The antimanic-like effects of andrographolide and quercetin

SUMMARY

Increased activity of the enzyme glycogen synthase kinase 3 beta (GSK3β) is shown to play a pivotal role in the pathophysiology of several psychiatric disorders, including bipolar disorder (BD). Lithium, the prototype mood stabilizer, is an inhibitor of GSK3β. In animal models of mania, GSK3β inhibitors reproduce behaviors that mimic the effects of lithium. The pharmacological management of BD consists of administration of mood stabilizers or antipsychotics associated to antidepressants and it often involves a myriad of adverse effects or non-responsiveness, which affect medication adherence and quality of life. The search for new therapeutic agents for BD is therefore necessary. Considering that the inhibition of GSK3β activity may display antimanic-like effects, we tested the effects of andrographolide (ANDRO), the major bioactive compound isolated from *Andrographis paniculata*, which is an inhibitor of GSK3β. Studies showed that ANDRO possesses several therapeutic properties, including anti-inflammatory, antioxidant, antibacterial, hepatoprotective, neuroprotective, among others. Both ANDRO and lithium have been shown to decrease GSK3β levels and increase the levels of p-Ser^{9}-GSK3β, the phosphorylated and inactive form of GSK3β .

Taking into consideration that GSK3β is an enzyme involved in the pathophysiology of BD and that GSK3β inhibition, such as induced by lithium, ameliorates manic symptoms, the effects of the chronic treatment with the GSK3β inhibitor ANDRO were tested in different animal models of mania, such as sleep deprivation (SD)-, methylphenidate- and lisdexamfetamine (LDX)-induced hyperlocomotion, increases in 50-kHz ultrassonic vocalizations (USVs) and oxidative stress. We also evaluated the effects of ANDRO in the levels of GSK3β and p-Ser^{9}-GSK3β in the prefrontal cortex (PFC) and striatum of mice. A summary of the results is given below.

SD resulted in hyperlocomotion and treatment with lithium, 0.5 mg/kg ANDRO, and 2.0 mg/kg ANDRO blocked SD-induced hyperlocomotion. SD decreased the p-Ser^{9}-GSK3β/GSK3β ratio in the PFC. Both lithium and 2.0 mg/kg ANDRO increased the p-Ser^{9}-GSK3β/GSK3β ratio in the PFC.

Methylphenidate administration increased locomotor activity compared to the control group and treatment with lithium, 0.5 mg/kg ANDRO, and 2.0 mg/kg ANDRO

blocked methylphenidate-induced hyperlocomotion. Methylphenidate reduced the p-Ser^{9}-GSK3β/GSK3β ratio in the striatum. Both lithium and 2.0 mg/kg ANDRO increased the p-Ser^{9}-GSK3β/GSK3β ratio in the striatum.

LDX increased locomotor activity in rats, which was prevented by chronic treatment with lithium or 2.0 mg/kg ANDRO. LDX administration increased the number of 50-kHz USVs, which was also prevented by chronic treatment with lithium or 2.0 mg/kg ANDRO. Lithium and 2.0 mg/kg ANDRO also prevented LDX-induced increases in lipid peroxidation (LPO), an oxidative stress parameter in the striatum. There was a positive correlation between LDX-induced hyperlocomotion and LDX-induced increases in 50-kHz USVs and LPO.

Both 10 and 40 mg/kg quercetin prevented SD-induced hyperlocomotion. Quercetin reversed the SD-induced decrease in glutathione (GSH) levels in the PFC and striatum. Quercetin also reversed the SD-induced increase in LPO in the PFC, hippocampus, and striatum. Pearson's correlation analysis revealed a negative correlation between locomotor activity and GSH in the PFC in sleep-deprived mice and a positive correlation between locomotor activity and LPO in the PFC and striatum in sleep-deprived mice.

Chronic but not acute treatment with quercetin (10 and 40 mg/kg) blocked methylphenidate-induced hyperlocomotion. Chronic treatment with lithium and quercetin blocked the methylphenidate-induced increase in LPO levels in the striatum.

Overall, the results show that chronic treatment with ANDRO prevented hyperlocomotion induced by SD and methylphenidate, while increasing the p-Ser^{9}-GSK3β/GSK3β ratio in the PFC and striatum of mice, respectively. ANDRO also prevented LDX-induced hyperlocomotion and increases in the number of 50-kHz USVs, while also preventing LDX-induced LPO in the striatum of rats. Quercetin also prevented SD and methylphenidate-induced hyperlocomotion, while also preventing SD-induced decreases in GSH in the PFC and striatum, and LPO in the PFC, hippocampus and striatum. Quercetin also blocked methylphenidate-induced hyperlocomotion, and methylphenidate-induced increase in LPO levels in the striatum. Thus, both ANDRO and quercetin appears to possess antimanic-like effects and they are promising agents to be thoroughly investigated for the management of mania in BD.