DIFFERENT STRIATAL C-FOS EXPRESSION FOLLOWING CO-ADMINISTRATION OF DELTA-9-TETRAHYDROCANNABINOL WITH HALOPERIDOL OR CLOZAPINE

Paola Casti,[a] Giorgio Marchese,[a] Angela Sanna,[a] Gianluca Casu,[a] Gabriele Pinna Spada,[a] Luca Pani[a,b]

[a]Neuroscienze PharmaNess S.c.a r.l., c/o POLARIS, Edificio 5, Loc.Piscinamanna, 09010 Pula (CA), Italy
[b]C.N.R. Istituto di Tecnologie Biomediche, Sezione di Cagliari, c/o Neuroscienze PharmaNess S.c.a r.l.

Dopaminergic and cannabinoidergic systems are both involved in the control of movement and functional interaction between two systems have been demonstrated. Recent studies indicated that CB_1 stimulation might exacerbate extra-pyramidal symptoms (EPS) induced by D_2 blockade. In line with these evidences, we demonstrated in a previous study, that haloperidol but not clozapine administration in rats induced high level of catalepsy when associated with Δ^9- tetrahydrocannabinol (THC).
Furthermore, several studies demonstrated that haloperidol, but not clozapine increases c-Fos immunoreactivity (IM) in rat striatum. These results indicate that the different propensity of typical with respect to atypical antipsychotics in inducing EPS is related to the different levels of D_2 blockade in nigro-striatal system, and suggest that c-Fos is a suitable tool to investigate on activation of brain areas following drugs administration.

In this study we investigated the physiological mechanisms underlying the different cataleptic states induced by haloperidol and clozapine when associated with THC, by analysing the level of c-Fos expression in striatum through western blot and stereological immunocytochemistry techniques.

Western Blot and stereological immunocytochemistry analyses indicated that Δ^9-THC (0,5 mg/kg, i.p) administration increased striatal c-Fos IM induced by haloperidol (0.1 mg/kg, s.c.). Conversely, clozapine (10 mg/kg, s.c.), Δ^9-THC and co-administration of clozapine with Δ^9-THC did not alter c-Fos IM in striatum compared to vehicle. Furthermore stereological data highlighted that enhancement of c-Fos expression induced by Δ^9-THC and haloperidol association is highest in dorsal-lateral part of striatum, where dopamine D_2-receptors are more densely distributed and co-localized with CB_1 receptors.

The present results indicate that the different cataleptic states induced by Δ^9-THC in haloperidol- and clozapine-treated rats are correlated with different level of c-Fos IM in striatum, suggesting that CB_1- and D_2-receptor systems might also concur in regulating striatal c-Fos expression.