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Effects of oxytocin on early development, exploratory and social behavior of rats chronically exposed to sodium valproate

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Background

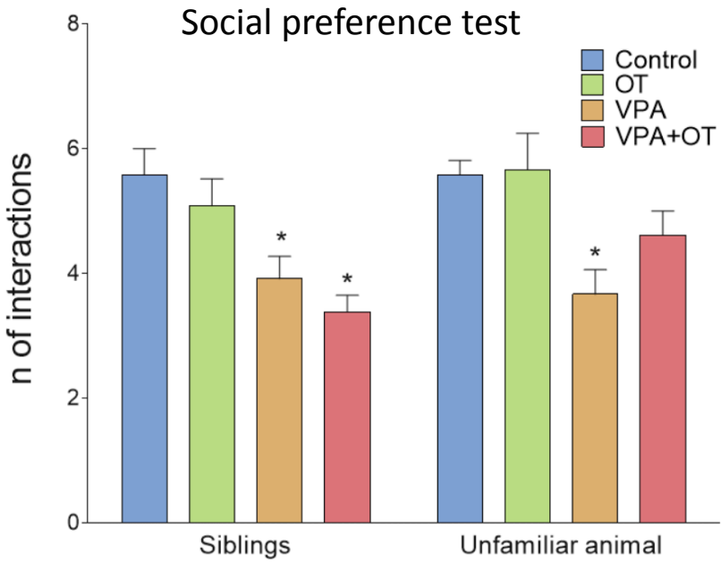
Oxytocin (OT) system is a promising target for neuropsychological disorders as autism spectrum disorders, associated with disrupted socialization and “social anxiety”, decreased empathy manifestations and inadequate social reactions (detachment, aggressiveness etc.). To assess potential therapeutic properties of OT on ASD-like symptoms in animals we choose a model, based on postnatal administration of valproic acid (VPA), chronically. Postnatal administration of VPA known to reproduce wide range of behavioral abnormalities, similar to ASD: disrupted sensory gating, decreased manifestations of social behavior and anxiety, thereby, “valproate models” are validated and widely used as models of ASD.
A significant number of studies are focused on effects of acute OT administration in behavioral models of ASD, while in described work we used chronic intranasal administration of OT on 1-14 PND in animals, chronically exposed to valproic acid (VPA). Since rodents are born in an altricial state, nervous system of rat pups 1-14 PND go through phase of rapid maturation with high level of synaptogenesis, approximately as human bran on the third trimester of prenatal development [1]. Thus we administrated OT during the period of early development to reduce possible pathological effects of VPA on brain development.

Experimental design

Results

«Negative» and «neutral» OT outcome

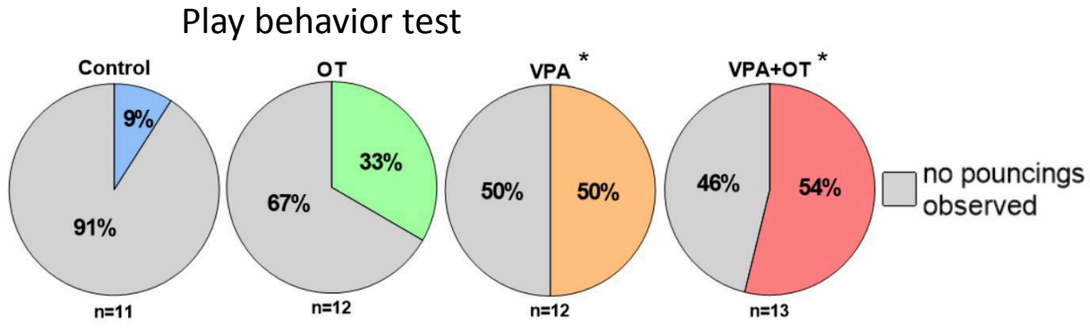
Social preference test



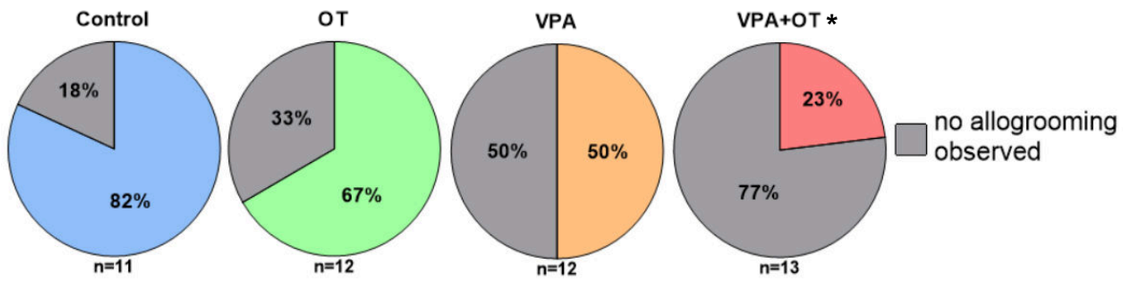
In social preference test animals exposed to VPA demonstrated a reduction in social interactions: they showed decreased frequency of visiting section with a sibling and unfamiliar animal, and in play behavior, they acted more aggressively than control animals. Animals from VPA-OT group spent less time interacting with another animal, and, similarly to VPA group, demonstrated more aggressive way of playing with less mutual grooming and tactile activity. Moreover, control-OT animals had a slight reduction of play behavior.

Play behavior test

Percent of observed acts of pouncing in the group

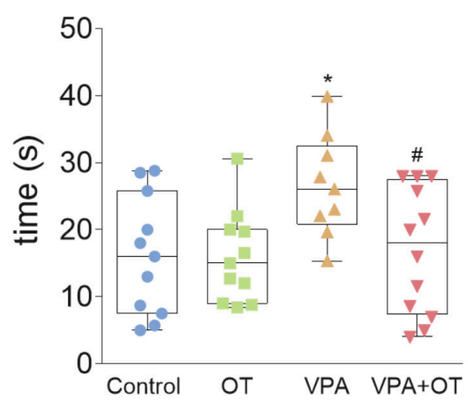


Percent of observed acts of allogrooming in the group



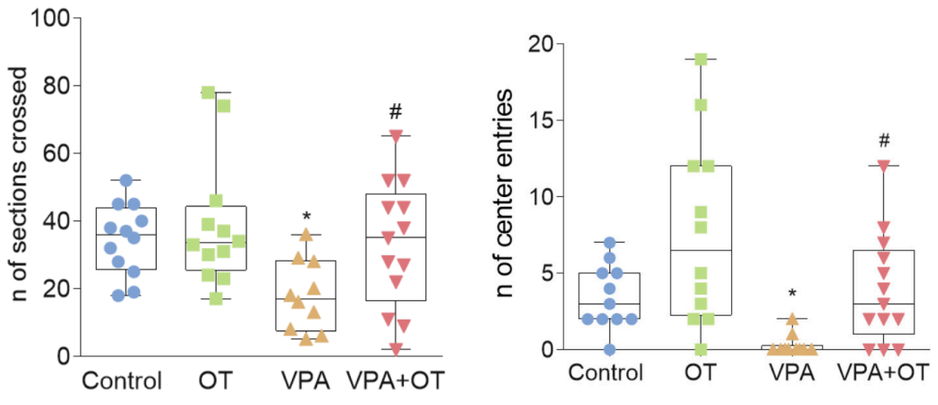
«Positive» OT outcome

Latency of circle crossing in gait-reflex test



Rats exposed to VPA showed retarded gaiting reflex in early postnatal period.
VPA-animals with chronic OT administration did not differ from control group in this test.

Locomotor activity and anxiety in open field test



Rats exposed to VPA showed decreased locomotor activity and increased anxiety. VPA-animals with chronic OT administration did not differ from control group in this test.

*** - p<0,05 - represent significant differences vs. Control group**
 # - p<0,05 - represent significant differences vs. VPA group
In “open field” and ”social preference ” tests – one-way ANOVA, Sidak’s multiple comparison test
In “play behavior” test – Fisher’s exact test

Discussion

VPA produce hyperexitatory effects in the brain and enhanced sensory gating, which can provide an explanation for increased anxiety and delayed social interaction [1]. Divergent social effects of chronic intranasal oxytocin administration already were described in mice. It can be explained by a reduction of OT receptors throughout the brain, induced by chronic administration of the peptide [2]. Therefore, animals exposed to VPA already had a deficiency of social interaction, consequently, OT administration aggravates this condition. Anxiolytic activity of OT provides by inhibition of amygdala activity [3] and reduction of stress-hormones release [4]. This study leads to the conclusion that postnatal VPA model provides opportunities to assess autistic-like features as anxiety and social interaction impairment and to challenge oxytocin usage in the treatment of autism spectrum disorders.

Conclusions

- Chronic postnatal VPA administration induced disruption in locomotor gating reflex, anxiety and decreased locomotor activity in open field, reduced social interaction in “social preference test”. Furthermore aggressive behavior significantly enhanced in VPA group.
- Oxytocin diminished anxiety of animals exposed to VPA, and partially enhanced maturing of motor reflexes; however, oxytocin increased the reduction of social behavior observed in VPA animals.
- Oxytocin did not have an influence on locomotion and exploration of control animals but reduced social interaction of control rats.

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The authors declare no conflict of interests