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Oxytocin, GABA, and dopamine interplay in autism

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Oxytocin plays an important role in brain development and is associated with various neurotransmitter systems in the brain. Abnormalities in the production, secretion, and distribution of oxytocin in the brain, at least during some stages of the development, are critical for the pathogenesis of neuropsychiatric diseases, particularly in the autism spectrum disorder. The etiology of autism includes changes in local sensory and dopaminergic areas of the brain, which are also supplied by the hypothalamic sources of oxytocin. It is very important to understand their mutual relationship. In this review, the relationship of oxytocin with several components of the dopaminergic system, gamma-aminobutyric acid (GABA) inhibitory neurotransmission and their alterations in the autism spectrum disorder is discussed. Special attention has been paid to the results describing a reduced expression of inhibitory GABAergic markers in the brain in the context of dopaminergic areas in various models of autism. It is presumed that the altered GABAergic neurotransmission, due to the absence or dysfunction of oxytocin at certain developmental stages, disinhibits the dopaminergic signaling and contributes to the autism symptoms.

Key words: oxytocin, GABA, dopamine, neurite outgrowth, autism

The autism spectrum disorder (ASD) is represented by a group of altered neurodevelopmental conditions that develop with a wide range of symptoms and severities. Several studies have claimed that there is a common pathology in autism and schizophrenia that links alterations in dopaminergic system, which is influenced by GABAergic neurons providing them with inhibitory or disinhibition effects. Many review articles have also emphasized that the peripheral oxytocin levels may be reduced in ASD. This review is focused on the interrelationship interpretation of OXY with components of the dopaminergic system, GABA inhibitory neurotransmission, and their altered neurodevelopmental conditions.

Oxytocin functions

Oxytocin (OXY) has been regarded as a reproductive hormone important for birth and lactation, but recently is widely recognized as a neurotransmitter and neuromodulator in the brain (Rigney et al. 2022; Althammer 2023). Moreover, the roles of OXY, its receptors, and their alterations are linked to the pathogenesis of neurodevelopmental diseases, which are currently being extensively studied (Yamasue and Domes 2018; John and Jaeggi 2021).

OXY is involved in the recognition of social stimuli and the regulation of social behavior in humans, rodents, and number of other animals (Ferguson et al. 2001; Gordon et al. 2011; Rigney et al. 2022). It is known that in the brain, the majority of OXY is produced in the certain hypothalamic nuclei (hypothalamic paraventricular nucleus-PVN, hypothalamic supraoptic nucleus-SON, and their accessory nuclei), from where it is distributed to many areas of the brain. It is also widely accepted that OXY is transported in the brain along axons and dendrites indicating that it is released in different modes from

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somata, dendritic stores, or synaptic varicosities (Tobin et al. 2011; Grinevich and Ludwig 2021). These conditions give a relatively large variability of possible changes or abnormalities that can lead to more or less serious neurodevelopmental consequences.

OXY is distributed to sensory areas of the brain, which are essential for the social relevant stimuli distinguishing, but it is also transported to dopaminergic areas of the brain, which are important for strengthening the meaning of social stimuli (Lefevre et al. 2021; Inoue et al. 2022). It is not surprising that disorders of social behavior have complex causes, the common denominators, of which are not easy to identify. At least in animal models, it has been confirmed that OXY in the sensory areas of the brain has acute impact on the discrimination of socially relevant stimuli (Lukas et al. 2013; Oettl et al. 2016). Moreover, the release of OXY in the dopaminergic areas of the brain may influence the value of social stimuli (Nunes et al. 2021; Inoue et al. 2022; Jing and Shan 2023). A number of studies links the OXY system to many other neurotransmitter systems including gamma-aminobutyric acid (GABA)-producing neurons with modulation of their inhibitory activity (Baskerville and Douglas 2010; Bowen et al. 2015; Smith et al. 2016; Maniezzi et al. 2021).

Modulation of OXY and/or GABA affects social behavior. It is assumed that their interplay is very important for different brain regions (Li et al. 2019). Therefore, abnormalities in the production or secretion of OXY, at least during some stages of the development, are very critical for the pathogenesis of neuropsychiatric diseases, which include a disorder of social perception or the interpretation of social stimuli. It is evident that changes in the OXY system in the brain interfere with the neurobiological parameters underlying social behavior.

Autism spectrum disorder

The recent meta-analyses and review studies have emphasized that the peripheral OXY levels may be reduced in autism spectrum disorder (ASD) (Yamasue and Domes 2018; John and Jaeggi 2021). ASD represents a group of altered neurodevelopmental conditions that develop with a wide range of symptoms and severities. Classic symptoms of autism cover language development delay, social deficits, and repetitive behavior. Nevertheless, autistic patients often suffer from hyper- or hypo-reactivity to sensory inputs or unusual interests in some sensory aspects of the environment (Grapel et al. 2015). In general, autistic patients have alterations in the processing of social and nonsocial stimuli, which results in specific interests accompanied by restrictive and repetitive patterns of behavior (Babinska et al. 2017; Clements et al. 2018).

It is very likely that the differences in the processing of stimuli in the sensory neural pathways in the neurotypical population and autistic patients depend on the connectivity of the individual brain areas. Although the sensory nerve pathways are relatively well-known and well-described, their development or alterations of the connections with individual brain areas that process sensory stimuli is far from to being clarified. It is assumed that the motivation of autistic patients to interact with stimuli from the external environment is significantly different from that of the neurotypical population. Several studies have confirmed that deficits in perception, attention, and integration of sensory information in autistic patients and autism-like animal models are related to alterations in brain dopaminergic regions (Fernandez et al. 2018; Kosillo and Bateup 2021; Dougnon and Matsui 2022). Moreover, local sensory and dopaminergic areas of the brain are very strongly influenced by GABA inhibitory neurotransmission (Roberts et al. 2021). It has been known for a long time that both dopamine and GABA neurotransmitter systems interact with OXY in the regulation of social behavior (Baskerville and Douglas 2010). If there are certain abnormalities in any of these components, one of the possible consequences is social perception disorder that is a part of ASD.

Dopaminergic system in autism

Dopaminergic pathways in the brain are involved in numerous physiological processes including movement, cognition, executive functions, reward, and motivation (Nieoullon and Coquerel 2003; Salamone et al. 2016; Zhou et al. 2023). Anatomically, the dopaminergic system in the brain is formed by the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways (Mehta et al. 2022). However, recent studies have revealed relatively large heterogeneity in the dopaminergic cell populations and their connections with various other neurotransmitter systems (Gordon-Fennell and Stuber 2021; Gaertner et al. 2022). In particular, dopaminergic projections from the ventral tegmental area (VTA) to the striatal accumbens nucleus (mesolimbic pathway) or cortical dopaminergic projections (mesocortical pathway) are important for reward processing, cognitive processes or sensory gating. Therefore, they may be important in the regulation of social behavior (Kosillo and Bateup 2021).

In the context of the subject of the present review, it is essential to note that the most recent study has demonstrated that OXY plays a crucial role in the prosocial behavior and so-called gating of social reward in these dopaminergic brain areas (Hung et al. 2017). Moreover, electrophysiological recordings of dopaminergic neurons indicate that both administering OXY and using optogenetic methods to activate OXY-releasing terminals are effective in increasing neuronal activity in the VTA. However, this action leads to a decrease in the activity within the substantia nigra pars compacta (Xiao et al. 2017).

In connection with social motivation and reward processing, the association between alterations in the activity of dopaminergic nerve pathways and the etiology of autism is well known with dopamine hypothesis of autism (Paval and Miclutia 2021; Paval 2023). Deregulation of dopaminergic pathways could contribute to the behavioral manifestations of ASD, while there are several studies involving patients as well as animal models that characterize changes in the individual dopaminergic sub-areas such as the VTA as well as the striatum (Manz et al. 2019; Brandenburg et al. 2020; Kosillo and Bateup 2021). Some studies have claimed that there is a common pathology in autism and schizophrenia that links alterations in dopaminergic system (Eyles et al. 2012). These dopaminergic neurons are influenced by GABAergic neurons, which provide them with inhibitory or disinhibitory inputs (Rahaman et al. 2022). Recent studies described that the sources of GABA in the dopaminergic regions of the brain are relatively heterogeneous and include VTA and the rostromedial tegmental area (Soden et al. 2020; Miranda-Barrientos et al. 2021).

GABA alterations in dopaminergic areas in autism

GABA is a neurotransmitter that plays an important role in regulating the brain activity, cognition, and behavior. There is an enormous amount of evidence that points to a relatively abundant distribution of GABA in many areas of the brain. In addition, GABA along with activation of its receptors has proved link to the development of the nervous system (Bolneo et al. 2022). It is now relatively well known how GABAergic interneurons proliferate, migrate, and reach their final destinations within the cortical and subcortical regions of the brain as it has been shown, based on several genetic, epigenetic, and neural activity aspects (Zhu et al. 1999; Tang et al. 2021). GABA has long been considered to be the main inhibitory neurotransmitter in the adult and developed brain. However, it is necessary to keep in mind that in the early stages of the development, GABA acts as an excitatory neurotransmitter and it can potentially influence many processes including the development of dopaminergic nerve pathways.

Changes in the GABAergic system or its developmental abnormalities in the dopaminergic brain areas can lead to many pathological consequences and neuropsychiatric diseases (Reynolds and Flores 2021; Yu et al. 2021). More concretely, alterations in GABAergic system have been implicated in the pathophysiology of autism (Zhao et al. 2022).

The dysfunction of the GABAergic system has been described in several animal models of ASD and some of them involve dopaminergic areas (Chao et al. 2010; Martella et al. 2018). These studies point to the reduction of GABAergic signaling in dopaminergic areas, which can be related to stereotypic and restricted autistic behaviors. Moreover, many other studies suggest that disruption in GABAergic system may contribute to the core features of the disorder, such as deficits in social communication, restricted interests, and repetitive behaviors (Coghlan et al. 2012; DeMayo et al. 2021). GABA disruption has also been associated with impairments in language and memory as well as difficulties in motor coordination (Coghlan et al. 2012; Barnes et al. 2015; Umesawa et al. 2020). In addition to behavioral investigations, imaging techniques are important when involving human subjects. The recent neuroimaging studies point to an association between disturbed levels of the GABA in autistic patients and, at the same time, abnormalities in neural circuits (Fung et al. 2021; Maier et al. 2022).

Specific changes, a decrease or an increase in GABA levels, depend on the analyzed brain areas. The focus on dopaminergic brain areas and at the same time the analysis of GABA-producing inhibitory neurons is methodologically and technically complex. The other issue represents resolution and the signal detection limits of imaging techniques. The authors of above-mentioned studies themselves have pointed an inconsistency in the findings and their functional association with GABA metabolism or the imbalance of excitatory and/or inhibitory signals in the brain. Another recent study, using transcriptomics and neuroimaging datasets from ASD subjects, points to the fact that the spatial distribution of GABAergic receptors correlates with atypical connectivity, especially regarding the processing of sensory information (Babij et al. 2023).

From the perspective of experimental studies, an important finding is that GABA cell-type-specific changes in social reward dopaminergic circuits were found in mouse autism model (Bariselli et al. 2016). Some recent findings have indicated that changes in inhibitory interneurons in dopaminergic areas or abnormalities in the production or function of GABA or its receptors in dopaminergic projection areas, play an important role in the autism models (Yoo et al. 2018; Bukatova et al. 2021). These studies point to the fact that abnormalities in the GABAergic system are complex at several levels.

In individuals with autism, it has been found that the GABA system is deregulated, which can lead to an increased level of excitation in the brain. This increased excitation can manifest itself in the form of repetitive behaviors, hyperactivity, and aggression (Marotta et al. 2020). The increased level of excitation in the brain in autism depends on the degree of depolarization of individual neurons. Many areas of the brain differ greatly in the composition of neuronal populations and thus the production of neurotransmitters, including GABA. In this context, one possible line of evidence in the pathogenesis of autism, is a change in the generation of GABAergic interneurons or alteration in their differentiation during development. Several studies have shown a decrease in the number of GABAergic neurons or a disturbance in the differentiation of GABAergic interneurons during the development in an animal model of autism (Chao et al. 2010; Sgado et al. 2013; Zhao et al. 2022). Our studies have also shown reduced expression of inhibitory GABAergic markers and GABA receptor subunits in the dopaminergic brain areas in the mouse model of autism (Bukatova et al. 2021).

Another interesting concept is the connection between GABAergic Purkinje neurons in the cerebellum and dopaminergic areas in the VTA. The recent study has suggested that reduction in GABAergic pathway enzymes in the cerebellum may affect the activity of VTA neurons and consequently the social behavior in the mouse model of autism (Ma and Kwan 2022).

Complexity of GABA alterations in autism

The sources of GABA in the brain are heterogeneous and very diverse, therefore, it is necessary to remember that more areas of the brain are involved. Findings coming from the animal autism models have shown that the GABA transition from excitatory to inhibitory is postnatally altered (Tyzio et al. 2014; Roux et al. 2018). Recent studies have also pointed to the fact that strengthening as well as the weakening of the GABAergic neurotransmission can be related to the etiology of autism (Dickinson et al. 2016; Yang et al. 2021). However, at the same time, excitatory-inhibitory imbalance in autistic patients or animal autism models does not have to be accompanied by changes in GABA levels (Horder et al. 2018). Many results associated with measurements of excitatory-inhibitory balance in autism models are controversial and there is an intensive discussion about them, mainly in relation to the methodological differences in the measurements of individual parameters (Dickinson et al. 2016). The most recent findings have shown that the imbalance in neurotransmission in autism is a consequence of developmental changes in several genes that determine the ion channels in the inhibitory neurons (Berto et al. 2022). It is likely that the role of excitatory/inhibitory imbalance in individual areas of the brain or nerve pathways is very important for understanding the changes of GABA in autism. It should be kept in mind that abnormalities in GABAergic neurotransmission can mean disturbances in the inhibitory nerve circuits or atypical or desynchronized activities of individual pathways (Kana et al. 2007; Hanaie et al. 2018).

OXY, GABA, and dopamine interplay: impact on the neuronal development

OXY directly interferes with GABAergic activity. One of recent studies has demonstrated that OXY release enhances the activity of VTA dopaminergic neurons, but indirectly inhibits them via the local GABAergic neurons (Xiao et al. 2017). Others have shown that OXY enhances the function of GABA by binding to a specific type of $GABA_A$ receptors (Bowen et al. 2015; Smith et al. 2016). Although the direct mechanisms and relationships between OXY and GABAergic receptors are not completely clear, these studies indicate that OXY may affect the GABAergic neuronal activity and local GABA release. It has been suggested that OXY increases both phasic and tonic GABAergic currents (Maniezzi et al. 2021). These authors explain the GABA effects by the distribution of perisynaptic GABAergic receptors and their biophysical features, which generate slower inhibitory postsynaptic potentials. When GABA release is massive, the neurotransmitter also binds to the extrasynaptic GABA receptors resulting in an increase of the tonic GABAergic current (Maniezzi et al. 2021).

OXY receptors are also related to dopamine receptors, whereby some studies have evidenced their mutual dimerization (Romero-Fernandez et al. 2013; Amato et al. 2023). These interconnections represent important conditions for the role of OXY in the regulation of both GABAergic and dopaminergic pathways (Figure 1). As mentioned above, the development of dopaminergic midbrain areas, including the VTA and their projection areas such as the accumbens nucleus, play a role in establishing the social behavior (Bissonette and Roesch 2016). Therefore, even more significant may be the relationships between OXY, GABA, and dopamine during the early stages of development.

GABA receptor activation in the early stages of neuronal network formation in the central nervous system leads to depolarization of the plasma membrane, which results in the stimulation of neurite growth and impact on the synaptogenesis (Wu and Sun 2015; Peerboom and Wierenga 2021). The processes of neurogenesis, neurite growth, and synapse formation, especially in the postnatal period of the life, are regulated by many factors and neuropeptides including OXY (Bakos et al. 2016; Lestanova et al. 2016; Eiden et al. 2022).

It is likely that the interaction of OXY with GABA signaling in the early stages of the development of the nervous system can participate in the regulation of neurite growth. The decrease in the depolarizing activity of GABA in the developing brain and the loss of its effect on the formation of neurites can be replaced by more specific effects of OXY. Although this hypothesis has to be proven, the effects of OXY on neurite growth have already been repeatedly demonstrated. For example, OXY affects the neurite outgrowth of primary hippocampal neurons and SH-SY5Y cells, which are used as an *in vitro* model of dopaminergic neurons (Zatkova et al. 2018; Reichova et al. 2021). It is also known that the timing of the change in GABA function from depolarizing to inhibitory is regulated by OXY (Leonzino et al. 2016). A shift in the action of GABA from excitatory to inhibitory is caused by a decrease in the intracellular Cl^- concentration, resulting in hyperpolarization and inhibition. The decrease in intracellular Cl^- concentration is mainly due to the delayed expression of a K-Cl co-transporter (KCC2) (Ben-Ari 2002; Leonzino et al. 2016). This postnatal GABA shift regulated by OXY is important for the maturation and function of the neuronal circuits. In principle, the effect of OXY is highly dependent on the distribution of OXY receptors and their subsequent signaling cascades (Busnelli and Chini 2018). For this reason, coupling the signaling cascades of the OXY receptor with the following morphological changes in neurons could be very important.

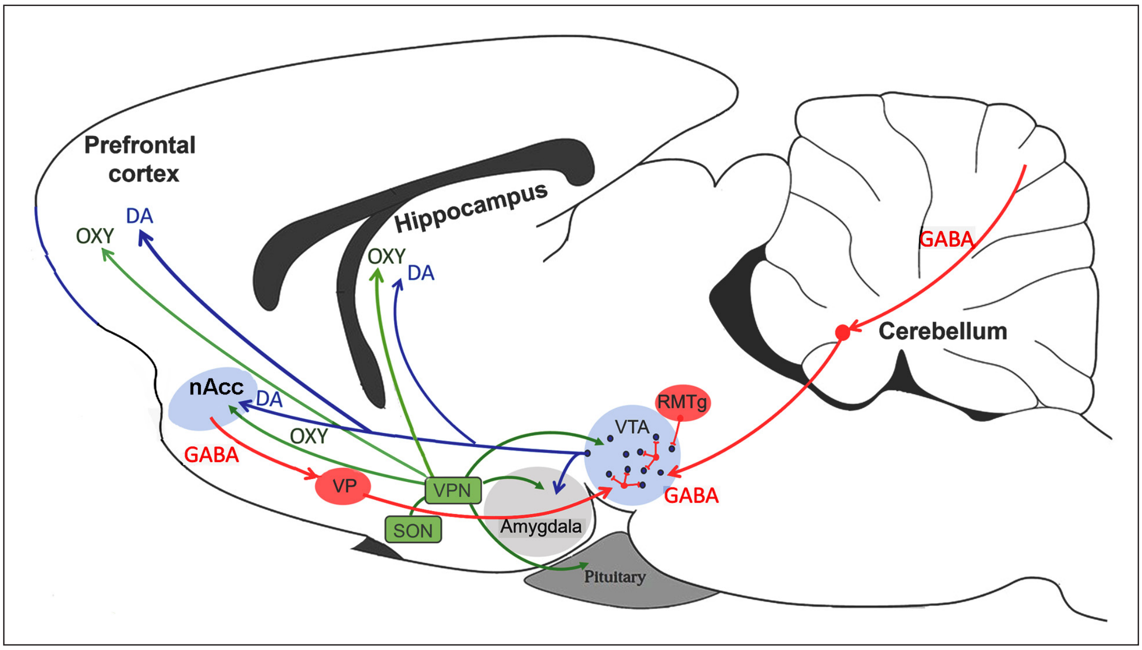

Figure 1. An anatomical scheme (sagittal view) of the rat neural pathways involved in the regulation of social behavior. Relationships of oxytocin (OXY) pathways (green) with several components of the dopaminergic (DA) system (blue) and gamma-aminobutyric acid (GABA) inhibitory neurons (red). Abbreviations: nAcc – accumbens nucleus; PVN – hypothalamic paraventricular nucleus RMTg – rostromedial tegmental nucleus; SON – hypothalamic supraoptic nucleus; VP – ventral pallidum; VTA – ventral tegmental area (modified according to Paxinos and Watson 1997).

One of the possibilities, although still not fully clarified, is the effect of OXY on the endoplasmic reticulum or intracellular calcium with the subsequent induction of neurite growth (Zatkova et al. 2018; Havranek et al. 2023). In addition to the effects of OXY on neurite growth, some studies have also indicated that activation of the OXY receptor modulates the expression of synaptic proteins with the potential to influence postnatal synaptogenesis (Zatkova et al. 2019; Reichova et al. 2021). The effect of OXY on the local GABAergic neurons in dopaminergic areas of the brain can potentially affect development of social behavior. It has been found an association between alteration in OXY producing neurons and development of dopaminergic neurons with a functional impact on the social behavior in zebrafish (Nunes et al. 2021). Therefore, the possibility that OXY recruits GABAergic interneurons and affects the dopaminergic regions of the brain is important. Failure of normal OXY production or its function during brain development may be associated with the pathogenesis of several neurodevelopmental diseases, from which ASD is one of the most relevant.

Conclusion

GABAergic neurons affect the development and function of dopaminergic brain areas. However, they can also be under the influence of OXY, which is involved in neurogenesis and neuritogenesis. Altered GABAergic neurotransmission, due to the absence or dysfunction of OXY at certain developmental stages, may disinhibit the dopaminergic signaling and contribute to the autism symptoms. Thus, the OXY, GABA and dopamine interplay in the development of the central nervous system as well as the alterations in the GABAergic system in autism could be helpful in the resolving of certain medical treatments.

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