INHIBITION OF 5-ALPHA REDUCTASE RESCUES PSYCHOTIC- AND MANIC-LIKE PHENOTYPES INDUCED BY SLEEP DEPRIVATION

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Alterations of sleep patterns are prominent in a broad array of neuropsychiatric disorders (Benca et al, 1992). Sleep Deprivation (SD) leads to several perceptual and cognitive abnormalities (Killgore, 2010; Daviaux et al, 2014); furthermore, psychotic and manic symptoms can be triggered or exacerbated by SD (West et al, 1962; Wehr et al, 1987); accordingly, SD-subjected rats exhibit a wide array of manic-like behavioural manifestations (Gessa et al, 1995). Along these lines, it has been shown that sleep-deprived rats and humans develop deficits in the prepulse inhibition (PPI) of the acoustic startle reflex (Frau et al, 2008; Petrovsky et al, 2014), and PPI deficits are observed in schizophrenia and mania (Braff et al, 2001; Perry et al, 2001). Nevertheless, the neurobiological correlation between sleep deprivation and neuropsychological disorders remains largely elusive.

Given the extensive involvement of neuroactive steroids in psychopathology, we hypothesized that 5α-reductase (5αR), the rate-limiting enzyme in the conversion of progesterone into the neurosteroid allopregnanolone, may be responsible of the behavioural complications of SD. We first tested whether rats exposed to SD may exhibit brain-regional alterations in 5αR isoenzymes and neuroactive steroid levels; then, we assessed whether the behavioural and neuroendocrine alterations induced by SD may be differentially modulated by the administration of the 5αR inhibitor finasteride, as well as progesterone and allopregnanolone. We found that SD selectively enhanced 5αR expression and activity, as well as AP levels, in the prefrontal cortex; furthermore, finasteride (10-100 mg/kg, IP) dose-dependently ameliorated PPI deficits, hyperactivity, and risk-taking behaviours, in a fashion akin to the antipsychotic haloperidol and the mood stabilizer lithium carbonate. PPI deficits were exacerbated by allopregnanolone (10 mg/kg, IP) and attenuated by progesterone (30 mg/kg, IP) in SD-subjected, but not control rats. Finally, the microinfusions of finasteride (0.5 □g/side) in the prefrontal cortex were able to ameliorate PPI deficits induced by SD.

Collectively, these results provide the first-ever indication that 5αR mediates a number of psychosis- and mania-like complications of SD through imbalances in cortical levels of neuroactive steroids.

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