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Makale Türü Sistematik Derleme

Oxytocin and vasopressin levels in maltreated children: A systematic review

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ABSTRACT

Objective: The present study aimed to focus on the neurobiological basis of childhood maltreatment. **Method:** A systematic review approach was followed by focusing on the possible links among oxytocin, vasopressin, and child maltreatment. The review included research based on data examining the role that being exposed to any kind of maltreatment during childhood plays. The review was not limited to a specific period. However, reviews, systematic reviews, dissertations, congress papers, and studies in languages other than Turkish and English were excluded. The search was concentrated on the Web of Science, PubMed, Science Direct, Scopus, EBSCO Host, and Google Scholar databases including the keyword combinations. **Results:** The review between December 2021 and April 2022 revealed 49 research studies that reported data from a total of 13979 participants (3981 children and adolescents, 9998 adults). Studies reviewed contained demographically diverse samples from a wide range of Western cultural contexts. **Conclusion:** The findings are promising in terms of clinical implications as there are considerable links between OXT and child maltreatment. However, more studies are needed to understand the nature of these links.

Keywords: Oxytocin, vasopressin, child abuse

İstismara ve ihmale maruz çocuklarda oksitosin ve vazopressin seviyeleri: Sistematik derleme

ÖZET

Amaç: Bu çalışma, çocukluk çağındaki istismarın ve ihmalin nörobiyolojik temellerine odaklanmayı amaçlamıştır. **Yöntem:** Çalışma oksitosin (OXT), vazopresin (VP) ve çocuk çağı istismarı ve ihmali arasındaki olası ilişkilere odaklanılarak sistematik bir inceleme yaklaşımı ile gerçekleştirilmiştir. Çalışmaya, çocukluk çağında maruz kalınan kötü muamelenin rolünü inceleyen araştırmalar dahil edilmiş; dahil edilen araştırmalarda herhangi tarih sınırlamasına gidilmemiştir. Ancak Türkçe ve İngilizce dışındaki dillerdeki derlemeler, sistematik derlemeler, tezler, kongre bildirileri ve çalışmalar kapsam dışı tutulmuştur. İnceleme, anahtar kelimelerin çeşitli kombinasyonlarını içermiş ve Web of Science, PubMed, Science Direct, Scopus, EBSCO Host ve Google Scholar veri tabanlarında yoğunlaşmıştır. **Bulgular:** Araştırma kapsamında yapılan sistematik incelemede toplam 13979 (3981 çocuk ve 9998 yetişkin) katılımcıdan elde edilen 49 araştırmaya ulaşılmıştır. İncelenen çalışmaların, ağırlıklı olarak Batı toplumlarında olmak üzere, demografik olarak farklı kültürel bağlamlarından çok çeşitli örneklemler içerdiği görülmüştür. **Sonuç:** OXT ve çocuklara kötü muamele arasında önemli bağlantılar olduğu; ancak, bu bağlantıların doğasını anlamak için daha fazla çalışmaya ihtiyaç duyulduğu görülmektedir. Bununla birlikte bulgular, klinik implikasyonlar açısından dikkat çekicidir.

Anahtar Kelimeler: Oksitosin, vazopresin, çocuk istismarı

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INTRODUCTION

Child maltreatment is among the most prevalent public health problems in the modern world and has become an international issue. The World Health Organization (WHO) defined the concept as intentional or unintentional attitudes and behaviors of societies, countries or individuals' that negatively affects a child's development and health.[1] The concept is an umbrella term that refers to all forms of neglect and abuse towards children across all developmental stages, resulting in physical and psycho-social effects in both the short and long term.[2-8] According to the reports of UNICEF and the WHO, around 25-50% of children around the world are subjected to maltreatment.[9,10]

The determinants of child maltreatment refer to an ecosystem involving a combination of multiple risk factors related to family, child, environment, and nature.[11,12] A vast majority of the studies in the literature focus on the psycho-social determinants of the concept, and it is seen that neurobiological effects have become a subject of increased concern in recent years. In these studies, it was found that the mother's interaction with the infant in the pre- and post-natal periods plays a crucial role in bonding, while the functions of oxytocin (OXT) and vasopressin (VP) molecules affect human behaviors. The interaction of environmental factors with neurobiological determinants forms unique neural pathways.[13-15] This formation process, which is the result of neural plasticity, occurs in the early stages of the brain development of females and proceeds into the most biologically productive years in life by the formation of a unique neural plasticity.[16]

OXT and arginine VP neuropeptides have important roles in regulating the conditioning and extinction of anxiety and fear, as well as complex social cognitions and behaviors such as attachment, social exploration, recognition, and aggression throughout mammalian evolution.[17] OXT is a hormone with a peptide structure consisting of nine amino acids and is released from the supraoptic and paraventricular nuclei of the hypothalamus.[18] It is considered to play crucial roles in concepts such as perceiving emotional facial expressions, attachment, reproduction, social relationships, intimacy, parenthood and child care, while also decreasing the cortisol levels and response to stress; supporting the development of trust, bonding and social interaction.[19,20] Additionally, it directly and indirectly affects brain anatomy and allows for elaboration of the human neocortex and thus of cognition and language. In general, it acts in a way that allows for the high social sensitivity and adaptation necessary for a child's upbringing and human sociability.[21] By dynamically regulating the autonomic nervous system, its effects on antioxidant, anti-inflammatory and vagal pathways help explain the common adaptive consequences of social behavior for emotional and physical health. On the other hand, VP the sequence of which is only two amino acids different to OXT, plays a crucial role in cardiovascular and autonomic regulation, social functions and recognizing facial expressions.[22] Both OXT and VP are synthesized in the supraoptic and paraventricular nuclei of the brain. VP is also synthesized in the suprachiasmatic nucleus. For peripheral release, both are carried to posterior hypothalamus by neuro-secretory axons before being transmitted to the pituitary. They both affect various parts of the central nervous system in terms of reproductive, social and aggressive behaviors. They both have roles in labor control, regulation of blood pressure, breastfeeding, and sexual behavior. They function in generating maternal closeness and care, strengthen trust and promote psycho-social maturation of the infant. These hormones can decrease or increase the responses of the post-synapse to neurotransmitters. Thus, they have the capacity to influence functions such as food intake, reward, memory, learning, social behaviors and metabolism.[23]

Starting from the prenatal period, the development of the human brain involves functions such as neural proliferation, cell differentiation, axonal growth, apoptosis, myelination and synapse formation. The organization and regulation of brain development is controlled by chemical markers, hormones such as OXT and VP, neurotrophins and neurotransmitters.[24] By the modulation of anxiety and fear response, they regulate amygdala activity and hypothalamic-pituitary-adrenal axis by projections to the hypothalamic structures and brain stem. Both neuropeptides are synthesized in hypothalamus, primarily in large magnocellular neurons whcih project axons to the posterior pituitary. Most OXT and VP molecules are released by this way, through the axon projections, and are prevented to re-enter the central nervous system through the blood brain barrier. The release and synthesis of OXT and VP in the CNS is particularly important for their effect on the social behavior. The genetic and functional variations of these neuropeptided may result in social deficits and neurodevelopmental disorders such as autism spectrum disorder. Through neuronal networks, various synaptic formations take place in the brain development of the newborn. These synapses may change in response to the intensity of stimuli and experiences and synaptic plasticity may occur. Neurons not used in synapses disappear by selective apoptosis in the post-natal period. If newborn babies do not receive the positive stimuli they need in critical periods, brain regions will develop abruptly in the neocortical organization.[25] Whenever their needs are not met appropriately and they receive no response whenever they cry, the brains of the infants experience a series of anomalous influences in the amygdala, septal region and cingulate cortex.[26] In this critical process, along with environmental factors such as food, radiation and

infection; neglect and abuse may also harm the acceleration of children's brain development. Even though OXT and VP come from the same ancestor, it can be seen that they play adverse roles. That is, while OXT is related to nurturing and caring, VP is related to the aggressive attitude of the mother towards her child. As VP causes an increase in blood pressure, it increases the risk of the diseases group that includes post-traumatic stress disorder and cardiovascular diseases.[27] Oxytocin, on the other hand, is thought to have a protective role in preventing post-traumatic stress disorder.[28]

The literature discussed above shows that OXT and VP are among the most interesting molecules for modern neuroscience. However, although the subject has recently become a major topic of interest for researchers, the roles of OXT and VP in the neurobiological fundamentals of child maltreatment remain poorly understood and a subject of concern. Within the scope of the current developments in neuroscience, the present study aimed to focus on the neurobiological basis of childhood maltreatment by conducting a systematic review of the studies examining the possible links between OXT, VP and child maltreatment.

METHODS

The present study aimed to conduct a review on OXT and VP in maltreated children. In the study, a systematic approach was followed by focusing on the possible links among OXT, VP and child maltreatment.

Criteria for inclusion and exclusion

The study included researches based on data from child, adolescent and adult samples examining the role of being exposed to any kind of maltreatment during childhood. The review was not limited to a specific period of time. However, reviews, systematic reviews, dissertations, congress papers and studies in languages other than Turkish and English were excluded.

Procedure

The search of the databases was carried out by three independent researchers between December 2021 and April 2022 in accordance with the guidelines of the Centre for Reviews and Dissemination developed by York University National Institute of Health Research.[29] The search was concentrated on the Web of Science, PubMed, Science Direct, Scopus, EBSCO Host and Google Scholar databases including the keyword combinations "oxytocin", "vasopressin", "child maltreatment", "child abuse", "child neglect", "childhood adversity", "childhood trauma" and "early life stress".

In the search procedure, a total number of 9,706 studies about OXT and 7,151 studies about VP were reviewed. Consequently, 49 studies were classified as appropriate according to the inclusion criteria and were therefore included in the review. The procedure is shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Fig. 1).

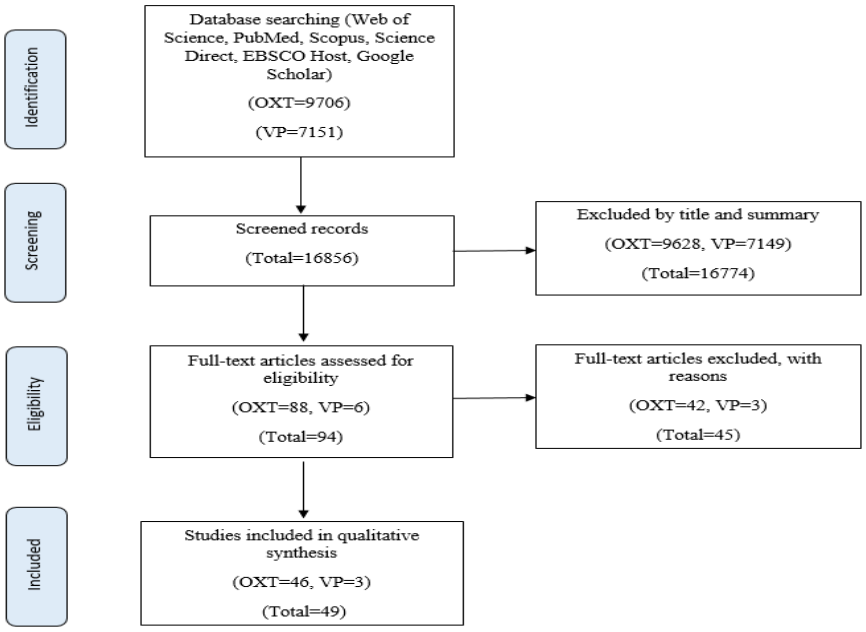

Figure 1. PRISMA Flowchart

RESULTS

The results of the review of researches related to OXT and VP in maltreated children are presented in Table 1.

Table 1. Results of the review of researches related to OXT and VP in maltreated children

Subjects	Child Maltreatment Type	Compound	Findings	Reference
19 men	Early parental separation	OXT level (24 IU intranasal OXT T)	Intranasal OXT resulted in attenuated cortisol decreases in subjects with early parental seperation.*	Meinlschmidt et al. [30]
22 women	PA, SA, EA, PN, EN	OXT level	CSF OXT concentrations significantly decreased in M women.*	Heim et al.[31]
313 M, 282 NM children	PA, SA, N, EM	Oxytocin receptor gene (OXTR) (rs53576)	NM children with AA or AG genotypes of OXTR displayed greater levels of resilient functioning.**	Cicchetti et al.[32]
47 females	Parental love withdrawal	OXT level	OXT on prosocial attitudes, behaviors, and concerns related to experiences of parental love withdrawal.*	Huffmeijer et al.[33]
971 adults	PA, SA, EA, PN, EN	OXTR (rs53576)	An interaction of OXTR rs53576 genotype and positive family environment predicted resilient coping/positive affect.*	Bradley et al.[34]
26 adults	PA, SA, EA, PN, EN	OXT level (24 IU intranasal OXT)	Patients with borderline personality disorder showed an avoidant reaction to angry faces which was abolished in the OXT condition.*	Brüne et al.[35]
615 females	PN, EA, PA, SA	OXT level	Attachment system stress was affected by OXT levels.*	Munro[36]
213 females, 75 males	EA, PA, N	OXTR (rs53576)	A significant moderating role of OXTR genotype was found in the relation between childhood maltreatment and depression.*	McQuaid et al.[37]
102 females, 32 males	EM	OXT level (24 IU	OXT was associated with memory impairment in participants with a history of EM.**	Bhandari et al.[38]
32 men	PA, SA, EA, PN, EN	intranasal OXT) OXT level (24 IU intranasal OXT)	OXT had opposite effects with increased hormonal reactivity and increased limbic deactivation*	Grimm et al.[39]
263 M, 162 NM adolescents	SA, PA, PN, EM	OXTR (rs53576)	OXTR interacted significantly with maltreatment status in predicting perceived social support.*	Hostinar et al.[40]
18 males	PA, SA, EA, PN, EN	OXT level	OXT moderated the rest–task interaction between pgACC-amygdala rs-FC and stress-induced pgACC deactivation.**	Fan et al.[41]
50 females	N	OXT level (24 IU intranasal OXT)	The effects of OXT on superior temporal gyrus activation, Mind in the Eyes Test, performance are moderated by experiences of love withdrawal. *	Riem et al.[42]
37 M, 36 NM children	PA	Urinary OXT OXT level	Girls with a history of physical abuse had higher levels of urinary OXT. **	Seltzer et al.[43]
5 female, 26 male cocaine dependent adults	CM	OXT level (40 IU intranasal OXT)	CM modified the relationship between intranasal OXT and cortisol reactivity. *	Flanagan et al.[44]
49 women, 31 men	PA, SA, EA, PN, EN	OXT level	Less severe physical abuse was significantly associated with higher OXT concentration.*	Mizuki[45]
38 M children	N, PA, SA, EA	OXT level	M children in "Settled" environments have a marked increase in bedtime salivary OXT levels.*	Mizushima et al.[46]
171 females, 138 males	PA, SA, EA, PN, EN	OXTR (rs53576)	Structural magnetic resonance imaging data revealed a strong interaction between rs53576 genotype and CM.**	Dannlowski et al.[47]
18 abstinent patients, 18 controls	N	OXT level	OXT serum levels were significantly higher among abstinent patients and positively correlated with mother neglect.**	Gerra et al.[48]
20 females, 46 males	PA, SA, EA, PN, EM	OXT level	A significant negative correlation was found between mean baseline OT and EM.**	Riem et al.[49]
2180 with depression and anxiety disorders, 387 controls	PA, SA, EA, PN, EN	OXTR (rs2254298, rs53576, rs2268498)	OXTR was found to play a role in social processes and underlying characteristics of anxiety and depression.*	Tollenaar et al.[50]
23 boys and 5 girls	CM	Salivary levels of OXT	Salivary OXT concentrations were increased to various degrees after the activity sessions in younger boys.*	Yuhi et al.[51]
691 boys, 900 girls	PA, EA	OXTR (rs53576)	M female OXTR rs53576 G allele carriers exhibited more behavioural problems.*	Andreou et al.[52]
49 postpartum women	PA, SA, EA, PN, EN	OXT level	Plasma OXT levels were not significantly associated with CM.	Boeck et al.[53]
314 mother-infant dyads	PA, SA, EA, PN, EN	OXTR (rs53576)	Maternal history of CM strongly predicted disorganization and classification for mothers with more plasticity alleles of OXTR.*	Ludmer et al.[54]
39 M, 27 NM women	PA, SA	OXT level	Plasma OXT levels were not significantly associated with CM.	Mielke et al.[55]
49 mothers	PA, SA, EA, PN, EN	OXTR protein expressions	A significant association was found between CM and an alteration of OXTR protein expression.**	Krause et al.[56]

Table 1. (*continued*)

Subjects	Child Maltreatment Type	Compound	Findings	Reference
28 postpartum women	CM	OXT level	A significant interaction was found between OXT and SA on impaired bonding.*	Lara-Cinismo et al.[57]
25 first time expectant fathers	EA, PA, N	VP level (20 intranasal IU)	Effects of VP in the anterior cingulate cortex, paracingulate gyrus and supplemental motor area were stronger in fathers who experienced lower levels of love-withdrawal.*	Thijssen et al.[58]
488 M, 488 NM adolescents	PA, SA, EA, PN, EN	OXTR (rs237885)	Potential synergic additive interactions between the rs237885 TT genotype and PA were found.*	Zhang et al.[59]
614 adults	EA	OXTR (rs53576)	Participants with homozygous for the G allele of OXTR rs53576 who reported higher levels of EA were likely to have more supportive family relationships than A carriers.*	Ebbert et al.[60]
57 males	PA, SA, EA, PN, EN	OXT level	A significant interaction between callous-unemotional traits and EN on mean daily OXT was observed.*	Fragkaki et al.[61]
44 M, 41 NM children	PA, SA, EM, N	DNA methylation of OXTR	The M group showed higher CpG 5,6 methylation and confirmed negative correlations of gray matter volume in the left orbitofrontal cortex with CpG 5,6 methylation.**	Fujisawa et al.[62]
251 adults	PA, SA, EM, N	OXT genotypes (OXTR and CD38)	The OXTR gene did not relate to lifetime suicide ideation, nor did it moderate early onset maltreatment risk.	Handley et al.[63]
67 cocaine-dependent participants	PA, SA, EA, PN, EN	OXT level (40 IU intranasal OXT)	OXT reduced fMRI response to cocaine cues in men with a history of childhood trauma.*	Joseph et al.[64]
22 pregnant women	CM	OXT level	OXT was relatively high in women with post-traumatic stress disorder compared with controls.*	Li et al.[65]
61 females, 60 males	PA, SA, EA, PN, EN	OXT level	EN was associated with lower plasma OXT levels and insecure attachment representations.**	Müller et al.[66]
54 females	EM	OXT level	There was no significant correlation between EM and baseline OXT levels.	Riem et al.[67]
54 females, 26 males	PA, SA, EA, PN, EN	OXT level (24 IU intranasal OXT)	In participants with a history of early adversity, emotion recognition was more accurate under OXT compared to placebo.*	Schwaiger et al.[68]
110 females	CM	OXTR (rs237895)	CM was associated with maternal insensitivity in high−OXTR-expressing T-allele carriers.**	Toepfer et al.[69]
2020 females	CM	OXTR (rs53576, rs2254298)	Early threat exposure and OXTR variation predicted general psychopathology in women who were threat-exposed and carrying rs53576.*	Byrd et al.[70]
100 male adolescents	PA, SA, EA, PN, EN	OXT level (24 IU intranasal OXT)	Salivary OXT increased significantly after OXT administration in M adolesecents.*	Fragkaki et al.[71]
35 females, 28 males	EN	OXTR (rs53576, rs2254298)	The interaction of the rs2254298 A risk allele and EN was associated with reduced left hippocampal volume.*	Womersley et al.[72]
237 females, 164 males	CM	OXTR (rs53576)	OXTR rs53576 moderated the impact of childhood adversity on general trust.**	Zheng et al.[73]
1804 males	CM	OXTR (rs53576, rs237987)	Significant interaction found between OXTR variations and childhood maltreatment, which could predict the risk of borderline personality disorder. **	Zhang et al.[74]
21 females, 13 males	CM	OXT level (24 IU intranasal OXT)	Intranasal oxytocin modulates threat salience among childhood trauma-exposed individuals.**	Sippel, et al.[75]
23 NM, 26 M adults	CM	OXTR (rs53576)	CM associated with an upregulation of OXTR expression.*	Almeida et al.[76]
70 fathers with their 2- to 12-month-old infants	N	OXT level (24 IU intranasal OXT), VP level (20 IU intranasal)	Fathers who had higher levels of emotional neglect were less sensitive during play in the OXT condition. No effects were found of OXT and VP administration on parenting behaviors of fathers.	Witte et al.[77]
70 first-time fathers	PA, EN	OXT level (24 IU intranasal OXT), VP level (20 IU intranasal)	Fathers' childhood history of PA, EN did not moderate the effects of VP and OXT administration on neural reactivity.	Witte et al.[78]

* = $p < 0.05$; ** = $p < 0.01$; *CM*., child maltreatment; *EA*., emotional abuse; *EM*:., emotional maltreatment; *EN*., emotional neglect; *EPS*., early parental separation; *M*., maltreated; *NM*., non-maltreated; *N*., neglect; *PA*., physical abuse, *PN*., physical neglect; *SA*., sexual abuse

The studies included in the review are shown in chronological order. Of the 49 articles included in the review, subjects, child maltreatment types, compounds and findings were extracted by three independent researchers.

Subjects: In the review, it was seen that in 49 studies included in the review, data from a total of 18979 participants (3981 child and adolescent, 9998 adults) were reported. Studies reviewed contained samples that were demographically diverse from a wide range of Western cultural contexts. The studies were all conducted between 2007 and 2022. Eight of the studies included child samples, while the rest of them included adult subjects.[32,40,43,51,52,59,62,71,77] Of the studies which included adults, 13 of them only consisted of mothers.[32,33,36,44,53,55-57,65,67,69] One study included both mothers and infants.[54] A wide variety of sample sizes were observed in the studies. The largest sample was 2,180, while the smallest sample was 15.[36,50] The majority of the studies were case-control studies that

recruited participants from hospitals or local child protection services.

Child maltreatment type: Child maltreatment is a concept that refers to a wide variety of parental attitudes and behaviors. It may occur in vague and abstract forms as much as concrete and active ways. Hence, the search of the literature covered the combinations of all related key words beyond the keywords of "maltreatment", "abuse" and "neglect". Most studies examined physical, sexual, emotional abuse, and physical and emotional neglect, which were assessed by standard measures. The most commonly administered instrument was the Childhood Trauma Questionnaire. A number of studies specifically examined emotional maltreatment[38,48,72], while others examined constructs including various maltreatment types such as early parental separation[30], parental love withdrawal[33], maternal love withdrawal[42], childhood trauma[57], early life stressors[65], early threat exposure[69] and childhood adversity.[73]

Compound

Of the reviewed studies, ten of them[30,35,38,39,42,44,75,77,78] administered intranasal OXT (16, 24 IU), using a placebo-control design, 17 of them examined plasma, urinary and salivary OXT concentrations.[32,33,36,41,43,45,48,49,51,53,55-57,61,65-67] It is seen that in the studies different evaluation methods are used for OXT and VP levels in urine and salivation. Reference values vary according to the kits used in the research. On the other hand, in plasma, internationally recommended reference units are 1.5±0.2 µU/ml (SEM) for non-pregnants and 4.2±1.1 µU/ml (SEM) in the second stage of labor. Of the studies, 16 of them examined the effects of the OXTR genotype[31,33,36,46,49,51,53,58,61,62,68,69,71-73,75]. Three studies involved intranasal VP (20 IU) administration.[58,77,78]

RESULTS

A number of studies administered intranasal OXT to explore the central OXT changes in participants with adverse childhood experiences. In these studies, OXT administrations resulted in attenuated cortisol decrease[30], affected avoidant reactions to social threat in adults who had borderline personality disorder[35], was associated with memory impairment in participants with a history of emotional maltreatment[38], cortisol reactivity in cocaine dependent individuals with a history of child maltreatment[44], modulated by early life stress in the limbic system during acute psychosocial stress[39], and reduced fMRI response to cocaine cues in men with a history of childhood trauma.[64] In a study which examined the effects of OXT on the abilities of emotion recognition in adults with a history of childhood adversity, it was found that emotion recognition was more accurate under OXT compared to placebo.[68] In one study, the salivary OXT level increased significantly after OXT administration in maltreated adolescents.[71] The present study included only three studies related to the effects of VP. In the study of Thjissen et al. a VP administration showed effects in the supplemental motor area and anterior cingulate cortex and paracingulate gyrus in fathers who experienced parental love withdrawal.[58] However, in the studies of Witte et al. VP administrations, along with OXT, did not effect parenting behaviors[77] and did not moderate the relationship between neural activity and childhood history of physical abuse and emotional neglect.[78]

A number of the studies examined OXT concentrations in populations with a history of childhood maltreatment. These studies found that cerebrospinal fluid OXT concentrations were significantly low in maltreated women[49], OXT was related to experiences of parental love withdrawal on prosocial attitudes, behaviors and concerns[33], attachment system stress affected OXT levels[36], OXT moderated the rest–task interaction between stress-induced pregenual anterior cingulate cortex. (pgACC) deactivation and pgACC-amygdala rs-FC[41], girls with histories of physical abuse had higher levels of urinary OXT[42], OXT concentrations were associated with severe physical childhood abuse[45], mother neglect[48], emotional maltreatment[49,61,66,67], sexual abuse[57] and post-traumatic stress disorder in participants with a history of early life stressors.[65] One of the studies examining the effects of the nature of subsequent environment on cortisol and OXT secretion found that maltreated children in settled environments had a marked increase in bedtime salivary OXT levels.[46] In another study, concentrations of salivary OXT were found to increase after some drum playing activity sessions in younger boys.[51] Contrary to the findings above, in two of the studies, plasma OXT levels were not significantly associated with childhood maltreatment.[53,5]

When the effects of the OXTR genotype on child maltreatment were examined, it was seen that rs53576 is the most examined variant and was shown to increase resilient functioning[32], interact with positive family environments in predicting resilient coping/positive affect[34], play a moderating role in the association between depression and childhood maltreatment[35], interact with maltreatment status in predicting perceived social support[40], have a strong association with childhood maltreatment[47,76], was related to conduct problems[52], predicted disorganization and classification in mothers with more plasticity alleles[54], associated with higher levels of emotional abuse[60] and maternal insensitivity[69], and moderated the effect of childhood adversity on general trust.[73,74]

In some studies, rs237885, rs2254298, rs2268498 and rs237987 were shown to be among the other genotypes that play roles in childhood maltreatment. In these

studies, it was found that the OXTR (rs2254298, rs53576, rs2268498, rs237987) played a role in social processes and underlying characteristics of depression and anxiety[50], potential synergic additive interactions were evident between the rs237885 TT genotype and physical abuse[59], early threat exposure and OXTR variation predicted general psychopathology in women who were carrying rs53576 and were threat-exposed[70] and the interaction of the rs2254298 a risk allele and emotional neglect was associated with reduced left hippocampal volume.[72] In a study that examined the development of suicide ideation and infancy onset maltreatment, it was found that the OXTR did not moderate early onset maltreatment risk, nor was it related to lifetime suicide ideation.[63] In addition to genetic variants, OXTR was examined in terms of DNA methylation and protein expressions. In one study, the maltreated group showed higher of methylation CpG (regions of DNA where guanine nucleotide follows a cytosine nucleotide), which was negatively correlated with gray matter volume in the left orbitofrontal cortex with CpG methylation[62], while another provided evidence showing a significant correlation among childhood maltreatment and an alteration in OXTR protein expression.[56] In the study of Zheng et al., OXTR variations were found to be related with childhood maltreatment which also predicted the risk of borderline personality disorder in males.[74]

DISCUSSION

The search of the related literature revealed a total number of 49 research studies examining the possible links between OXT, VP and child maltreatment published between 2007 and 2022. In the majority of the reviewed studies, statistically significant associations were found between child maltreatment and OXT. Out of 49, three of the studies focused on VP and only one of them provided evidence showing its role in child maltreatment. Insignificant findings were found in six studies. In summary, it can be concluded that in almost all articles examined, possible links between OXT and child maltreatment were clarified. These links were more evident in emotional maltreatment and neglect. Emotional neglect in childhood affects fear and avoidance of social situations, which are two important aspects of social dysfunction, through plasma OXT levels and attachment representations.[66] Exposure to maltreatment during this period appears to be associated with decreased cerebrospinal fluid OXT concentrations, with a particularly strong effect reported with emotional abuse.[32] In many of the studies discussed above it has been shown that OXT receptor protein expression is decreased in adults who has a history of childhood maltreatment and especially insecure attachment. These studies provided findings related to the relationship between childhood maltreatment and OXTR protein expression, which is a sign of chronic changes in the neurobiological system related to attachment. OXT is important for the regulation of complex social cognition and behavior. Common variants of the OXTR are associated with social behavioral phenotypes. Imaging studies show that these variants affect brain regions important for social behavior.[47,79] The G-allele of the OXTR is a vulnerability factor for specific changes in the limbic structures of people with adverse childhood experiences. Carriers of the A allele of the OXTR are argued to be resistant to the effects of severe childhood problems and protect against emotional dysregulation and disordered attachment.[80]

According to the findings presented in this study, it is thought that OXT may have crucial importance in establishing the basis for parents to give care and show love and affect to their children, and these children becoming adults capable of securely bonding with their own children. In this procedure, the neurobiological and chemical-sensory systems affect the infant-mother bond in a dichotomous way. In other words, if the baby receives the care in an emotionally responsive way, the biochemical structure of the brain is healthily formed, and it is stored in memory. However, if the infant is neglected or emotionally rejected, the neuronal mechanisms operate accordingly and store negative emotions.[81] The findings of the present study related to the effects of OXT on child maltreatment might be considered as considerable proof that along with mental factors, neurobiology may have an impact on healthy parental bonding.

An overview of the researches included in the present study revealed that many studies on OXT have focused on mothers. When these studies are examined, clear links are seen related to the role of OXT in their childhood maltreatment experiences and their bonding with their children. It can be suggested that the mothers who have experiences of childhood maltreatment have difficulties in perceiving the emotional cues in their own infants, avoid physical contact and show insufficiencies and discrepancies in responding to the emotional needs of the infants. The infant perceives these negative attitudes and behaviors as a threat. These experiences activate the neural pathways responsible for the feelings of fright, as the survival response causes the hyperactivation of the HPA axis and extreme glucocorticoid release.[82] Thus, it can be suggested that the anxiety and fright experienced by the baby has negative impacts on the development of the hippocampus in particular. In line with this suggestion, in the present study, it was seen that many studies showed that a low level of OXT plays a role in depression, anxiety and trauma in maltreated samples. Therefore, it could be suggested that traumatic childhood experiences such as abuse, and neglect may increase the risk of stress-related emotional, cognitive and behavioral disorders. The emergence of this path may start with the avoidance of contact and results in

insecure bonding in early years. The interaction between the mother and the infant determines the quality of attachment. Secure attachment with the mother is suggested to be associated with self-esteem, self-respect, quality of life, affective characteristics, psychological well-being and a sense of identity.[83] Based on these suggestions in addition to the findings of the present study, it can be argued that OXT may play protective roles in avoiding emotional disturbances related to childhood maltreatment. As shown in the majority of the reviewed researches, intranasal administrations have significant effects in regulating the OXT levels in samples with experiences of childhood maltreatment. However, it should be noted that the results of intranasal administration of OXT are in a wide range, and the evidence for its potential benefit in the treatment of anxiety and depression is insufficient.[84] It has no significant effect on emotion recognition, its effect on theory of mind is weak and it causes a threat situation in healthy individuals.[85] It also increases the startle response and improves the recognition of basic emotions, especially fear and anger[86], as it modulates the activity in brain areas associated with cognitive emotion and reward in post-traumatic stress disorder.[887]

CONCLUSION

In the study, considerable links were found with child maltreatment in 41 of 46 studies on OXT and only 1 of 3 studies on VP. It is noteworthy that the studies on the subject heavily focused on OXT, and the studies on VP were few in number. More studies are needed to understand the nature of links with child maltreatment, particularly for VP. Although this review only included a limited number of research papers, it provides an overall insight into the subject of concern. Nevertheless, it should be noted that it does not provide direct evidence indicating whether the suggested links represent causal and direct relationships. However, the findings are promising in terms of clinical implications. Nurturing physical contact and the presence of social support may improve the bond among the parents and the child. Hence, OXT administrations may be considered as a form of pharmacotherapy for people who suffer from the emotional impacts of childhood maltreatment. Besides this clinical implication, it should be noted that OXT is released during supportive and warm contact with parents. It is of crucial importance that parents are provided a basic level of knowledge and awareness related to how their attitudes and behaviors towards their children affect their brain and emotional development.

Author contributions

Study idea/design: ABA, MEU
Data collection: AK, GİI, UB
Data analysis and interpretation: UB, HŞ
Literature review: AK, GİI, UB
Writing of the article: HŞ, MEU
Critical review: ABA, SY
Final approval and responsibility: ABA, UB

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