

Activation of PPAR γ receptor by natural agent andrographolide reduces alcohol drinking and stress-induced relapse in Marchigian-Sardinian alcohol-preferring (msP) rats.

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Andrographis Paniculata, (*A. Paniculata*, fam. Acanthaceae) is an herbaceous plant commonly used in Siddha, Ayurvedic and tribal medicines, whose main active ingredient andrographolide is thought to exert its pharmacological properties through a peroxisome proliferator activated receptor gamma (PPAR γ)-mediated mechanism (Hanke Orozco et al, 2006). Work from our laboratory has recently shown the therapeutic potential of PPAR γ agonist pioglitazone in alcohol- and other drug-related disorders (Stopponi et al, 2010; De Guglielmo et al, 2015).

Here we examined the effect of *A. paniculata* and andrographolide on alcohol intake and seeking in genetically selected alcohol preferring msP rats. The two-bottle free choice paradigm was used to assess voluntary alcohol drinking while yohimbine-stress and environmental cues were used to evoke alcohol seeking in animals that previously underwent alcohol self-administration and extinction training. Subchronic treatment with *A. paniculata* (0, 15, 150 and 450 mg/kg) significantly reduced voluntary alcohol intake. The extract (0, 150 and 450 mg/kg) also abolished the reinstatement of previously extinguished alcohol-paired responses when elicited by the pharmacological stressor yohimbine (1.25 mg/kg, i.p.) but did not affect cue-induced reinstatement of alcohol seeking. Reduced alcohol consumption was also observed with andrographolide (0, 5, 10 mg/kg). Importantly, the effect of andrographolide (10 mg/kg) was blocked by intracerebroventricular pretreatment with the selective PPAR γ antagonist GW9662 (5 μ g/rat), suggesting that the effect is mediated by PPAR γ receptors in the central nervous system.

Altogether these data further demonstrate that PPAR γ receptor may serve as a potential target for treatment of alcoholism.