The impact of lithium on prooxidant-antioxidant balance in human plasma *in vitro* and in neuronal cell lines

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Lithium

Medical use

✓ first-line treatment of manic episodes;

✓ treatment option for bipolar depressive episodes;

✓ augmentation therapy of medication-resistant depression or schizophrenia.

Mechanism of action

✓ ion transport,

✓ neurotransmitter signaling,

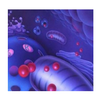
✓signal transduction (phosphoinositide cycle, adenylyl cyclase G proteins, protein kinases),

✓gene expression,

✓neuroplasticity and cytoskeletal remodeling,

✓ **neuroprotection and antioxidation**

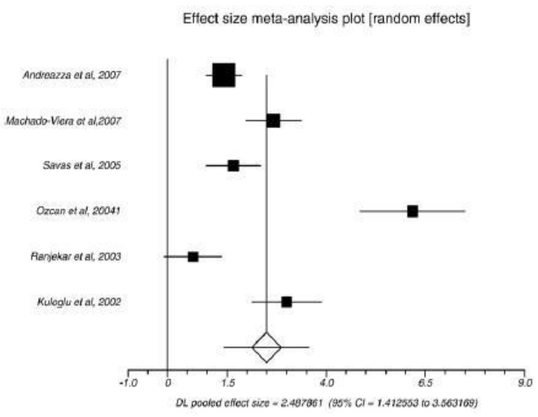
Introduction



Oxidative stress

„disturbance in prooxidant-antioxidant balance in favour of the former, leading to potential damage" *(Sies, 1991)*

- patients with BD have increased lipid peroxidation (acute manic and depressive epizodes, remission);
- a potential role of glutamate-induced oxidative stress in BD?
- excessive generation of ROS triggered by mitochondrial dysfunction in BD?



Andreazza et al., 2008

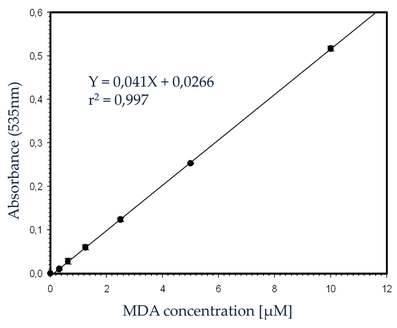
Methods

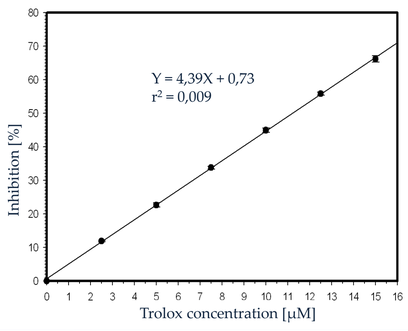
Human plasma *in vitro:*

-plasma samples from healthy volunteers ;

-plasma incubation (24h, 37 C):
- without the drug;
- with lithium alone (0,67 or 1,0mmol/l);
- with lithium and haloperidol (10ng/ml)

Lipids peroxidation (LP) measurement by the concentration of thiobarbituric acid reactive substances (TBARs) (Rice-Evans).



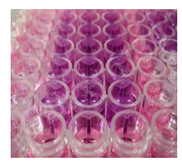


Determination of **total antioxidant capacity (TAC)** with ABTS radical cation ($ABTS^{+\cdot}$) decolorization assay (Re).

Neuroblastoma

SH-SY5Y cells were used. Two kinds of experiments were performed:
✓Cells were treated with various concentrations of lithium (0,67mmol/l and 1,00 mmol/l) and haloperidol (10ng/ml) for 48h;
✓ Cells were pretreated with various concentrations of lithium (0,67mmol/l and 1,00 mmol/l) and haloperidol (10ng/ml) for 24h and then treated with hydrogen peroxide (150µM) for another 24h;
✓Lipid peroxidation and cell viability were measured.

Oxidative stress level was assessed by **lipid peroxidation** measurement (Rice-Evans method).



Cell viability was measured by MTT assay - colorimetric assay for measuring the activity of enzymes that reduce MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) to purple formazan dyes.

Statystical analysis

The scientific statistic software Statistica 10.0 was employed.

Results

We observed:

➢ no influence of lithium on lipid peroxidation (fig. 1) nor TAC (fig. 2) in human plasma *in vitro;*

➢ increase in lipid peroxidation in samples with combination of lithium and haloperidol in human plasma *in vitro* (fig. 1); no differences in TAC between the samples;

➢ no influence of lithium, haloperidol and combination of lithium and haloperidol on lipid peroxidation in SH-SY5Y neuroblastoma cells (fig. 3);

➢ no influence of pretreatment with lithium, haloperidol and combination of lithium and haloperidol on lipid peroxidation in SH-SY5Y neuroblastoma cells treated with hydrogen peroxide (fig. 4);

➢ higher viability in SH-SY5Y neuroblastoma cells cultures incubated with lithium (fig. 5); no influence of haloperidol and combination of lithium and haloperidol on cells viability.

Human plasma *in vitro*

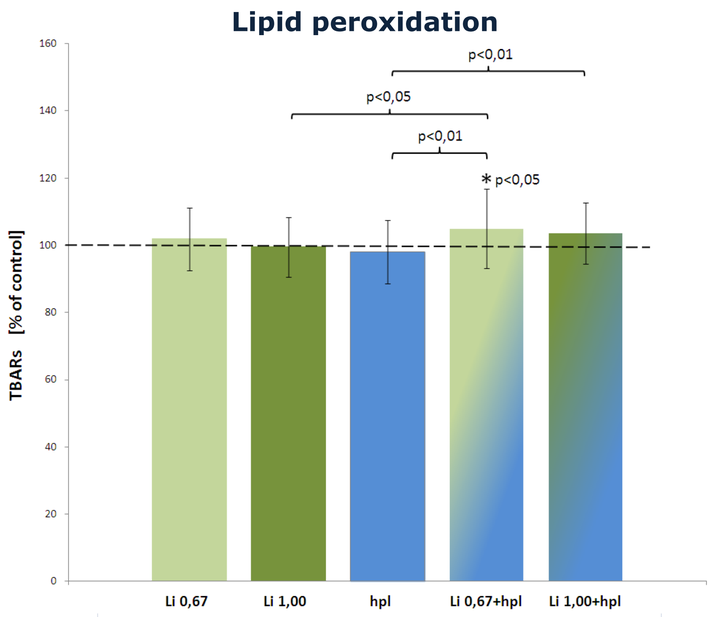


Fig. 1. Effect of lithium and haloperidol on TBARs levels in human plasma *in vitro.* Values represent mean ± SD; * p<0,05 compared to control (ANOVA, *post hoc* Tukey test).

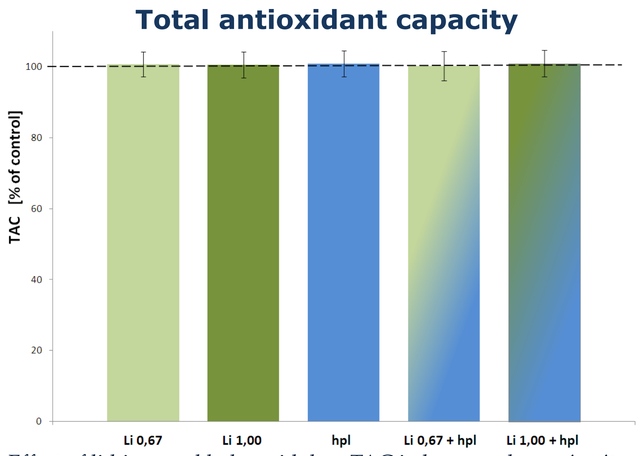


Fig. 2. Effect of lithium and haloperidol on TAC in human plasma *in vitro.* Values represent mean ± SD (ANOVA).

Neuroblastoma SH-SY5Y

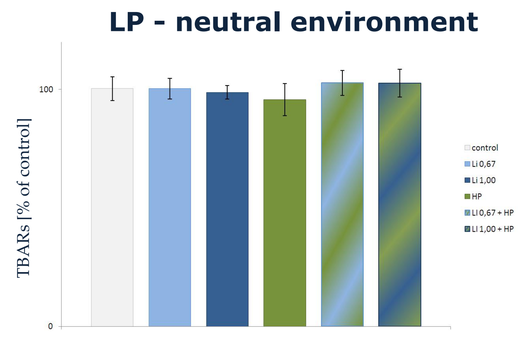


Fig. 3. Effect of lithium and haloperidol on TBARs levels in SH-SY5Y cells. Values represent mean ± SD; n=4 (ANOVA).

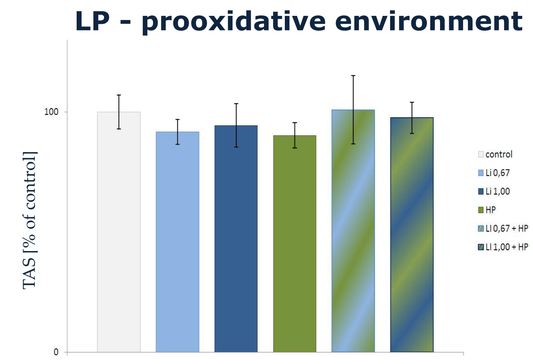
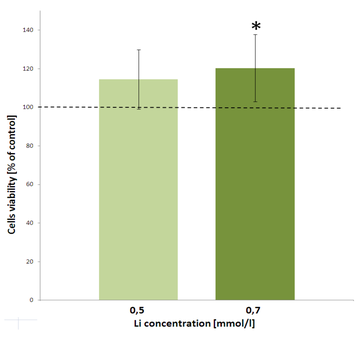


Fig. 4. Effect of lithium and haloperidol on TAC in SH-SY5Y cells exposed to H_2O_2. Values represent mean ± SD; n=3 (ANOVA).



Cells viability

Fig. 5. Effect of lithium on viability in SH-SY5Y neuroblastoma cells cultures. Values represent mean ± SD; * p<0,05 compared to control (ANOVA, *post hoc* Tukey test).

Conclusions

➢ lithium in concentrations used in psychiatry does not influence oxidative stress parameters in *in vitro* conditions (human plasma, neuroblastoma cells) in a short-period observation (24 or 48h) what is consistent with some of the previous studies;
➢ lithium in combination with haloperidol increases lipid peroxidation compared to control, lithium or haloperidol alone, thus one should be careful prescribing those drugs together; the mechanism may be responsible for some side effects (e.g. neurotoxicity) of the combination;
➢ inconsistency of research in the field causes necessity for furher studies to assses lithium impact on oxidative stress parameters: in *in vivo* conditions, in a long-period observation, in neutral and prooxidative environment (patients with bipolar disorder);
➢ further studies may provide additional data regarding the possible involvement of oxidative stress in the pathophysiology of BD and in the therapeutic effects of lithium.

Acknowledgments

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