P10

Effects of lithium and valproate on DNA damage and oxidative stress markers in an animal model of mania

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Introduction: Recent studies have suggested that oxidative stress and DNA damage may play a role in the pathophysiology of bipolar disorder (BD). In the present study, we investigated the effects of the mood stabilizers lithium (LI) and valproate (VAL) on amphetamine-induced oxidative stress and DNA damage in an animal model of mania.

Methods: In the first model, designed to mimic the management of acute mania (reversal model), adult male Wistar rats received d-amphetamine (AMPH) or saline for 14 days, and between the 8th and 14th day, rats were treated with LI, VAL or saline. In the second model, designed to mimic the maintenance treatment (prevention model), rats were pretreated with LI, VAL or saline, and between the 8th and 14th day, animals received AMPH or saline. We measured serum and hippocampal thiobarbituric acid reactive substances (TBARS), a marker of lipid peroxidation, and the activities of the antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT). Serum and hippocampal DNA damage were evaluated using the single cell gel electrophoresis (Comet assay), which detects DNA double- and single-strand breaks.

Results: In both models, LI reversed and prevented central (hippocampal) and peripheral (serum) AMPH-induced lipid peroxidation. VAL prevented hippocampal, and reversed and prevented peripheral AMPH-induced lipid peroxidation. More than 2-fold increase of hippocampal and 3-fold increase of serum SOD activity predicted higher lipid peroxidation. In both models, LI reversed and prevented central and peripheral AMPH-induced DNA damage, while VAL reversed hippocampal AMPH-induced DNA damage in the Reversal model.

Conclusions: These results further support that LI and VAL exert central and peripheral antioxidant effects *in vivo*, and suggest that LI and VAL may protect against oxidative stress-induced early DNA damage.

Keywords: mania, bipolar disorder, DNA damage, oxidative stress