Intranasal oxytocin ameliorates social deficits in the schizophrenia-relevant dysbindin-1 knockout mice

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Schizophrenia is a chronic enduring disorder ranked among the most debilitating mental illnesses. It is characterized by three broad types of symptoms: positive symptoms, negative symptoms, and cognitive deficits. While drugs currently available for the treatment of this disorder are effective for positive symptoms, negative symptoms and cognitive deficits still remain mainly untreatable.

Data from recent clinical studies on patients affected by schizophrenia treated with intranasal oxytocin suggest the potential of intranasal oxytocin as a new frontier for ameliorating social deficits in schizophrenia. However, the therapeutic properties of oxytocin in schizophrenia are still unclear and its mechanisms are unknown.

Intranasal administration might be a promising and non-invasive way of administration of neuropeptides: this administration route enables highly hydrophilic and high molecular weight molecules to bypass the blood-brain barrier permitting them to reach the brain in a non-invasive way.

Taking advantage of clinically-relevant mouse models, our study aimed at clarifying the effectiveness of oxytocin, for improving social abnormalities relevant to schizophrenia. In particular, the schizophrenia-relevant dysbindin-1 (Dys) knockout mutant mice were treated acutely or chronically with intranasal oxytocin.

We first evaluated social abilities of mutant and wild-type littermates, intranasally administered with oxytocin or vehicle towards novel or familiar-stimulus mice. To this aim we adopted a male-female social interaction task and a social habituation/dishabituation Task. In the male-female social interaction task, the male subject is exposed to an unfamiliar female stimulus mouse for 5 minutes. In the social habituation dishabituation task, an unfamiliar wild type stimulus mouse of same sex is introduced to the subject mouse (male or female) over five 1-min trials. For the first 4 trials, the stimulus mouse is the same and becomes, over time, more familiar (habituation phase). In the 5th trial, a completely new unfamiliar mouse is used as the stimulus mouse (dishabituation phase). In both paradigms, the videos of the task are registered and social behaviors manually scored. There was a significant dysbindin-1 genotype effect in the frequency of social behaviors but not in non-social behaviors. In fact, Dys knockout mice displayed a reduction of social abilities that are ameliorated both by chronic and acute intranasal oxytocin treatment. Reversal of social impairment was observed both in males in male-female social interaction and also in females in female-female social interaction towards an unfamiliar stimulus mouse. In contrast, as was recently published, social abilities of wild-type male mice were impaired by the same intranasal oxytocin treatments.

Finally, we also assessed social behaviors of dysbindin mutant and wild-type mice towards familiar littermate mice. To this aim, we adopted our recently developed machine-learning-based tracking algorithm that is able to automatically detect social behaviors of multiple interacting mice. Again, we found that untreated and vehicle-treated Dys knockout mice showed a significant reduction in the time spent in social interaction, as was also observed in the previous setting. This deficit was again rescued by chronic intranasal oxytocin.

These results indicate that acute, as well as chronic intranasal oxytocin treatments could rescue the social deficits produced by a schizophrenia-relevant reduction of dysbindin-1 levels. Importantly, these results highlight that while a prolonged over-stimulation of a 'healthy' oxytocinergic system might result in detrimental effects in social abilities, the opposite is true for a 'diseased' system.