Physiology and Pharmacology 29 (2025) 63-73
Experimental Research Article

The effects of oxytocin on anxiety and depression in the prenatal stress context in 3-NP injected rats

Fariba Khodagholi[1], Ali Maleki[1], Fereshteh Motamedi[1], Fatemeh Nasehi[2], Arman Zeinaddini Meymand[2], Forough Foolad[3], Mehdi Moslemi[1*]

1. Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. NeuroBiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Department of Physiology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

ABSTRACT

Introduction: Oxytocin (OXT) has attracted attention as an effective treatment for anxiety and depression. It also can prevent 3-NP-induced anxiety and depression. However, the effects of OXT can be context-dependent. The objective of this investigation was to explore how prenatal stress (PS) context modulates the effectiveness of OXT in mitigating anxiety- and depression-like behaviors induced by 3-NP, as well as alterations in antioxidant levels.

Methods: The dams underwent PS or PS+3NP treatments, and the effects of OXT on the anxiety-like behavior, and depression-like behavior in these treatment groups were evaluated via elevated plus maze and forced swim test respectively. The reduced glutathione (GSH) level was also measured in the striatum, hippocampus, prefrontal cortex, and amygdala.

Results: We found that PS per se and 3-NP in the context of PS increased anxiety and depression. These groups also had lower GSH levels in the brain regions examined. OXT pretreatment markedly increased the behavioral changes in the PS group and ameliorated the antioxidant changes. However, OXT pretreatment could not improve 3-NP-induced behavioral and GSH level changes in the context of PS.

Conclusion: These findings indicate that OXT improves PS-induced anxiety and depression and the antioxidant level changes, but we found that PS per se thwarts the protective effects of OXT in the 3-NP-induced anxiety and depression.

Keywords:
Oxytocin
3-NP
Prenatal stress
Depression
Anxiety

Introduction

Oxytocin (OXT) is suggested as an effective agent for treating anxiety and depression (Arletti and Bertolini 1987; Uvnas-Moberg et al., 1994; Yoshida et al., 2009). It also prevents anxiety and depression from beginning in Huntington's disease (HD) (Khodagholi et al., 2022). The context of individual differences is a factor that modulates the influences of OXT treatment (Bartz et al., 2011; Ma et al., 2018). For example, the effects of OXT on social sharing and social support seeking are context-dependent in human (Cardoso et al., 2016; Ma et al., 2018). The context-dependent effect of OXT is also seen in rats (e.g., for helping behavior) (Yamagishi et al., 2020).

* Corresponding author: Mehdi Moslemi, mehdimoslemi83@yahoo.com
Received 18 April 2024; Revised from 14 August 2024; Accepted 15 August 2024

Citation: Fariba Khodagholi, Ali Maleki, Fereshteh Motamedi, Fatemeh Nasehi, Arman Zeinaddini Meymand, Forough Foolad, Mehdi Moslemi. The Effects of Oxytocin on Anxiety and Depression in the Prenatal Stress Context in 3-NP injected Rats. Physiology and Pharmacology 2025; 29: 63-73. http://dx.doi.org/10.61186/phypha.29.1.63

Describing the factors that influence response to treatment can improve the success rate of OXT treatment. One source of individual difference is rooted back in the prenatal period, in which stress can leave long-lasting effects and even cause anxiety and depression (Mairesse et al., 2015; Vallee et al., 1997). On the other side, maternal stress during pregnancy can be regarded as a hard early life experience through making stable changes in epigenetic factors. Its effect can be observed and reflected in both behavioral and neurobiological factors (Amici et al., 2022; Nolvi et al., 2023).

Therefore, rats with prenatal stress (PS) potentially respond differently to OXT compared to the control group. The impact of PS and sex on the preventive role of OXT in HD-induced cognitive impairment has been previously described (Moslemi et al., 2020) and in addition, we reported that OXT has a protective effect against 3-NP induced anxiety and depression (Khodagholi et al., 2022), However, it is not clear if PS modulates the effect of OXT on preventing anxiety and depression from beginning in HD. Due to the autosomal dominant inheritance of HD and a major overlap between the onset age of its symptoms and the childbearing age (Duff et al., 2007; Roos 2010), there is a high possibility that these symptoms in either parent become a source of stress for the unborn children (Kinsella and Monk 2009). Therefore, describing the interactions between PS and OXT treatment in terms of preventing psychiatric symptoms of HD can improve patient selection for this treatment.

It has been shown that PS disturbs the function of different brain regions and causes a variety of neurological disorders in the offspring (Charil et al., 2010). PS impairs neurotransmissions (Wu et al., 2024) including the serotonergic pathway, and develops anxiety and depression in adulthood (Pereira-Figueiredo et al., 2014). PS also causes other neurologic symptoms including memory and cognitive dysfunctions (Charil et al., 2010). Additionally, similar symptoms like anxiety and depression-like behaviors, memory, and cognitive dysfunctions are also observed in HD (Walker 2007). As mentioned above we revealed that PS affects the protective influence of OXT on HD-induces cognitive impairment, however, the exact relationship between PS and HD needs further investigation.

HD is an inherited neurodegenerative condition marked by progressive movement impairments (de Boo et al., 1997), which inevitably leads to premature death (Solberg et al., 2018). In recent decades, the discovery of HD mutation and the interference of resultant protein in biological functions have partly unfolded the pathophysiology of HD (Sari 2011). HD is characterized by atrophy of basal ganglia and predominantly the neuron loss in the striatum (Walker 2007). In the subcellular pathophysiology, it is believed that the defective function of mitochondria is the core abnormality in HD (Costa and Scorrano 2012; Kim et al., 2010). The central role of mitochondria enables scientists to develop animal models of HD and test novel treatments.

3-Nitropropionic acid (3-NP) is a popular molecule replicating HD in animal models (Borlongan et al., 1997). It has been demonstrated that 3-NP interferes with the normal function of complex II enzymes in neural mitochondria and leads to a cascade of dysregulations like decreased adenosine triphosphate (ATP) production, oxidative stress with increased levels of reactive oxygen species (ROS), elevated concentration of intracellular Ca^{2+}, and ultimately cell death (Liot et al., 2009). These damages occur in broad neural structures (Hamilton and Gould 1987), although striatal and cortical lesions have attracted more attention in previous studies (Beal et al., 1993; La Fontaine et al., 2000) and it is well-known that 3-NP causes a selective degeneration in the striatum, therefore mimics HD pathophysiology (Borlongan et al., 1997; Kumar et al., 2012). It is noteworthy that the neurologic pathology starts long before the evident motor symptoms and manifests itself with psychiatric disorders, including anxiety and depression (Duff et al., 2007; Julien et al., 2007).

These symptoms restrict the daily living activities of patients (Hamilton et al., 2003), lead to their placement in nursing facilities (Wheelock et al., 2003), and generally impose an enormous burden on them (Paoli et al., 2017). 3-NP injected rats mimic the anxiety- and depression-like behaviors of HD (Khodagholi et al., 2022). Preventing the initiation of these psychiatric symptoms can enhance the patients' quality of life and may be more beneficial than treating the evident symptoms.

We previously showed that OXT can prevent 3-NP-induced anxiety and depression (Khodagholi et al., 2022) and since the OXT effects are context-dependent (Moslemi et al., 2020), herein, the objective of this investigation was to assess how OXT pretreatment impacts anxiety and depression in the rats in the context of PS and compare this effect between these rats and those

who have been injected with 3-NP in addition to PS. We also described the antioxidant level impacts of maternal stress per se and their response to OXT. In this regard, the level of reduced glutathione (GSH) was assessed in the striatum (ST), hippocampus (HIP), prefrontal cortex (PFC), and amygdala (AMY).

Materials and Methods

Experimental Design

The Animal Care Committee of Shahid Beheshti University of Medical Sciences authorized all experimental procedures and the experiments were carried out with permission from the institution's Ethics Committee (Ethics code: IR.SBMU.PHNS.REC.1398.159). Furthermore, the animals were treated in accordance with the guidelines provided by the National Institutes of Health for the Care and Use of Laboratory Animals, ensuring compliance with the specified protocols.

Adult Wistar rats were purchased from the Tehran Pasteur Institute and were kept under conventional laboratory conditions. Following mating, pregnant rats were assigned randomly to either the non-stressed or stressed groups. Modified prenatal stress was applied to the stressed group using the Pereira-Figueiredo et al. protocol by using a cylindrical restrainer (Pereira-Figueiredo et al., 2014). Following birth, all mother rats and their pups were left undisturbed in their cages until weaning at 21 days of age and were kept to adulthood. Afterward, male offspring of either stressed or non-stressed mothers were separated and divided into the following groups: 1-Control group whose mothers were not exposed to the stressor; 2-Stress group whose mothers were exposed to the stressor; 3-Sress+3-NP group that received 3-NP (20 mg/kg/day, i.p.) over a period of five consecutive days (Brouillet 2014) and their mothers were exposed to the stressor; 4-Stress + OXT group who received single-dose intracerebroventricular (ICV) injection of OXT (10 µg) and their mothers were exposed to the stressor; 5-Stress+3-NP+OXT group who received OXT twenty-four hours before the 3-NP treatment, and their mothers were subjected to the stressor. The OXT was injected at the age of 90 days and 3-NP was injected from the age of 91 days.

Behavioral assessments

Elevated plus maze (EPM): As described previously by Pellow (Pellow et al., 1985), the maze comprised two closed and two open arms. The enclosed arms were bordered by walls. The central part connected these four arms and was open around. The apparatus was raised to a height of 50 cm from the floor and was illuminated from the top. After placing the subjects in the central part of the maze, their behaviors were recorded for five minutes, recording the time spent in the open arm, closed arm, and center zone, and they were analyzed later.

Forced swim test (FST): To investigate depression-like behaviors, the FST was used (Porsolt et al., 1978). The animals were subjected to the experiment for two days. On each day, the animals were compelled to engage in forced swimming within a plastic cylinder containing clean water at a depth of 35 cm and maintained at the temperature of 24 °C. The animals were unable to exit the cylinder or provide support by touching the bottom of the cylinder. On the initial day, rats were subjected to fifteen minutes of pre-exposure to the test environment, and on the subsequent day, the subjects had to swim in the cylindrical chamber for five minutes. On the second day, the total duration of struggling, swimming, and immobility time were recorded.

Reduced glutathione level assay

The protein amount was determined in different samples based on the method of Bradford (Bradford 1976). GSH level was measured in all selected brain areas according to the Ellman method (Ellman 1959). Briefly, prepared samples were mixed with 10% trichloroacetic acid and centrifuged. Ellman reagent including DTNB was introduced into the supernatant and the absorbance was then assessed at 412 nm.

Statistical analysis

Experimental data were analyzed, after testing the normal distribution of data, using the conventional one-way analysis of variance (ANOVA) followed by multiple comparisons post hoc Tukey's comparison test. The results are presented as mean values standard error of the mean (SEM) with the numbers that have been mentioned in the figure legends. Statistically significant values were: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.0001$.

Results

The effect of Oxytocin on PS and 3-NP+PS induced anxiety-like behaviors in rats

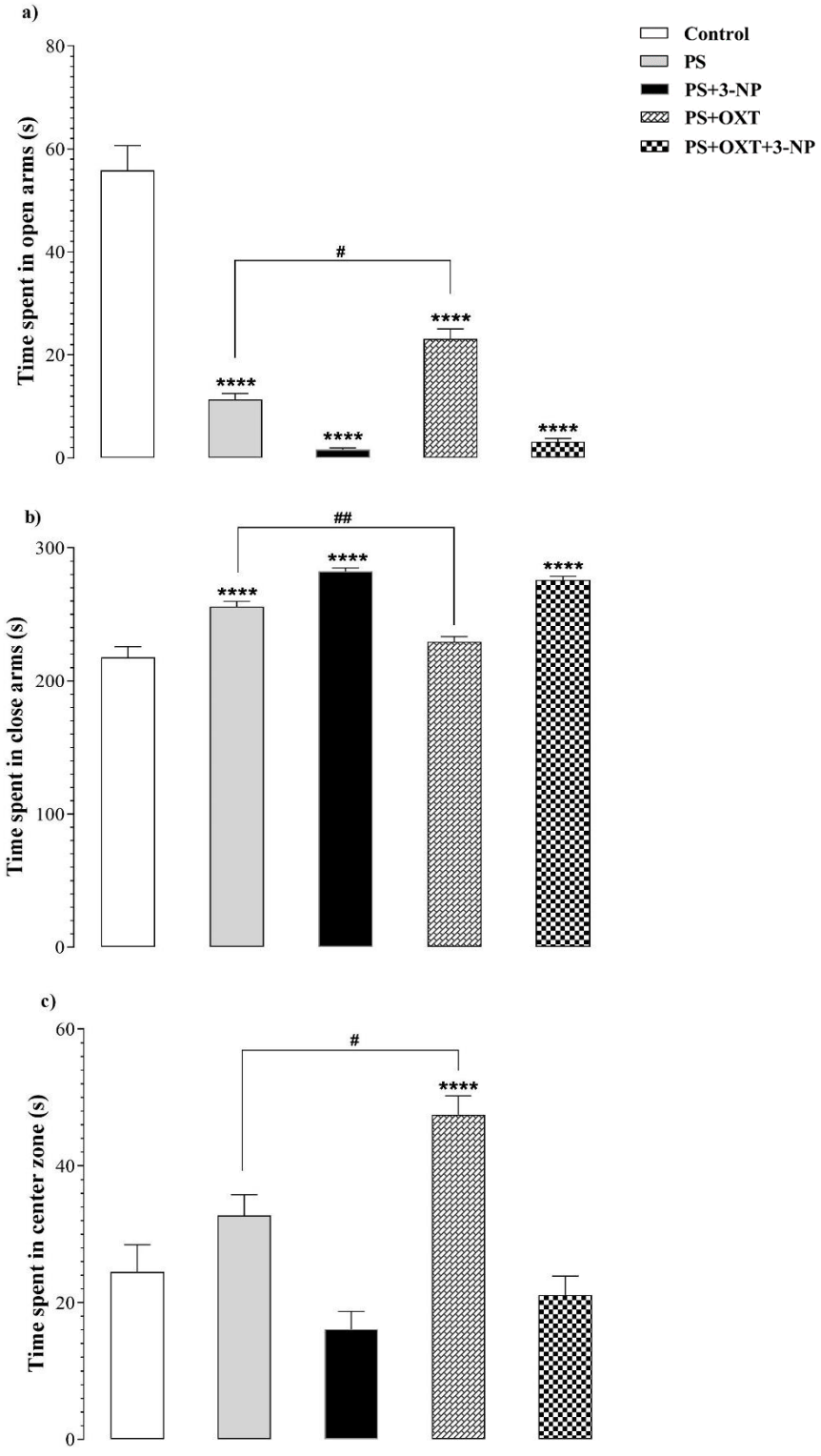

FIGURE 1. The behaviors of different groups of rats in the elevated plus maze (EPM). **a** The time spent in the open arms, **b** the time spent in the closed arms, and **c** the time spent in the center zone compartment. Data are presented as mean ± SEM (n=8/group). PS prenatal stress, OXT Oxytocin, 3-NP 3-Nitropropionic acid.

The one-way ANOVA analysis conducted on the data from elevated plus-maze revealed significant variations among the groups (Fig. 1) [$F_{(4, 35)} = 86.99$, the p-value was less than < 0.0001 for the duration spent in open arms (Fig. 1a), $F_{(4, 35)} = 36.50$, the p-value was less than < 0.0001 for the duration spent in close arms (Fig. 1b),

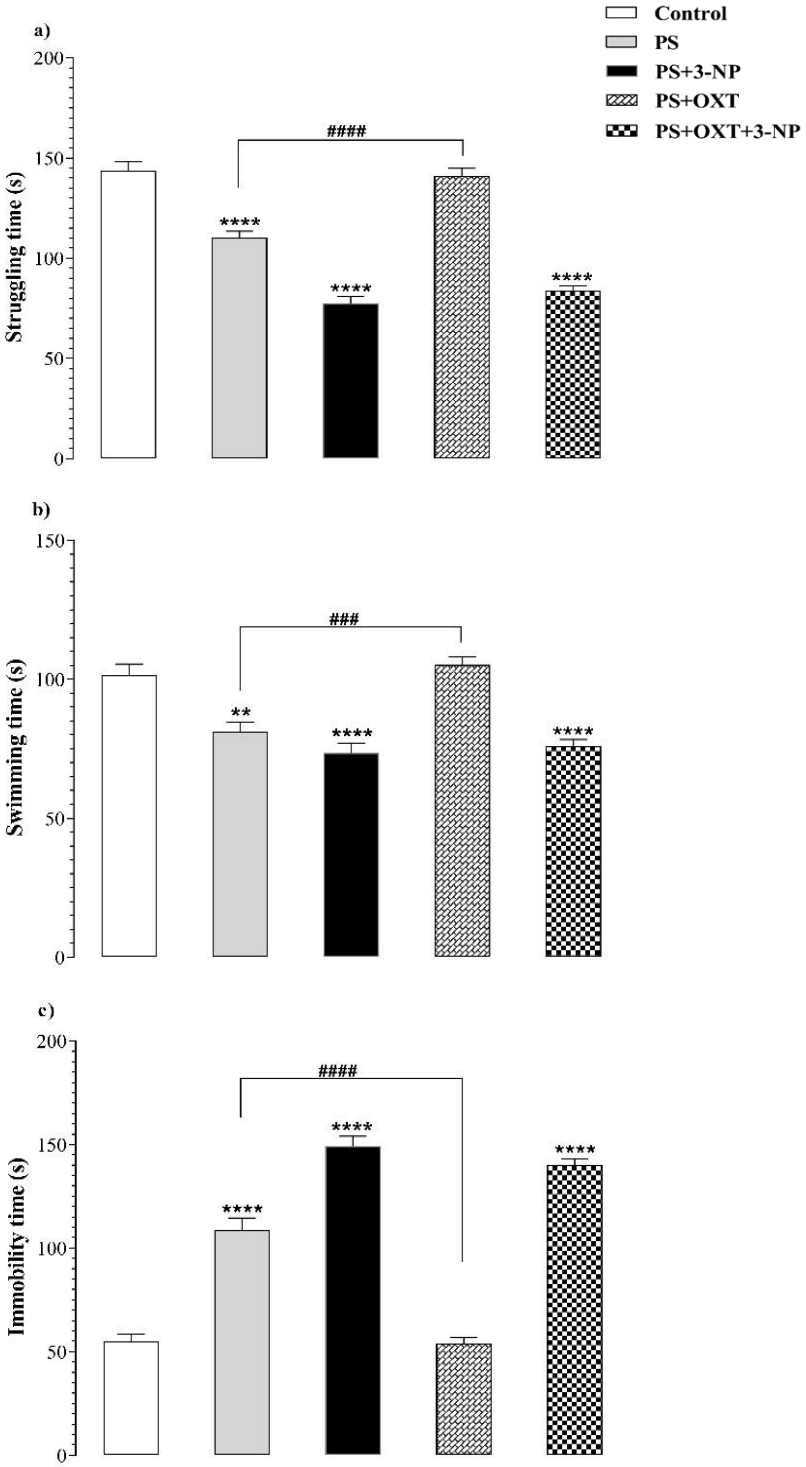

FIGURE 2. The behaviors of different groups of rats in the forced swim test (FST). **a** The struggling time, **b** swimming time, and **c** immobility time. Data are presented as mean ± SEM (n=8/group). PS prenatal stress, OXT Oxytocin, 3-NP 3-Nitropropionic acid.

and $F_{(4, 35)} = 15.99$, the p-value was less than< 0.0001 for the duration spent in the center zone (Fig. 1c)]. Post hoc analysis using Tukey's test indicated that both PS and PS+3-NP decreased the time rats spent in the open arms ($ps < 0.0001$), and led to a notable increase in the duration within the closed arms ($ps < 0.0001$) when contrasted with the control group.

The administration of OXT notably ameliorated PS-induced anxiety-like behaviors in the EPM in rats. PS+OXT group spent more time in open arms ($p < 0.05$)

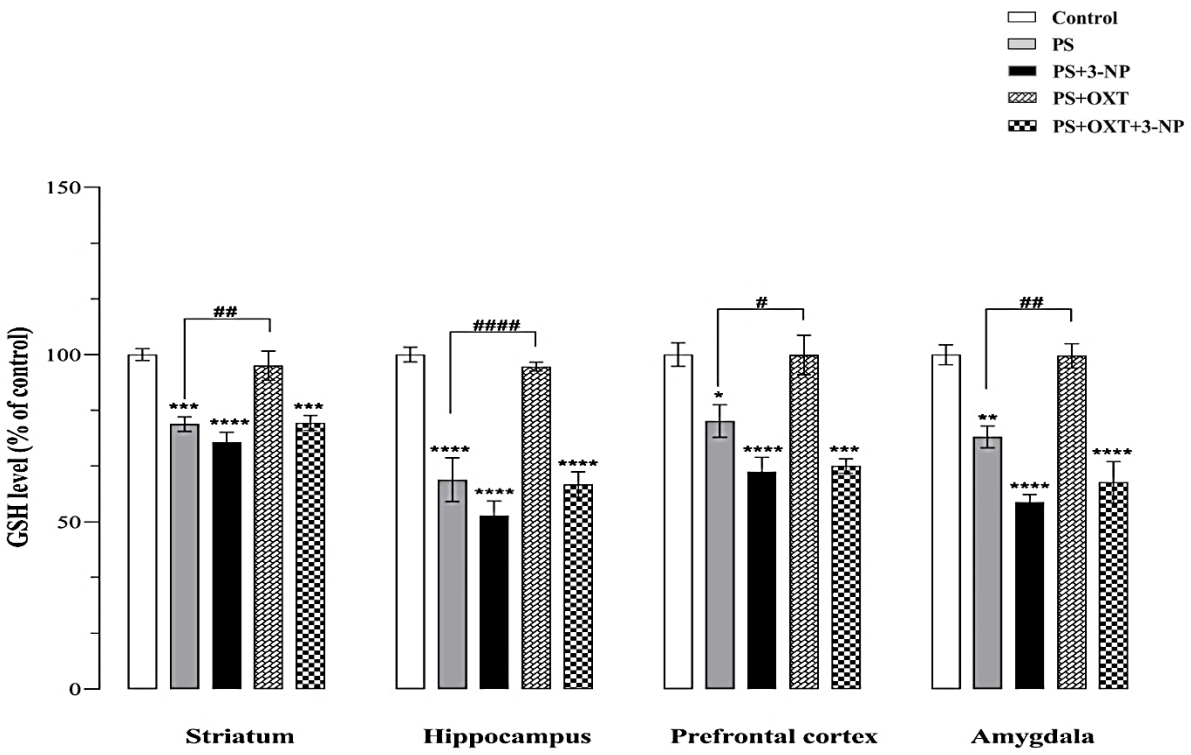

FIGURE 3. The relative level of GSH in the striatum, hippocampus, prefrontal cortex, and amygdala of rats. (n = 6/group). PS prenatal stress, OXT Oxytocin, 3-NP 3-Nitropropionic acid.

and the center zone ($p < 0.05$), and less time in closed arms ($p < 0.01$) compared to the PS group. On the contrary, OXT administration had no significant protective effects on the anxiety-like behaviors in EPM caused by 3-NP in the context of PS, and the behaviors of the PS+3-NP+OXT group and PS+3-NP group were not significantly different.

The effect of Oxytocin on PS and 3-NP+PS induced depression-like behaviors

Data analysis by one-way ANOVA test in the forced swim test showed significant differences among the groups [$F_{(4, 35)} = 75.18$, $p < 0.0001$ for the struggling time (Fig. 2a), $F_{(4, 35)} = 19.16$, $p < 0.0001$ for the swimming time (Fig. 2b), $F_{(4, 35)} = 121.4$, $p < 0.0001$ for the immobility time (Fig. 2c)].

Post hoc analysis (Tukey's test) showed that PS and PS+3-NP led to the development of severe depression-like behaviors in the forced swim test. In rats PS decreased struggling ($p < 0.0001$), swimming time ($p < 0.01$), and increased immobility duration ($p < 0.0001$) compared to the controls. OXT administration significantly increased struggling ($p < 0.0001$), and swimming time ($p < 0.001$) and significantly decreased immobility duration ($p < 0.0001$) in the PS+OXT group compared to the PS group.

Similar to the PS group, the PS+3-NP group showed depression-like behaviors in the FST. Rats in the PS+3-NP group had decreased struggling time (*ps* <0.0001), swimming time ($p < 0.0001$), and increased immobility duration ($p < 0.0001$) compared to the controls. However, OXT pretreatment in the PS+3-NP+OXT group did not alleviate depressive-like behaviors induced by 3-NP in the context of PS when compared to the PS+3-NP group in the rats.

The effect of Oxytocin on the reduced levels of GSH induced by PS and 3-NP+PS in various brain regions of rats

As depicted in Fig. 3, the findings revealed substantial disparities among groups regarding the GSH levels across the investigated brain regions [$F_{(4, 25)} = 16.91$, $p < 0.0001$ in the ST; $F_{(4, 25)} = 29.66$, $p < 0.0001$ in the HIP; $F_{(4, 25)} = 15.46$, $p < 0.0001$ in the PFC; and $F_{(4, 25)} = 27.93$, $p < 0.0001$ in the AMY].

PS group had significantly lower GSH levels in the

investigated brain regions compared to the controls [the ST (p-value was less than< 0.001), HIP (p-value was less than< 0.0001), PFC (p-value was less than< 0.05), and AMY (p-value was less than< 0.01)]. Similarly, the PS+3-NP group had significantly lower GSH levels compared to the controls [the ST (p-value was less than< 0.0001), HIP (p-value was less than< 0.0001), PFC (p-value was less than 0.0001), and AMY (p-value was less than< 0.0001) of rats].

OXT administration to those with prenatal stress increased the GSH level across all brain regions compared with the PS group [ST (p <0.01), HIP (*p* <0.0001), PFC (*p* <0.05), and AMY (p <0.01)]. However, the protective effects of OXT pretreatment on rats of PS+3-NP were more limited.

Discussion

This study evaluated the behavioral and antioxidant level changes following PS and PS+3-NP and questioned whether intracranial injection of OXT can prevent these changes. Another major objective of this investigation was to ascertain whether PS has any modulatory influence on the efficacy of OXT in preventing anxiety and depression induced by 3-NP. We chose ST, HIP, PFC, and AMY because of their extensive involvement in the pathophysiology of depression (Drevets 2000; Drevets et al., 2008) and anxiety (Charney and Deutch 1996; Engin and Treit 2007). Among the recently developed treatments for depression and anxiety, OXT has demonstrated promising advantages (De Cagna et al., 2019). This prompts inquiries into the effectiveness of OXT in the PS setting and its potential to mitigate anxiety and depression induced by HD in the context of prenatally stressed rats.

We found that rats with PS had higher anxiety- and depression-like behaviors. This is similar to previous findings (Mairesse et al., 2015; Morley-Fletcher et al., 2011; Vallee et al., 1997). In contrast, there are some reports that do not confirm the severe effect of PS (Sickmann et al., 2015; Van den Hove et al., 2014). It might be due to differences between the prepubertal stage and adulthood or differences between rat strains or study settings. Of course, it should not be neglected that early, middle, and late gestational stress duration as well as the severity, and kind of exposed stress can show different results.

Several mechanisms have been proposed explaining how prenatal stress influences adulthood anxiety and depression. One of the most important mechanisms is increased oxidative stress (Dowell et al., 2019). According to previous findings, prenatal stress increases the generation of neuronal nitric oxide synthase (Zhu et al., 2004) and ROS, while diminishing antioxidant capacity and GSH level in the brain (Bernhardt et al., 2017; Cao et al., 2014). These changes cause a disparity between oxidants and antioxidants, leading to oxidative stress. We found that rats with PS had consistently lower levels of GSH in their ST, HIP, PFC, and AMY. These changes show that GSH is reduced in combat with the adverse effects of ROS. The oxidative stress causes increased lipid peroxidation, DNA damage, and protein misfolding (Dowell et al., 2019). More importantly, it damages mitochondrial DNA (mtDNA) which interrupts mitochondrial bioenergetic function and deteriorates oxidative stress (Siddiqui et al., 2012). In addition, it has been demonstrated that prenatal treatment with N-acetylcysteine, the precursor of GSH, attenuates the behavioral and oxidative impacts of PS (Bernhardt et al., 2017).

The majority of these PS-induced changes can be reversed by the effects of OXT on the brain. At the top of these effects is the ability of OXT to stimulate the synthesis of ATP in the mitochondria. Two main pathways can be proposed for this boosting effect. First, OXT increases the intramitochondrial transport of Ca^{2+} (Gravina et al., 2011) and stimulates ATP synthesis (Griffiths and Rutter 2009). Second, OXT opens the mitochondrial ATP-dependent potassium (mitoKATP) channel which is involved in regulating mitochondrial energetic function and volume, and increases ATP synthesis (Paggio et al., 2019), decreases ROS formation (Bertero and Maack 2018), and ultimately brings cytoprotective effects (O'Rourke 2004). In this context, our findings indicate that OXT significantly alleviated anxiety- and depression-like behaviors in prenatally stressed rats and increased GSH levels in ST, HIP, PFC, and AMY of rats. It shows that OXT improves oxidative state by enhancing antioxidant capacity. It can be a putative explanation and part of the mechanism involved in the observed behavior as well.

A recently published study demonstrated the anxiolytic effect of OXT in rats that had prior exposure to PS (Maikoo et al., 2022). Although the conditions of stress exposure in terms of timing and duration differed from our experimental design, we found their findings intriguing. Their study revealed an increase in endog-

enous OXT secretion following OXT injection. They suggested that OXT might contribute to the increased secretion of opioids, proposing it as a potential underlying mechanism. Importantly, they also observed that centrally administered OXT had a more pronounced effect compared to systemic administration, which aligns with our chosen route of administration. Overall, our results provide further support for the protective effect of OXT against stress, particularly PS.

The biological changes in the models of HD overlap with those after PS, although they may not have identical intensities. In the HD models, whether the disease is replicated by transgenic animals or injection of 3-NP, the main pathology is increased oxidative stress and ROS (Liot et al., 2009; Siddiqui et al., 2012). It can cause changes like increased lipid peroxidation, nuclear DNA damage, protein misfolding, and eventually cell death (Dowell et al., 2019). Most importantly, oxidative stress damages mtDNA, which is highly prone to damage due to lower protective supports. It also impairs mtDNA repairs and decreases spare respiratory capacity (Liot et al., 2009; Siddiqui et al., 2012). We found that rats of the PS+3-NP group had higher anxiety- and depression-like behaviors in comparison to the controls, although not significant from PS-exposed rats. We also found that the levels of GSH in ST, HIP, PFC, and AMY were significantly lower in this group compared to controls. However, unlike the effective role of OXT on prenatal stress, when PS was applied as a context, its protective effect was suppressed.

We found that in the 3-NP injected rats with prior prenatal stress, administration of OXT could not improve the anxiety- and depression-like behaviors. It also did not normalize the changes in the level of GSH in either studied brain region. It means that the increased excitation led to oxidative stress. The present findings on the results of the 3-NP+PS group raise the concern that these effects could be due to 3-NP itself without the effects of PS, but as we previously revealed the ICV injection of OXT before 3-NP injection (i.p.) can significantly prevent anxiety and depression in adult Wistar rats (Khodagholi et al., 2022), it therefore seems that the context of PS has a role in preventing the protective effects of OXT against 3-NP toxicity. However, it is possible that chronic treatment with OXT or treatment with a higher dose reverses 3-NP-induced changes, even in those with PS. Additional behavioral and biochemical studies could confirm or reject this hypothesis.

Conclusion

Taken together, we conclude that PS induces anxiety- and depression-like behaviors and widely affects GSH levels across the brain. 3-NP treatment in the context of PS has similar patterns of behavioral and antioxidant consequences. Treatment with OXT reverses PS-induced changes. However, PS prevents the protective properties of OXT pretreatment on 3-NP-induced behavioral and antioxidant changes. We showed that the protective effects of OXT on 3-NP-induced mood disorders depend on the context.

References

Amici F, Röder S, Kiess W, Borte M, Zenclussen A C, Widdig A, et al. Maternal stress, child behavior and the promotive role of older siblings. BMC Public Health 2022; 22: 863. https://doi.org/10.1186/s12889-022-13261-2

Arletti R, Bertolini A. Oxytocin acts as an antidepressant in two animal models of depression. Life Sci 1987; 41: 1725-1730. https://doi.org/10.1016/0024-3205(87)90600-X

Bartz J A, Zaki J, Bolger N, Ochsner K N. Social effects of oxytocin in humans: context and person matter. Trends Cogn Sci 2011; 15: 301-309. https://doi.org/10.1016/j.tics.2011.05.002

Beal M F, Brouillet E, Jenkins B G, Ferrante R J, Kowall N W, Miller J M, et al. Neurochemical and histologic characterization of striatal excitotoxic lesions produced by the mitochondrial toxin 3-nitropropionic acid. J Neurosci 1993; 13: 4181-4192. https://doi.org/10.1523/JNEUROSCI.13-10-04181.1993

Bernhardt L K, Madhyastha S, Bairy L, Kishore A. Status of the brain antioxidant system at different growing periods after prenatal stress and N -acetyl cysteine administration. Folia Neuropathol 2017; 55: 38-48. https://doi.org/10.5114/fn.2017.66712

Bertero E, Maack C. Calcium signaling and reactive oxygen species in mitochondria. Circ Res 2018; 122: 1460-1478. https://doi.org/10.1161/CIRCRESAHA.118.310082

Borlongan C V, Koutouzis T K, Sanberg P R. 3-Nitropropionic acid animal model and Huntington's disease. Neuroscience & Biobehavioral Reviews 1997; 21: 289-293. https://doi.org/10.1016/S0149-7634(96)00027-9

Bradford M M. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Analytical biochemistry 1976;

72: 248-254. https://doi.org/10.1016/0003-2697(76)90527-3

Brouillet E. The 3-NP model of striatal neurodegeneration. Current Protocols in Neuroscience 2014; 67: 1-9. https: // doi.org/10.1002/0471142301.ns0948s67

Cao K, Zheng A, Xu J, Li H, Liu J, Peng Y, et al. AMPK activation prevents prenatal stress-induced cognitive impairment: modulation of mitochondrial content and oxidative stress. Free Radic Biol Med 2014; 75: 156-166. https://doi.org/10.1016/j.freeradbiomed.2014.07.029

Cardoso C, Valkanas H, Serravalle L, Ellenbogen M A. Oxytocin and social context moderate social support seeking in women during negative memory recall. Psychoneuroendocrinology 2016; 70: 63-69. https://doi.org/10.1016/j.psyneuen.2016.05.001

Charil A, Laplante D P, Vaillancourt C, King S. Prenatal stress and brain development. Brain research reviews 2010; 65: 56-79. https://doi.org/10.1016/j.brainresrev.2010.06.002

Charney D S, Deutch A. A functional neuroanatomy of anxiety and fear: implications for the pathophysiology and treatment of anxiety disorders. Crit Rev Neurobiol 1996; 10: 419-446. https://doi.org/10.1615/CritRevNeurobiol.v10.i3-4.70

Costa V, Scorrano L. Shaping the role of mitochondria in the pathogenesis of Huntington's disease. EMBO J 2012; 31: 1853-1564. https://doi.org/10.1038/emboj.2012.65

de Boo G M, Tibben A, Lanser J B, Jennekens-Schinkel A, Hermans J, Maat-Kievit A, et al. Early cognitive and motor symptoms in identified carriers of the gene for Huntington disease. Arch Neurol 1997; 54: 1353-1357. https://doi.org/10.1001/archneur.1997.00550230030012

De Cagna F, Fusar-Poli L, Damiani S, Rocchetti M, Giovanna G, Mori A, et al. The role of intranasal oxytocin in anxiety and depressive disorders: a systematic review of randomized controlled trials. Clin Psychopharmacol Neurosci 2019; 17: 1-11. https://doi.org/10.9758/cpn.2019.17.1.1

Dowell J, Elser B A, Schroeder R E, Stevens H E. Cellular stress mechanisms of prenatal maternal stress: Heat shock factors and oxidative stress. Neurosci Lett 2019; 709: 134368. https://doi.org/10.1016/j.neulet.2019.134368

Drevets W C. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Prog Brain Res 2000; 126: 413-431. https://doi.org/10.1016/S0079-6123(00)26027-5

Drevets W C, Price J L, Furey M L. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct 2008; 213: 93-118. https://doi.org/10.1007/s00429-008-0189-x

Duff K, Paulsen J S, Beglinger L J, Langbehn D R, Stout J C, Predict H D I o t H S G. Psychiatric symptoms in Huntington's disease before diagnosis: the predict-HD study. Biol Psychiatry 2007; 62: 1341-1346. https://doi.org/10.1016/j.biopsych.2006.11.034

Ellman G L. Tissue sulfhydryl groups. Archives of biochemistry and biophysics 1959; 82: 70-77. https://doi.org/10.1016/0003-9861(59)90090-6

Engin E, Treit D. The role of hippocampus in anxiety: intracerebral infusion studies. Behav Pharmacol 2007; 18: 365-374. https://doi.org/10.1097/FBP.0b013e3282de7929

Gravina F S, Jobling P, Kerr K P, de Oliveira R B, Parkington H C, van Helden D F. Oxytocin depolarizes mitochondria in isolated myometrial cells. Exp Physiol 2011; 96: 949-956. https://doi.org/10.1113/expphysiol.2011.058388

Griffiths E J, Rutter G A. Mitochondrial calcium as a key regulator of mitochondrial ATP production in mammalian cells. Biochim Biophys Acta 2009; 1787: 1324-1333. https://doi.org/10.1016/j.bbabio.2009.01.019

Hamilton B F, Gould D H. Nature and distribution of brain lesions in rats intoxicated with 3-nitropropionic acid: a type of hypoxic (energy deficient) brain damage. Acta Neuropathol 1987; 72: 286-297. https://doi.org/10.1007/BF00691103

Hamilton J M, Salmon D P, Corey-Bloom J, Gamst A, Paulsen J S, Jerkins S, et al. Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry 2003; 74: 120-122. https://doi.org/10.1136/jnnp.74.1.120

Julien C L, Thompson J C, Wild S, Yardumian P, Snowden J S, Turner G, et al. Psychiatric disorders in preclinical Huntington's disease. J Neurol Neurosurg Psychiatry 2007; 78: 939-943. https://doi.org/10.1136/jnnp.2006.103309

Khodagholi F, Maleki A, Motamedi F, Mousavi M A, Rafiei S, Moslemi M. Oxytocin prevents the development of 3-NP-induced anxiety and depression in male and female rats: possible interaction of OXTR and mGluR2. Cellular and Molecular Neurobiology 2022: 1-19.

Kim J, Moody J P, Edgerly C K, Bordiuk O L, Cormier K, Smith K, et al. Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. Hum Mol Genet 2010; 19: 3919-3935. https://doi.org/10.1093/hmg/ddq306

Kinsella M T, Monk C. Impact of maternal stress, depression and anxiety on fetal neurobehavioral development. Clin Obstet Gynecol 2009; 52: 425-440. https://doi.org/10.1097/GRF.0b013e3181b52df1

Kumar P, Kalonia H, Kumar A. Possible GABAergic mechanism in the neuroprotective effect of gabapentin and lamotrigine against 3-nitropropionic acid induced neurotoxicity. European journal of pharmacology 2012; 674: 265-274. https://doi.org/10.1016/j.ejphar.2011.11.030

La Fontaine M A, Geddes J W, Banks A, Butterfield D A. 3-nitropropionic acid induced in vivo protein oxidation in striatal and cortical synaptosomes: insights into Huntington's disease. Brain Res 2000; 858: 356-362. https://doi.org/10.1016/S0006-8993(00)01948-X

Liot G, Bossy B, Lubitz S, Kushnareva Y, Sejbuk N, Bossy-Wetzel E. Complex II inhibition by 3-NP causes mitochondrial fragmentation and neuronal cell death via an NMDA- and ROS-dependent pathway. Cell Death Differ 2009; 16: 899-909. https://doi.org/10.1038/cdd.2009.22

Ma X, Zhao W, Luo R, Zhou F, Geng Y, Xu L, et al. Sex- and context-dependent effects of oxytocin on social sharing. Neuroimage 2018; 183: 62-72. https://doi.org/10.1016/j.neuroimage.2018.08.004

Maikoo S, Wilkins A, Qulu L. The effect of oxytocin and an enriched environment on anxiety-like behaviour and corticosterone levels in a prenatally stressed febrile seizure rat model. IBRO Neuroscience Reports 2022; 13: 47-56. https://doi.org/10.1016/j.ibneur.2022.05.001

Mairesse J, Gatta E, Reynaert M L, Marrocco J, Morley-Fletcher S, Soichot M, et al. Activation of presynaptic oxytocin receptors enhances glutamate release in the ventral hippocampus of prenatally restraint stressed rats. Psychoneuroendocrinology 2015; 62: 36-46. https://doi.org/10.1016/j.psyneuen.2015.07.005

Morley-Fletcher S, Mairesse J, Soumier A, Banasr M, Fagioli F, Gabriel C, et al. Chronic agomelatine treatment corrects behavioral, cellular, and biochemical abnormalities induced by prenatal stress in rats. Psychopharmacology (Berl) 2011; 217: 301-313. https://doi.org/10.1007/s00213-011-2280-x

Moslemi M, Khodagholi F, Asadi S, Rafiei S, Motamedi F. Oxytocin protects against 3-NP induced learning and memory impairment in rats: Sex differences in behavioral and molecular responses to the context of prenatal stress. Behav Brain Res 2020; 379: 112354. https://doi.org/10.1016/j.bbr.2019.112354

Nolvi S, Merz E C, Kataja E-L, Parsons C E. Prenatal stress and the developing brain: Postnatal environments promoting resilience. Biological Psychiatry 2023; 93: 942-952. https://doi.org/10.1016/j.biopsych.2022.11.023

O'Rourke B. Evidence for mitochondrial K+ channels and their role in cardioprotection. Circ Res 2004; 94: 420-432. https://doi.org/10.1161/01.RES.0000117583.66950.43

Paggio A, Checchetto V, Campo A, Menabo R, Di Marco G, Di Lisa F, et al. Identification of an ATP-sensitive potassium channel in mitochondria. Nature 2019; 572: 609-613. https://doi.org/10.1038/s41586-019-1498-3

Paoli R A, Botturi A, Ciammola A, Silani V, Prunas C, Lucchiari C, et al. Neuropsychiatric Burden in Huntington's Disease. Brain Sci 2017; 7. https://doi.org/10.3390/brainsci7060067

Pellow S, Chopin P, File S E, Briley M. Validation of open:-closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods 1985; 14: 149-167. https://doi.org/10.1016/0165-0270(85)90031-7

Pereira-Figueiredo I, Sancho C, Carro J, Castellano O, Lopez D E. The effects of sertraline administration from adolescence to adulthood on physiological and emotional development in prenatally stressed rats of both sexes. Front Behav Neurosci 2014; 8: 260. https://doi.org/10.3389/fnbeh.2014.00260

Porsolt R D, Anton G, Blavet N, Jalfre M. Behavioural despair in rats: a new model sensitive to antidepressant treatments. Eur J Pharmacol 1978; 47: 379-391. https://doi.org/10.1016/0014-2999(78)90118-8

Roos R A. Huntington's disease: a clinical review. Orphanet J Rare Dis 2010; 5: 40. https://doi.org/10.1186/1750-1172-5-40

Sari Y. Huntington's Disease: From mutant huntingtin protein to neurotrophic factor therapy. Int J Biomed Sci 2011; 7: 89-100. https://doi.org/10.59566/IJBS.2011.7089

Sickmann H, Arentzen T, Dyrby T, Plath N, Kristensen M. Prenatal stress produces sex-specific changes in depression-like behavior in rats: implications for increased vulnerability in females. Journal of Developmental Origins of Health and Disease 2015; 6: 462-474. https://doi.org/10.1017/S2040174415001282

Siddiqui A, Rivera-Sanchez S, Castro Mdel R, Acevedo-Torres K, Rane A, Torres-Ramos C A, et al. Mitochondrial DNA damage is associated with reduced mitochondrial bioenergetics in Huntington's disease. Free Radic Biol Med 2012; 53: 1478-1488. https://doi.org/10.1016/j.freeradbiomed.2012.06.008

Solberg O K, Filkukova P, Frich J C, Feragen K J B. Age at death and causes of death in patients with Huntington disease in norway in 1986-2015. J Huntingtons Dis 2018; 7: 77-86. https://doi.org/10.3233/JHD-170270

Uvnas-Moberg K, Ahlenius S, Hillegaart V, Alster P. High doses of oxytocin cause sedation and low doses cause an

anxiolytic-like effect in male rats. Pharmacol Biochem Behav 1994; 49: 101-106. https://doi.org/10.1016/0091-3057(94)90462-6

Vallee M, Mayo W, Dellu F, Le Moal M, Simon H, Maccari S. Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. J Neurosci 1997; 17: 2626-2636. https://doi.org/10.1523/JNEUROSCI.17-07-02626.1997

Van den Hove D, Leibold N, Strackx E, Martinez-Claros M, Lesch K, Steinbusch H, et al. Prenatal stress and subsequent exposure to chronic mild stress in rats; interdependent effects on emotional behavior and the serotonergic system. European Neuropsychopharmacology 2014; 24: 595-607. https://doi.org/10.1016/j.euroneuro.2013.09.006

Walker F O. Huntington's disease. The Lancet 2007; 369: 218-228. https://doi.org/10.1016/S0140-6736(07)60111-1

Wheelock V L, Tempkin T, Marder K, Nance M, Myers R H, Zhao H, et al. Predictors of nursing home placement in Huntington disease. Neurology 2003; 60: 998-1001. https://doi.org/10.1212/01.WNL.0000052992.58107.67

Wu Y, De Asis-Cruz J, Limperopoulos C. Brain structural and functional outcomes in the offspring of women experiencing psychological distress during pregnancy. Molecular Psychiatry 2024: 1-18. https://doi.org/10.1038/s41380-024-02449-0

Yamagishi A, Okada M, Masuda M, Sato N. Oxytocin administration modulates rats' helping behavior depending on social context. Neurosci Res 2020; 153: 56-61. https://doi.org/10.1016/j.neures.2019.04.001

Yoshida M, Takayanagi Y, Inoue K, Kimura T, Young L J, Onaka T, et al. Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons in mice. J Neurosci 2009; 29: 2259-2271. https://doi.org/10.1523/JNEUROSCI.5593-08.2009

Zhu Z, Li X, Chen W, Zhao Y, Li H, Qing C, et al. Prenatal stress causes gender-dependent neuronal loss and oxidative stress in rat hippocampus. J Neurosci Res 2004; 78: 837-844. https://doi.org/10.1002/jnr.20338