleus | 7.11 ± 1.11 | 10.99 ± 2.81** | 11.36 ± 2.19 ^{†††} | 12.02 ± 2.54 | 0.049 | | |
| Substantia nigra | | | | | | | |
| Pars reticulata | 5.28 ± 0.39 | 7.26 ± 0.37*** | 8.55 ± 1.69 ^{†††} | 8.77 ± 1.14 | 0.020 | | |
| Pars compacta | 5.33 ± 0.36 | 7.43 ± 0.50*** | 8.33 ± 1.11 ^{†††} | 8.32 ± 0.87 | <0.001 | | |
| Pretectal area | 5.93 ± 0.43 | 8.17 ± 0.77*** | 6.63 ± 0.87 | 7.40 ± 1.01 | 0.012 | | |
| Superior colliculus | 6.07 ± 0.91 | 8.22 ± 0.62*** | 7.17 ± 1.00 [†] | 7.68 ± 0.83 | 0.008 | | |
| Deep layers | 6.87 ± 0.69 | 8.34 ± 0.97*** | 8.91 ± 1.06 ^{†††} | 8.43 ± 1.28 | 0.010 | | |
| Inferior colliculus | 8.29 ± 1.81 | 12.15 ± 2.89*** | 11.97 ± 1.41 ^{†††} | 12.50 ± 2.34 | 0.037 | | |
| Raphe median | 5.16 ± 1.41 | 6.46 ± 0.78* | 6.59 ± 0.61 [†] | 7.33 ± 1.07 | 0.031 | | |
| Raphe dorsal | 6.14 ± 0.70 | 7.33 ± 1.15 | 6.44 ± 0.59 | 6.90 ± 0.91 | 0.239 | 0.829 | 0.010 |
| Pedunculopontine tegmental nu | 4.82 ± 0.46 | 7.17 ± 0.41 | 4.62 ± 0.74 | 6.27 ± 0.99 | 0.152 | 0.029 | <0.001 |
| <i>Rhombencephalon</i> | | | | | | | |
| Flocculus | 6.71 ± 0.76 | 9.39 ± 0.88 | 8.14 ± 0.95 | 9.81 ± 2.36 | 0.311 | 0.071 | <0.001 |
| Cerebellar gray matter | 6.21 ± 0.92 | 7.49 ± 0.83 | 6.55 ± 1.24 | 7.24 ± 0.93 | 0.420 | 0.895 | 0.010 |
| Molecular layer cerebellar gray | 7.51 ± 1.10 | 10.51 ± 2.95 | 8.34 ± 1.81 | 9.86 ± 1.67 | 0.325 | 0.903 | 0.005 |

Table 1 Continued

| Brain region | Control diet | | LiCl diet | | LiCl diet × DOI interaction | LiCl effect | DOI effect |
|--|----------------|---------------------|----------------------------|---------------------|-----------------------------|-------------|------------|
| | Saline (n = 8) | DOI 1 mg/kg (n = 9) | Saline (n = 8) | DOI 1 mg/kg (n = 9) | P-value | P-value | P-value |
| Raphe magnus nu | 4.84 ± 0.56 | 6.35 ± 0.44*** | 5.70 ± 0.92 [†] | 6.08 ± 0.83 | 0.029 | | |
| Raphe pallidus nu | 4.22 ± 0.44 | 5.75 ± 0.65*** | 5.62 ± 0.90 ^{††} | 5.78 ± 0.58 | 0.005 | | |
| Locus coeruleus | 5.41 ± 0.51 | 7.78 ± 0.94*** | 7.31 ± 0.66 ^{†††} | 7.24 ± 0.50 | <0.001 | | |
| Cochlear nucleus | 6.99 ± 1.56 | 10.30 ± 1.78*** | 7.97 ± 0.94 | 9.01 ± 1.03* | 0.025 | | |
| Vestibular nu (medial) | 6.97 ± 0.71 | 9.98 ± 1.24*** | 9.34 ± 1.57 ^{†††} | 10.06 ± 0.90 | 0.009 | | |
| Spinal tract V nu | 6.12 ± 1.24 | 7.04 ± 1.01 | 6.55 ± 0.99 | 7.47 ± 1.24 | 0.997 | 0.296 | 0.029 |
| <i>White matter</i> | | | | | | | |
| Corpus callosum | 4.46 ± 0.51 | 5.76 ± 1.02 | 5.15 ± 0.81 | 6.01 ± 1.71 | 0.571 | 0.233 | 0.009 |
| Zone incerta | 5.47 ± 0.37 | 6.36 ± 1.01 | 5.18 ± 0.68 | 7.33 ± 1.52 | 0.079 | 0.342 | <0.001 |
| Internal capsule | 4.22 ± 0.44 | 5.01 ± 0.74 | 4.87 ± 0.87 | 5.60 ± 0.99 | 0.924 | 0.032 | 0.009 |
| Cerebellar white matter | 3.73 ± 0.83 | 4.56 ± 1.06 | 4.54 ± 0.70 | 3.87 ± 1.57 | 0.073 | 0.887 | 0.855 |
| <i>Non-blood-brain barrier regions</i> | | | | | | | |
| Subformal organ | 5.61 ± 0.64 | 6.17 ± 0.69 | 5.15 ± 0.85 | 5.95 ± 1.00 | 0.034 | | |
| Median eminence | 5.64 ± 0.51 | 6.49 ± 1.88 | 6.41 ± 0.68 | 7.26 ± 1.76 | 0.994 | 0.120 | 0.084 |
| Choroid plexus (third ventricle) | 18.18 ± 1.44 | 22.84 ± 3.70 | 25.15 ± 4.13 | 23.95 ± 7.35 | 0.108 | 0.030 | 0.335 |

Abbreviations: nu, nucleus; lat, lateral; med, medial; [†]k* = (ml/s/g) × 10⁻⁴. Each value is a mean ± SD.

Main effects not calculated if statistically significant Diet × Drug interaction.

In cases of statistically significant Diet × Drug interaction unpaired t-tests were realized. *p < 0.05; **p < 0.01; ***p < 0.001; control diet-DOI vs control diet-saline; LiCl diet-DOI vs LiCl diet-saline. [†]p < 0.05; ^{††}p < 0.01; ^{†††}p < 0.001; LiCl diet-saline vs control diet-saline.

vs saline injection) interaction with regard to k^* for AA* (Table 1). In 60 of the 70 regions, DOI compared with saline had a significant positive main effect on k^* , elevating k^* to the same extent in both the control diet- and LiCl-fed rats. In 13 of the 70 regions, LiCl feeding compared with control diet had a significant main effect on k^* , elevating k^* to the same extent following saline or DOI injection. Of the 13 regions, layers IV and VI of the auditory cortex, and medial habenular and parafascicular nucleus are considered to participate in auditory or visual circuitry (Brodal, 1981; Krout *et al*, 2001). Five of the 70 regions did not have a significant main effect of either DOI or LiCl.

Significant Diet \times Drug Interactions

In 24 of the 94 brain regions examined, the Diet \times Drug interaction was statistically significant. In 19 of the 24, unpaired *t*-tests showed that LiCl feeding compared with control diet elevated k^* significantly (after saline administration) Table 1). In 20 of the 24, unpaired *t*-tests also showed that DOI increased k^* significantly in the control diet but not in the LiCl-fed rats, thus, that LiCl blocked the DOI effect. Many of the 24 regions with statistically significant interactions belong to primary central visual and auditory neural systems (Brodal, 1981)—auditory cortex layer 1, medial geniculate nucleus, inferior colliculus, cochlear and vestibular nuclei, visual cortex layers I, IV, and VI, superior colliculus (superficial and deep layers), and lateral geniculate nucleus. Others of the 24—thalamic anteroventral nucleus (Rolls *et al*, 1977), the subthalamic nucleus (Matsumura *et al*, 1992), and pretectal area (Clarke *et al*, 2003)—also participate in visual-oculomotor-auditory circuitry. LiCl-affected regions also were the substantia nigra and locus coeruleus.

DISCUSSION

In contrast to the reported widespread potentiation induced by LiCl feeding of regional k^* responses to the cholinergic muscarinic receptor agonist, arecoline (Basselin *et al*, 2003b), the present study shows that LiCl feeding did not potentiate the k^* response to the 5-HT_{2A/2C} receptor agonist, DOI, in any of 94 brain regions examined (Table 1). In 70 of the 94 regions, the Diet \times Drug interaction was statistically insignificant and LiCl feeding neither potentiated nor depressed the k^* response to DOI. Indeed, the k^* response was positive and significant in 60 of the 70 regions (positive significant main effect of DOI).

The regions in which DOI increased k^* in control diet rats (Table 1) are known to have high densities of 5-HT_{2A/2C} receptors, particularly 5-HT_{2A} receptors (Sharma *et al*, 1997; Xu *et al*, 2000). DOI at 1.0 mg/kg increased k^* by 39% in the positively affected regions, compared with 60% reported after 2.5 mg/kg i.p. DOI. This difference is consistent with a dose effect. The increments in k^* caused by 2.5 mg/kg DOI could be blocked by preadministration of the 5-HT_{2A/2C} antagonist, mianserin, further supporting a 5-HT_{2A/2C}-mediated activation of PLA₂ (Qu *et al*, 2003).

Diet \times Drug interactions were statistically significant in 24 of the 94 regions examined, many of which belong to central visual and auditory circuits (see Results). In 19 of

the 24 regions, LiCl compared with control diet increased k^* significantly in the saline-injected rats, as reported previously (Basselin *et al*, 2003b). In 20 of the 24 regions, DOI compared with saline increased k^* significantly in control diet but not in LiCl-fed rats, showing that lithium blocked these DOI responses.

The LiCl-induced elevations in k^* for AA in central visual and auditory areas may reflect potentiation in these areas of their normal high activity (Mazziotta *et al*, 1982; Phelps *et al*, 1981; Sokoloff *et al*, 1977), which depends on serotonergic, cholinergic, and glutamatergic neurotransmission (Chalmers and McCulloch, 1991; Dringenberg *et al*, 2003; Ingham *et al*, 1998). They also may reflect lithium's stimulation of retinal and cochlear inputs to these areas (Jung and Reme, 1994; Pfeilschifter *et al*, 1988).

Chronic lithium is reported to increase the 5-HT concentration in the serotonergic synaptic cleft by reducing 5-HT₁ density, particularly the density of presynaptic 5-HT_{1B} receptors, but it does not appear to affect 5-HT_{2A/2C} receptor density (Friedman and Wang, 1988; Goodwin, 1989; Haddjeri *et al*, 2000; Januel *et al*, 2002; Massot *et al*, 1999; Mizuta and Segawa, 1988; Redrobe and Bourin, 1999). As 5-HT_{1B} receptors depress presynaptic 5-HT release, lithium's elevation of k^* for AA in auditory and visual areas may result from derepressed 5-HT release, elevated 5-HT in the cleft, or an increased 5-HT_{2A/2C}-mediated activation of PLA₂ (Januel *et al*, 2002; Redrobe and Bourin, 1999). A similar effect can occur in the substantia nigra and locus coeruleus, where 5-HT_{2A} and 5-HT_{1B} receptors are found (Aghajanian and Marek, 1999; Olijslagers *et al*, 2004; Sijbesma *et al*, 1991). On the other hand, lithium is reported not to change whole brain 5-HT turnover (Karoum *et al*, 1997), 5-HT release (Mork, 1998; Sharp *et al*, 1991), DOI-induced adrenocorticotrophic hormone (ACTH) release (Gartside *et al*, 1992), or DOI-evoked wet-dog shakes in ACTH-treated rats (Kitamura *et al*, 2002). Our finding that LiCl feeding did not change head-turning frequency in response to DOI may be related to these negative effects, or to lithium's lack of effect on DOI-induced elevations of k^* in 60 of the 94 brain regions examined (Table 1).

The LiCl-induced elevations in k^* for AA in visual and auditory areas of the rat brain may correspond to lithium's ability to potentiate the P1/N1 components of auditory evoked responses and the 65-P95 and P95-N125 components of visual evoked responses in humans (Fenwick and Robertson, 1983; Hegerl *et al*, 1990; Ulrich *et al*, 1990). These evoked responses are thought to depend on serotonergic transmission (Chalmers and McCulloch, 1991; Dringenberg *et al*, 2003; Hegerl *et al*, 2001; O'Neill *et al*, 2003). The elevations also may be related to the ability of toxic doses of lithium to cause auditory or visual hallucinations (Hambrecht and Kaumeier, 1993) or photophobia (Pridmore *et al*, 1996). On the other hand, lithium's blocking of the k^* increments in response to DOI, a recognized hallucinogen (Sadzot *et al*, 1989), in visual and auditory areas and the substantia nigra and locus coeruleus, may relate to its ability to reduce hallucinations in bipolar disorder (Goodnick and Meltzer, 1984; Potash *et al*, 2001; Rosenthal *et al*, 1979).

Lithium's potentiation of arecoline-induced increments in k^* for AA (Basselin *et al*, 2003b), but not of DOI-induced increments (Table 1), may relate to its ability to rectify

neurotransmission imbalance in bipolar disorder. These are proposed to consist of reduced cholinergic and elevated dopaminergic transmission, and disturbed serotonergic and NMDA transmission (see Introduction) (Bymaster and Felder, 2002; Janowsky and Overstreet, 1995; Mahmood and Silverstone, 2001). In support of this possibility is our abstract that LiCl feeding blocked elevations in k^* for AA in rats administered quinpirole, a dopaminergic D_2 receptor agonist (Basselin et al, 2003a).

Lithium's potentiation of arecoline-induced elevations in k^* in rats is consistent with its proconvulsant action with regard to cholinomimetics (Basselin et al, 2003b; Evans et al, 1990; Jope, 1993; Lerer, 1985; Morrisett et al, 1987). An increased availability of unesterified AA and some of its eicosanoid products could promote neuronal excitability, glutamatergic neurotransmission, and seizure propagation (Bazán, 1989; Kelley et al, 1999; Kolko et al, 1996; Kunz and Oliu, 2001; Li et al, 1997; Lysz et al, 1987; Strauss and Marini, 2002; Wallenstein and Mauss, 1984). In contrast to its effect on PLA_2 signaling via AA, LiCl feeding is reported to reduce brain phospholipase C activation by cholinomimetics (Casebolt and Jope, 1989; Ormandy et al, 1991; Song and Jope, 1992).

The lack of potentiation by lithium of the DOI-induced elevations in k^* is consistent with lithium not being a proconvulsant for serotonergic drugs, at least with regard to AA signaling (Shimizu and Wolfe, 1990). Although LiCl feeding is reported to augment 'convulsion-like' EEG changes following 8 mg/kg i.p. DOI (Moorman and Leslie, 1998; Williams and Jope, 1994; Williams and Jope, 1995), this effect cannot be ascribed to 5-HT_{2A/2C} receptor activation, as 8 mg/kg DOI also stimulates cholinergic (Obata et al, 2003; Ramirez et al, 1997), glutamatergic (Scruggs et al, 2000), dopaminergic (Kuroki et al, 2003) and GABAergic receptors (Abi-Saab et al, 1999). That lithium also does not modify convulsant thresholds to NMDA, kainic acid, bicuculline, or pentylenetetrazole further argues for a selective cholinergic proconvulsant effect (Ormandy et al, 1991).

LiCl's potentiation of k^* responses to arecoline but not to DOI suggests that lithium can modulate receptor-initiated PLA_2 -signaling depending on the receptor, the PLA_2 enzyme, or the G-protein that couples the receptor to PLA_2 (Axelrod, 1995; Chen et al, 1999; Cooper et al, 1996). Three major PLA_2 enzymes occur in brain—a Ca^{2+} -dependent cytosolic c PLA_2 selective for AA, a Ca^{2+} -dependent secretory s PLA_2 , and a Ca^{2+} -independent i PLA_2 selective for docosahexaenoic acid (22:6 n-3), another polyunsaturated fatty acid found usually at the sn-2 position of phospholipids (Clark et al, 1995; Dennis, 1994; Murakami et al, 1999; Strokin et al, 2003). Although we do not know which PLA_2 enzymes mediate the k^* responses to arecoline and DOI, LiCl feeding to rats is reported to downregulate brain mRNA and activity levels of c PLA_2 but not of s PLA_2 or i PLA_2 (Bosetti et al, 2001; Rintala et al, 1999; Weerasinghe et al, 2004).

It is unlikely that lithium's different effects on the k^* responses to arecoline and DOI are due to its modulating G proteins coupled to $M_{1,3,5}$ or 5-HT_{2A/2C} receptors. The G_{α_q} subunit of the G proteins that couple these to phospholipase C or PLA_2 (Chen et al, 1999; Cooper et al, 1996; Roth et al, 1998; Sidhu and Niznik, 2000) is not markedly affected by

LiCl feeding (Dwivedi and Pandey, 1997) or by exposing rat brain cortical membranes to chronic lithium (Wang and Friedman, 1999).

In contrast to the ability of 1.0 and 2.5 mg/kg i.p. DOI to increase k^* for AA (Table 1 and Qu et al, 2003), DOI at 2.5 and 50 mg/kg i.p. in unanesthetized rats decreases regional cerebral metabolic rates for glucose, rCMR_{glc}, measured with 2-deoxy-D-glucose (Freo et al, 1991). These latter decreases correspond to reduced firing rates of serotonergic neurons (Ashby et al, 1990; Bloom, 1985). The opposing effects of DOI on k^* compared with rCMR_{glc} illustrate that the fatty acid and 2-deoxy-D-glucose methods image different aspects of brain functional activity. The former images PLA_2 -mediated signal transduction via AA in cell bodies or dendrites, whereas the latter reflects the energy-consuming firing of axonal terminals of these cell bodies (Qu et al, 2003; Rapoport, 2003; Sokoloff, 1999).

In summary, (i) 5-HT_{2A/2C}-mediated PLA_2 signaling via AA can be imaged as regional brain increments in k^* for AA in response to 1 mg/kg i.p. DOI in unanesthetized rats; (ii) LiCl feeding does not potentiate k^* responses to DOI in any brain region, but blocks the responses in certain visual and auditory areas, the substantia nigra, and locus coeruleus; (iii) LiCl feeding does not affect baseline values of k^* in most brain regions, but increases baseline k^* in visual or auditory regions; (iv) LiCl feeding does not significantly alter head turning frequency in response to DOI.

ACKNOWLEDGEMENTS

We thank Dr Karen Pettigrew for her statistical advice.

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