DYSREGULATION OF BDNF SIGNALING IN THE AMYGDALA OF RATS LACKING THE SEROTONIN TRANSPORTER FOLLOWING LONG-ACCESS COCAINE SELF-ADMINISTRATION

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Introduction: The amygdala is a subcortical gray matter structure deeply involved in mediating the negative emotinal state observed during withdrawal from drugs of abuse. Of note, evidence exists that the amygdala plays a key role in cocaine addiction, driving, through structural and functional changes, the transition from non-compulsive to compulsive use of the psychostimulant. These findings are further reinforced by evidence from human neuroimaging that pointed out relevant implications of the amygdala in cocaine addiction. Brain-derived neurotrophic factor (BDNF) is a well-known neurotrophic factor that has been characterized as a key player in neuroplasticity, including drug addiction. Notably, BDNF is regulated by serotonin and inherited serotonin transporter down-regulation is associated with increased vulnerability to cocaine addiction.
Since the role of serotonin in cocaine addiction, especially in amygdala, is still limited, here we focused on investigating the role of BDNF signaling subserving the transition from hedonic- versus compulsive-like cocaine -self-administration in rodents lacking the serotonin transporter ($SERT^{-/-}$).

Materials and methods: Male $SERT^{-/-}$ rats were generated by induced mutagenesis and outcrossed with commercially available Wistar rats for at least ten generations. Animals were subjected to cocaine self-administration through jugular vein catheters. Food pellets and water were available ad libitum, except during the cocaine self-administration sessions. Seven days after surgery, rats were trained to self-administer cocaine (0.5 mg/kg/infusion) and, two days later, rats were allowed to self-administer cocaine during daily 6 h sessions (Long Access-LgA), for a total of 17 days.
Twenty hours following the last cocaine self-administration session, rats were sacrificed by decapitation and brains immediately collected. Then, the central nucleus of amygdala was punched (coordinates between bregma -1.72 mm and bregma -3.48 mm) and tissues were processed for molecular analysis: total RNA and proteins were extracted and analyzed via Real-Time PCR and western blots, respectively.

Results: In line with previous results, $SERT^{-/-}$ rats displayed a higher number of total cocaine-reinforced lever presses with respect to $SERT^{+/+}$ rats. We also found that LgA cocaine self-administration reduces BDNF expression in the central nucleus of amygdala of $SERT^{+/+}$ rats, which goes along with increased activity of its high-affinity receptor TrkB (Y706) and an increase in Akt-dependent intracellular signaling cascade. Interestingly, in the amygdala of cocaine-naïve $SERT^{-/-}$ rats we found changes in the BDNF system that recapitulate those observed in the same brain region of cocaine-exposed $SERT^{+/+}$ rats. Finally, we observed that LgA cocaine self-administration alters BDNF intracellular signaling in the central amygdala of $SERT^{-/-}$ rats in an opposite way when compared to $SERT^{+/+}$ rats.

Discussion and conclusions: These results suggest that the liability of $SERT^{-/-}$ rats to compulsive cocaine intake may, at least in part, depend upon lack of SERT. Our molecular findings show that the perturbation of BDNF signaling in the central nucleus of amygdala may contribute to the increased vulnerability to cocaine addiction observed in $SERT^{-/-}$ rats.