Nandrolone decanoate-THC co-treatment prevent the depressive-like phenotype induced by chronic anabolic androgenic steroids exposure during adolescence

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Nandrolone decanoate (ND) is a well-known anabolic androgen steroid (AAS) that is widely abused not only among athletes and bodybuilders, but also among people who attend gyms seeking enhanced physical strength or body appearance. Abuse of AAS has been associated with a wide range of physical and psychiatric adverse effects such as violent aggression and depression. Nowadays, there is a growing number of adolescents who use and abuse AAS. As a result of the substantial neurobiological changes that characterize this life stage, adolescents seem to exhibit extreme sensitivity to the detrimental effects of drug abuse. Indeed, we recently showed that exposure to nandrolone decanoate (ND, 15 mg/kg daily for 14 days, i.m.) during adolescence but not adulthood, induced depressive-like symptoms in male rats.

Since *Cannabis sativa* is the illicit substance most produced and abused in the world especially among adolescents, our aim was to evaluate the effect of a co-administration of ND and THC, the psychotropic constituent of *Cannabis sativa*.

To this aim we treated adolescent male rats for 14 days with ND (15mg/kg i.m.), THC (5mg/kg i.p.) or both drugs and 24 h after the last injection we performed behavioral tests to assess the presence of depressive- and anxiety-like symptoms.

As expected, animals treated only with ND showed a significantly increased time spent in immobility and decreased time spent swimming in the forced swim test (FST). No alterations were recorded in THC group with the exception of an increased climbing. Surprisingly, ND/THC co-treatment prevented the behavioral despair induced by ND alone in the FST.

Similarly, ND alone induced anxiety-like behaviors as demonstrated by the significant reduction of entries in the open arms of the elevated plus maze (EPM), paralleled by a trend of reduction of time spent in them. Once again, the group of animals that received both substances did not show the anxiety-like behaviors induced by ND alone.

Moreover we analyzed the cellular proliferation in the dentate gyrus of hippocampus and p-CREB expression in cerebral areas as prefrontal cortex, nucleus accumbens and amygdala since they have been demonstrated to be involved in mood disorders.

No changes have been observed in the cellular proliferation in dentate gyrus of hippocampus after ND treatment.

Moreover when we analyzed p-CREB expression, we observed a slight, although not significant, increase of IR-pCREB cells in nucleus accumbens of ND-treated animals. Instead this slight alteration was not observed in co-treated animals. No differences were observed in IR-pCREB cells in the other areas.

As a whole these results provide evidence that depressive- and anxiety-like behaviors induced by ND exposure during adolescence were prevented by THC co-exposure. This suggest that manipulation of the endocannabinoid system could be an effective tool to treat depression and anxiety induced by steroid abuse in adolescence.