SOCIETÀ ITALIANA DI FARMACOLOGIA

MODELLO PER INVIO RELAZIONE DI METÀ E FINE PERIODO

NOME E COGNOME: Giorgia Targa

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DIPARTIMENTO (in caso di borsa per soggiorno all'estero specificare l'ente presso cui si è svolta la ricerca):

Ricerca svolta presso il Dipartimento di Neuroscienze dell'Università di Mons (Belgio)

TUTOR (in caso di borsa per soggiorno all'estero specificare il tutor dell'ente presso cui si è svolta la ricerca):

Dott.ssa Damiana Leo (PhD)

TIPOLOGIA DI BORSA RICEVUTA: Borsa di Ricerca SIF per brevi periodi all'estero

TIPOLOGIA DI RELAZIONE (es.: metà periodo o finale): metà periodo

TITOLO DELLA RELAZIONE: Unveiling the mechanisms underlying dopamine-glutamate interaction in bipolar disorder

RELAZIONE:

The goal of this project is to study the role of glutamate in dopamine transporter knockout (DAT KO) rats, a transgenic animal model of DAT deficiency. These animals present increased dopaminergic transmission that is possibly involved in endophenotypes of disorders such as in the manic stage of bipolar disorder, ADHD and schizophrenia. Indeed, DAT KO rats show symptoms such as mania-like switching, hyper motivation, hyperactivity and risky decision making (Leo et al., 2018).

Dopamine and glutamate interact in the striatum influencing neural excitability and promoting synaptic plasticity (Nair et al., 2014). The main ionotropic glutamate receptors, NMDA and AMPA, colocalize with striatal dopaminergic receptors in the postsynaptic medium spiny (MS) neurons, where they mediate top-down control, reward processing and depressive mood (Tarazi & Baldessarini, 1999). However, little is known concerning the molecular mechanisms underlying the crosstalk between dopamine and glutamate.

Preliminary data performed in Italy showed an extensive reorganization of the glutamate synapse in the striatum of DAT KO rats. To summarize, DAT KO animals show a reduced expression of AMPA and NMDA receptors in the post synaptic density, the active part of the synapse, paralleled with an increased expression at the extra-synaptic sites. This suggests an intensified lateral trafficking of the receptors toward the extra-synaptic sites. These data suggest that the hyperdopaminergic condition caused by DAT deletion induces a depotentiation of the glutamate synapse.

To strengthen these molecular results, at the Department of Neuroscience of the University of Mons, we performed electrophysiological experiments in *ex vivo* striatal slices (Villers & Ris, 2013).

Thus, we evaluated indicators of striatal neuroplasticity, such as paired-pulse ratio and long-term depression (LTD) formation, which are processes strongly dependent on dopamine. Notably, to induce LTD in the striatum, we used theta-burst stimulation (TBS) protocol, which consists in producing a strong, long-lasting potentiation of EPSCs in naïve animals, strictly dependent on the activation of NMDA receptors and Ca^{2+}/CaM-dependent protein kinase II (CaMKII) (Tsvetkov et al., 2004)(Ko et al., 2008).

Both in dorsal and ventral striatum, wild-type (WT) and DAT KO animals didn't show any difference in paired-pulse ratios suggesting the absence of changes in short-term synaptic plasticity. LTD, in the dorsal striatum, was similarly induced in both groups, suggesting that any difference was found in the basal glutamatergic transmission; nevertheless, in ventral striatum, DAT KO rats show a strong impairment in producing LTD.

Furthermore, since the interaction of glutamatergic and dopaminergic pathways at the dendritic spines of MS neurons is fundamental for the modulation of motor functions and since it was already demonstrated that DAT KO rats show marked hyperactivity and hyperlocomotion, we performed footprint test to analyze gait alterations, such as stride length, stance length, base width, and paws overlap (Bain et al., 1989) (Sugimoto & Kawakami, 2019). In DAT KO animals motor disorders were observed, in particular, these animals present a shorter stride length while a greater base width compared to WT animals.

Lastly, to better understand this motor impairment, DAT KO rats underwent the hotplate test. This test is commonly used for pain assessment and nociception, but it can also be used to find impairments in sciatic nerve functionality. DAT KO animals spent more time on the hotplate, an effect probably due to a sensory and/or motor impairment in the sciatic nerve. Hence, to be able to discriminate between these two components, sciatic nerves, which are responsible for motor and sensory functions, and dorsal root ganglion (DRGs), which instead encase only the primary afferent sensory neurons, were collected, and will be analyzed in University of Milan (Faroni et al., 2014)(Middleton et al., 2021).

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Leo, D., Sukhanov, I., Zoratto, F., Illiano, P., Caffino, L., Sanna, F., Messa, G., Emanuele, M., Esposito, A., Dorofeikova, M., Budygin, E. A., Mus, L., Efimova, E., Niello, M., Espinoza, S., Sotnikova, T. D., Hoener, M. C., Laviola, G., Fumagalli, F., … Gainetdinov, R. R. (2018). Pronounced hyperactivity, cognitive dysfunctions, and BDNF dysregulation in dopamine transporter knock-out rats. *Journal of Neuroscience*, *38*(8), 1959–1972. https://doi.org/10.1523/JNEUROSCI.1931-17.2018

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Data 04/06/2022 Firma Giorgia Targa

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