DEFICIENCY OF SEROTONIN AT CENTRAL OR PERIPHERAL LEVEL ALTERS NEUROPLASTIC AND EPIGENETIC MECHANISMS IN ADULT RATS

Giulia Sbrini[1] , Paola Brivio[1] , Natalia Alenina[2] , Judith Homberg[3] , Francesca Calabrese[1]

[1] Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan - Italy, [2] Cardiovascular and Metabolic Diseases, Max-Delbru¨ck-Center for Molecular Medicine (MDC), Berlin, Berlin - Germany, [3] Department of Cognitive Neuroscience, Centre for Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, Nijmegen - The Netherlands

Background: Serotonin (5-HT) is synthesized from the amino-acid tryptophan thought the action of the rate-limiting enzyme tryptophan hydroxylase (Tph) that exists in two isoforms. The isoform 1, mainly present in the enterochromaffin cells, is responsible for the production of serotonin in the periphery while the isoform 2, located in the raphe nuclei, selectively acts in the brain. Interestingly, in humans, alterations in the serotoninergic transmission are related to an increased susceptibility to develop psychiatric pathologies. On these bases, by using Tph1-/- and Tph2-/- rats, characterized by the absence of serotonin respectively at the periphery or in the brain, we evaluated the contribution of the two pools of 5-HT on brain functions from a behavioral and molecular point of view.

Material and methods: Male Tph1-/- rats were obtained thought injection of CRISPR virus, while male Tph2-/- rats were created with the zinc finger nuclease technology. Behavioral tests were performed at adulthood and molecular analyses were conducted with the real-time PCR in the prefrontal cortex. Data were analyzed with unpaired Student's T-test.

Results: Tph1-/- rats showed a normal hedonic response during the sucrose consumption test and a normal explorative-like behavior in the open field test. Moreover, they demonstrated reduced anxiety during the elevated plus maze test suggesting that the absence of serotonin at the periphery may alter brain functions. Tph2-/- rats instead exhibited an increased aggressiveness and reduced social interaction. At molecular level, we found increased levels of Brain-derived neurotrophic factor (Bdnf) (total Bdnf: +24%, p=0,153; Bdnf long 3'UTR: +24% p<0,05; Bdnf isoform IV -2% p= 0,891; Bdnf isoform VI: +34% p<0,05; vs Tph1+/+) in Tph1-/- rats. Similarly, Bdnf transcription was up-regulated (total Bdnf: +37%, p<0,05; Bdnf long 3'UTR: +32% p<0,05; Bdnf isoform IV +45% p<0,05; Bdnf isoform VI +34% p<0,01; vs Tph2+/+) in Tph2-/- rats. In line with the increased neuroplasticity, mutant rats showed alterations in the epigenetic mechanisms with an increased expression of Growth Arrest And DNA Damage Inducible Beta (Gadd45β) (+21%, p<0,05 vs Tph1+/+) in Tph1-/- rats and decreased Histone deacetylase 1 (Hdac1) mRNA levels in Tph2-/- rats (-15% p<0,05 vs Tph2+/+).

Discussion and conclusion: The results obtained in Tph1-/- rats, suggest that the depletion of the 5-HT at the periphery may alter brain functions. Indeed the lack of serotonin at the periphery produces reduced anxiety paralleled by an increased expression of Bdnf and of Gadd45β. Moreover, the absence of the neurotransmitter in the brain results in an increased aggressiveness and major social isolation with increased levels of Bdnf and a reduced Hdac1 expression. In conclusion, our data confirm the central role of the central and peripheral serotonin in the control of brain functions and the usefulness of Tph1-/- and Tph2-/- rats as tools to study psychiatric pathologies.