Chapter

Oxytocin and Neuroprotective Effects

Oytun Erbaş and İlknur Altuntaş

Abstract

The neurohormone oxytocin (OT), consisting of nine amino acids, is produced in the hypothalamus and secreted from the posterior lobe of the pituitary gland. Recent studies show that OT can affect the course of the disease and is promising in the treatment of neurodegenerative disorders, due to its therapeutic properties and benefits. Histological and biochemical findings of the studies on vincristine-induced neuropathy, cisplatin-induced cytotoxicity, diabetic neuropathy, rotenone-induced Parkinson's disease, hypoxia, and stroke, which are reviewed in this chapter, revealed that OT significantly prevented neuronal damage with its anti-inflammatory and antioxidant properties. Therefore, the neuroprotective effects of OT and the underlying molecular mechanisms continue to attract the attention of scientists.

Keywords: oxytocin, neurohormone, neuroprotection

1. Introduction

The neurohypophyseal nonapeptide hormone oxytocin (OT), the first peptide hormone to have its structure determined [1], plays an important role in social behavior across a wide variety of species [2, 3]. The word 'oxytocin' was coined from the Greek words (ω k ν ξ, τ o k ox ξ) meaning 'quick birth' after its uterine-contracting properties were discovered by Dale [4]. OT's repertoire has expanded to maintain a central role in more complicated aspects of reproductive behavior. For these reasons, it is called the great facilitator of life [5] (**Figure 1**).

OT is synthesized at the paraventricular (PVN), supraoptic nuclei (SON), and intermediate accessory nuclei of the hypothalamus and transported through the axons of these cells to the posterior pituitary gland [6]. From the posterior pituitary, OT reaches the general blood circulation. It is also produced by different peripheral tissues, such as skin, placenta, ovary, testis, thymus, pancreas, adipocytes, kidney, heart, and blood vessels [7]. OT acts as a hormone in the peripheral circulation and as a neurotransmitter/neuromodulator in the central nervous system [8].

The neurohormone OT is an effective stimulant of the uterine contraction and is used primarily to induce or reinforce labor in obstetrics [9]. OT facilitates the expulsion of milk from the mammary gland during nursing. The release of OT from the posterior pituitary is stimulated by tactile sensory inputs from the nipple. Milk-ejection is the only physiological function known to absolutely require OT [10]. For both men and women, OT is released during sexual stimulation and orgasm, may reduce urine volume and induce natriuresis through co-activation of vasopressin receptors, and is involved in the modulation and regulation of the hypothalamic–pituitary–adrenal (HPA) axis [11]. Moreover, OT plays a role in the

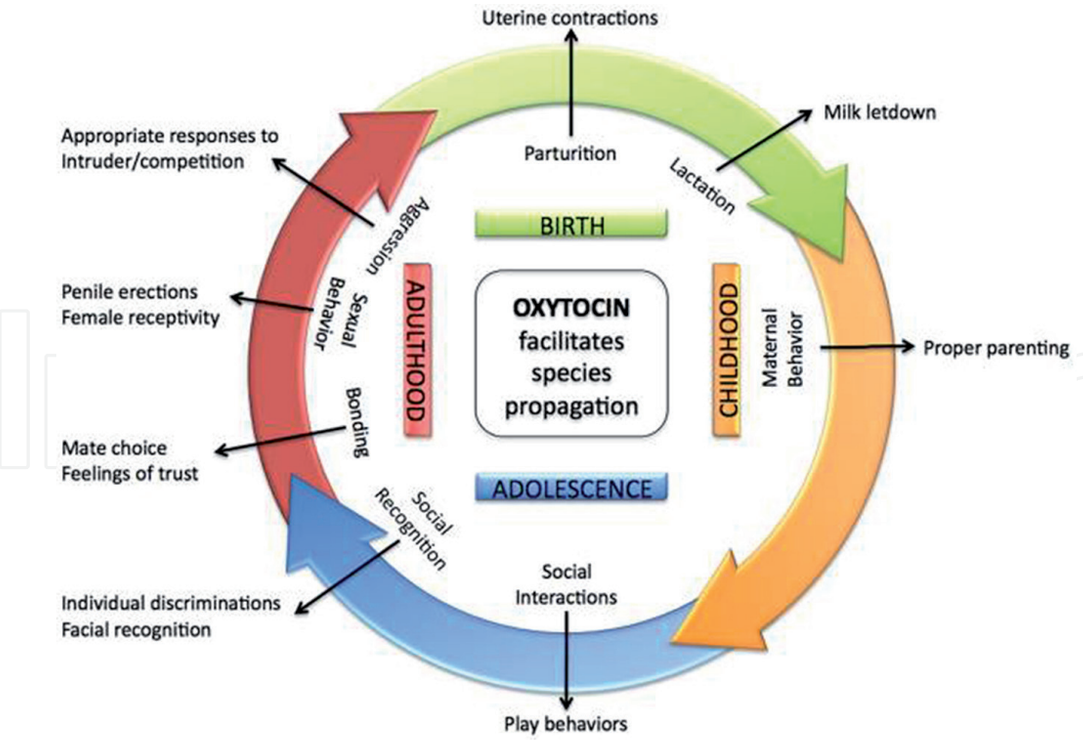

Figure 1.
A simple cycle of life illustrates numerous points at which OT may affect behaviors and physiology to facilitate the propagation of the species [5].

endocrine and paracrine activities such as various sexual and maternal behaviors, social recognition, aggression, neuromodulation, cognition, and tolerance development; however, the mechanism is still unclear [2, 12, 13].

The central neuropeptidergic effect of OT has continued to be studied in the social behavior of various species (in humans and animal models) to date. Nagasawa *et al*. summarized the behavioral and physiological oxytocin-induced effects with the title of "summary of the role of the oxytocin system in reciprocal communication" in **Figure 2** [14].

According to the figure, the central OT secretion is stimulated by multiple sensory signals in mammals. Increased OT release is important in the development of physiology and behavioral functions, and also causes a decrease in pain and stress.

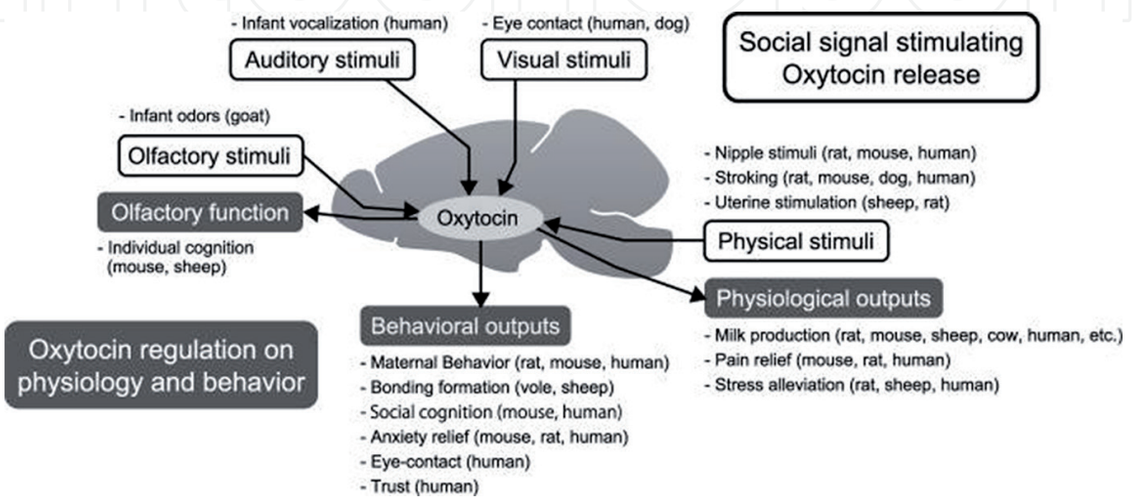

Figure 2.
"Summary of the role of the oxytocin system in reciprocal communication" Nagasawa et al. [14].

2. Chemical properties of oxytocin

Oxytocin (seq;CYIQNCPLG), a neurohypophysial peptide hormone, consists of nine amino acids (H-Cys(1)-Tyr-Ile-Gln-Asn-Cys(1)-Pro-Leu-Gly-NH2) linked with a [1-6] disulfide bond and a semi-flexible carboxy amidation tail [15] (**Figure 3**). This results in a peptide constituted of a rigid N-terminal cyclic 6-residue ring structure and a flexible COOH-terminal alpha amidated three-residue tail [5].

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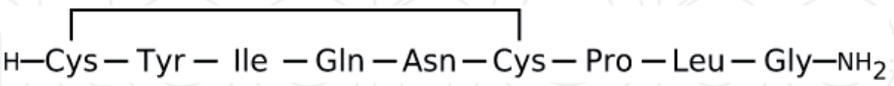

L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparagyl-L-cysteinyl-L-prolyl-L-leucyl-glycinamide (1->6)-disulfide [15].

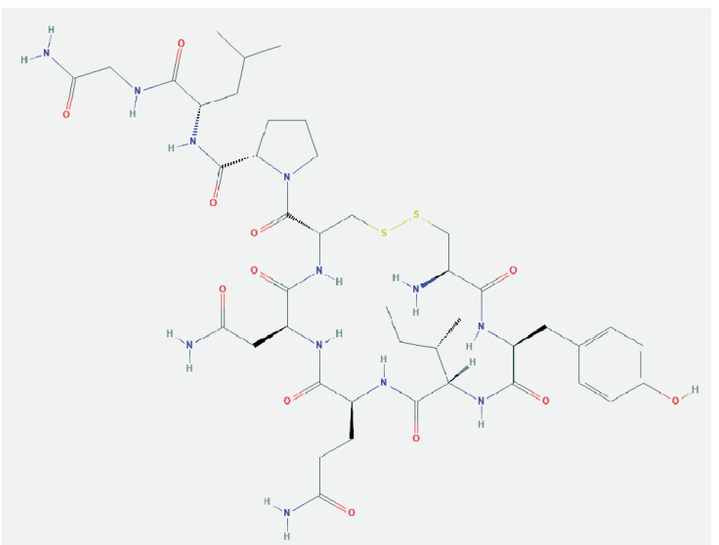

Figure 3.
Chemical structure depiction of oxytocin (OT). Molecular formula: $C_{43}H_{66}N_{12}O_{12}S_2$/Molecular weight: 1007.2 g/mol [15].

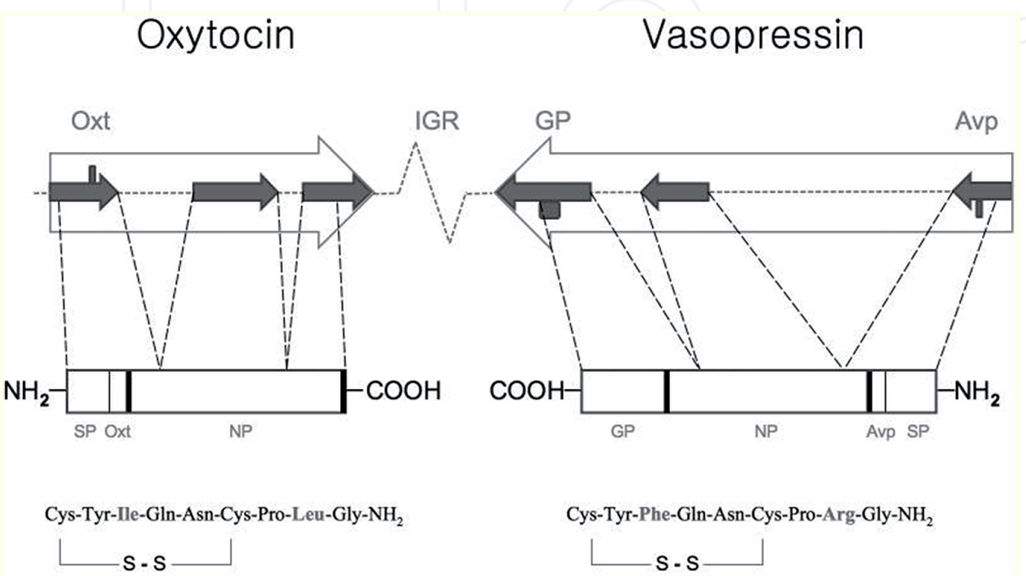

Figure 4.
"Schematic diagram of the oxytocin (OT) and vasopressin (AVP) genes (large arrows), preprohormones (boxes), and neuropeptides (bottom)" [16].

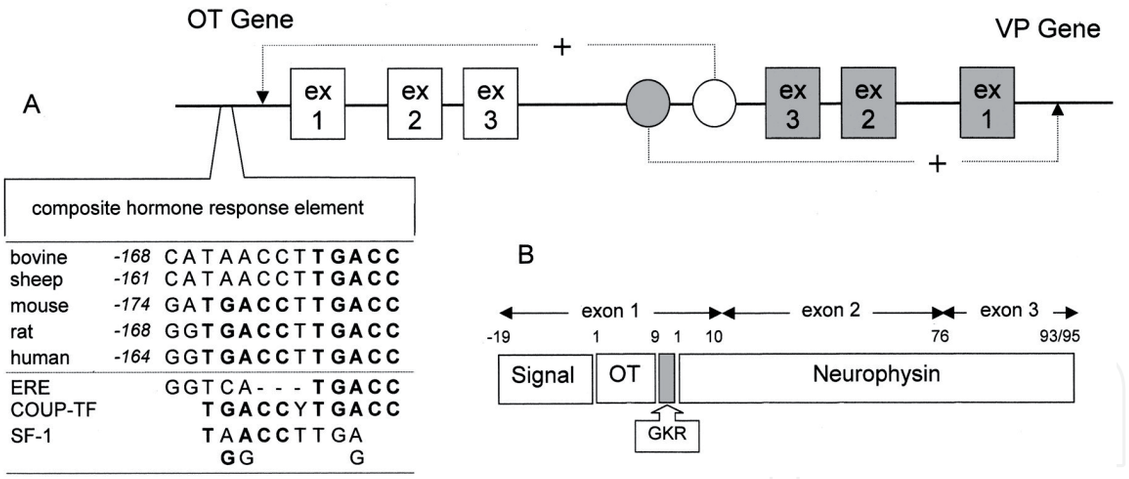

Figure 5.
"Organization of the oxytocin (OT) and vasopressin (VP) gene structure including a schematic depiction of the putative cell-specific enhancers (open circle, enhancer of OT gene; shaded circle, enhancer of VP gene)" [9].

The structure of OT is very similar to another nonapeptide, entitled vasopressin (AVP/arginine vasopressin), which differs from OT by only two amino acids in positions 3 and 8 (**Figure 4**) [16], (**Figure 5**) [9]. OT and AVP genes in the mouse, rat, and human genomes are located on the same chromosome separated by a short (3.5–12 kbp) intergenic region but are in opposite transcriptional orientations [17–20]. They are synthesized in the brain's hypothalamic paraventricular and supraoptic nuclei [21].

3. Oxytocin receptor, cellular actions, and signaling

OT is currently known to have only one receptor (OTR/oxytocin receptor), which forms together with the related V1a, V1b, and V2 vasopressin receptor subtypes a subfamily of the large G protein-coupled receptor (GPCR) superfamily, one of the most abundant protein classes in the mammalian genome [16, 22]. OT shows its biological activity through the GPCR, which is widely expressed throughout the body, including the central and peripheral nervous systems. Heterotrimeric G-proteins are composed of α, β, and γ subunits [23]. These receptors are characterized by seven putative transmembrane domains, three extracellular, and three intracellular loops (**Figure 6**) [9, 22, 24].

The group of OT and vasopressin receptors is well suited for receptor structure–function analysis, because it comprises four related receptors that bind, with varying degrees of specificity, the two closely related peptide ligands, OT and vasopressin [25].

OTR can be coupled to different G proteins, leading to different intracellular pathways. It is possible that these various signaling pathways are differentially expressed in neuronal versus peripheral tissues [26].

The quality of specific acute or long-term neuronal effects of OT is dependent on the regional and subcellular presence of OTR, the characteristics of OT-OTR binding, and subsequent activation of intraneuronal signaling cascades. In addition, the formation of OTR homodimers or heterodimers with other receptors is likely to influence OTR affinity and downstream signaling [23]. The classical signaling pathway associated with the OTR involves a phospholipase C-mediated increase in phosphoinositide hydrolysis, activation of protein kinase C, and a rise in intracellular calcium [27, 28]. The proliferative effects of OT are mediated primarily by the activation of the MAP kinase pathway, involving different G protein-linked pathways as well as receptor tyrosine kinase transactivation [29].

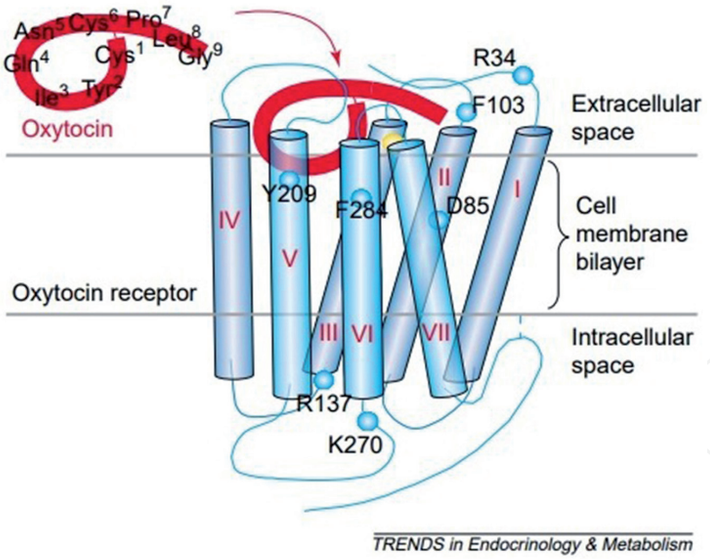

Figure 6.
"Schematic model of the structure of the OT receptor and its interaction with the ligand" (Zingg HH and Laporte SA, 2003) [22].

OT-induced Ca2 influx also seems to play a role in neuronal OT responses. On a cellular level, the OTR activates numerous Ca2-related and MAPK-related signaling cascades in a variety of cell types [23].

Given the multiple signaling pathways in which OTR binds, the development of pathway-specific ligands will be important in elucidating the different OTR-linked pathways, as well as developing more specific agonists and antagonists for future therapeutic applications.

4. Neuroprotective effects of oxytocin hormone

In mammals, increasing brain OT levels promotes attachment and attachment behavior, facilitates parental behavior, social recognition, and memory between relatives, and establishes emotional bonds between animals and caregivers [11, 30–32]. In humans, it has been also shown to increase trust and generosity, strengthen emotional and cognitive empathy, and reduce social-anxiety and fear-related behavior [33, 34]. In line with these findings, impaired social behavior profiles have been associated with reduced central endogenous OTergic activity. Depletion of OTergic signaling through genetic change of the OT gene or receptor has caused convincing social deficiencies, social amnesia, malfunctions in breastfeeding and maternal nutrition, and decreased infant ultrasonic sounds in response to social isolation, but normal birth and sexual behavior [35–37].

Abnormal brain development, during embryogenesis, fetal development, or early postnatal periods, can generate cognitive dysfunction as well as neurological, emotional, and behavioral disorders. Disturbed brain OTergic signaling has been implicated in several psychiatric disorders where social dysfunction is a core symptom (autism spectrum disorder, social anxiety, borderline personality disorder, addiction, and schizophrenia) [31, 37, 38].

There are several animal studies in the literature showing neuroprotective effects of OT. These neuroprotective effects of OT hormone include social neuroprotection, oxygen–glucose deprivation resistance, immune system modulation, anti-apoptotic, anti-inflammatory, and antioxidative functions [38, 39].

Due to the therapeutic properties and health benefits of OT, it can be thought that OT and OT-like molecules are a part of 'natural medicine' that can both prevent and treat diseases and affect the course of many diseases [20].

Understanding the complex actions of OT requires awareness that OT regulates not only the brain and reproductive system but also the immune and autonomic nervous systems. For example, evidence supporting the coordinated effects of acetylcholine (the neurotransmitter in the preganglionic sympathetic and parasympathetic neurons) and OT regulate the autonomic nervous system [40].

The therapeutic effects of the OT hormone have been studied in a variety of pathological conditions, both *in vitro* and *in vivo*.

OT treatment in rats induces several long-lasting anti-stress effects, for example, subchronic OT treatment of males and females rats produces a long-lasting change in spontaneous motor activity, nociception threshold, and weight gain [41].

In many studies, the antiepileptic properties of OT have been emphasized which have positive effects on neurobehavioral pathologies such as autism and psychosis, and it has been shown that it has healing effects on these diseases with its anti-inflammatory and antioxidant properties [42].

It has been revealed that OT modulates the immune and anti-inflammatory response thus reducing inflammatory cytokines production (TNFα; tumor necrosis factor-alpha; is a multifunctional cytokine and IL-6 (interleukin 6)); added to its remarkable anabolic properties on many peripheral organs and on the immune system development [38, 43, 44].

Studies demonstrate the therapeutic effects of both melatonin and OT on critical disease polyneuropathy (CIP) are remarkable. These effects appear to be associated with suppression of cytokine production and improvement in antioxidant capacity [45].

4.1 Vincristine-induced neuropathy

In a study, scientists evaluated the therapeutic potential of OT and liraglutide (LIR), which is a long-acting human glucagon-like peptide-1 (GLP-1) analog, in a rat model of vincristine-induced neuropathy [46]. Vincristine (VCR) is a vinca alkaloid, is known to cause various neurological dysfunctions, antitumoral, and the most neurotoxic agent and it has been used for the treatment of numerous tumors [47, 48]. GLP-1 is a polypeptide hormone composed of 30 amino acids, which is mainly secreted from intestinal L cells in response to nutrient ingestion [49]. Recent studies have indicated that GLP-1 analogs may have therapeutic effects against central and peripheral degenerative changes in animal models of neurodegenerative diseases [50]. GLP-1 exerts its neurotrophic effects through GLP-1 receptors (GLP-1Rs), which are detected particularly on neurons throughout the central and peripheral nervous system [51]. Histological and biochemical findings of the study revealed that both OT and liraglutide significantly prevented neuronal damage by suppressing lipid peroxidation and inducing NGF (nerve growth factor) expression in VCR-received rats [46].

4.2 Cisplatin-induced cytotoxicity

Platinum drugs are compounds containing metal ions that form binding sites for proteins, nucleic acids, and other cellular molecules. This property is largely responsible for the biological activity of drugs as well as their toxicity [52]. Peripheral neurotoxicity is the dose-limiting factor for clinical use of platinum derivatives, a class of anticancer drugs that includes cisplatin, induce decreased

neural transmission rate, loss of vibration and position senses, tingling paresthesia, dysesthesia, loss of tendon reflexes, tremor, ataxia, and muscle weakness [53, 54].

Cisplatin (CP) was the first heavy metal compound to be used as antineoplastic, and since its approval by the FDA in 1978, it is one of the most widely used for the treatment of various solid tumors such as lung, ovary, testis, bladder, head, and neck, and cervical and endometrial cancers [55, 56].

The mechanisms suggested explaining the neurotoxicity of these drugs are dorsal root ganglia alteration, oxidative stress involvement, and mitochondrial dysfunction. These alterations are able to stop DNA replication and cell cycle, inhibit DNA repair mechanisms, and induce cell death through apoptosis [57]. Oxidative stress, DNA damage, and inflammatory cytokines play a major role in the mechanism of cisplatin-induced cytotoxicity. Cisplatin increases the production of free oxygen radicals and decreases the antioxidants, thus resulting in the deterioration of the oxidant/antioxidant balance and accumulation of reactive oxygen radicals (ROS) in tissues [58]. Akman *et al.* clearly demonstrated the protective effect of OT in cisplatin-induced neurotoxicity [12]. The neuroprotective effect seems to be associated with antioxidant (by the suppression of lipid peroxidation and increasing the antioxidative capacity) and anti-inflammatory (by decreasing the plasma TNF-α levels) activity of OT [12]. The imbalance between oxidative and antioxidative mechanisms may play an important role in triggering axonal injury [59]. Axonal transport is important for axonal integrity. Excessive ROS production causes distal axonal degeneration and interruption of axonal transportation. It is demonstrated that OT decreases the free oxygen radicals in the brain membranes, prevents low-density lipoprotein oxidation, and inhibits lipid peroxidation [60, 61]. OT decreases the levels of proinflammatory mediators such as TNF-α, IL-4 (interleukin 4) and 6, macrophage inflammatory proteins 1a and 1b, monocyte chemoattractant protein-1, and vascular endothelial growth factor in lipopolysaccharide-induced inflammatory response and endotoxemia [62].

4.3 Diabetic neuropathy

Present results also demonstrate that OT appears to alleviate the harmful effects of hyperglycemia on peripheral neurons by suppressing inflammation, oxidative stress, and apoptotic pathways [63]. Excessive ROS accumulation leads to an increase in mitochondrial inner membrane permeability. Hyperglycemia also increases oxidative stress and inhibits mitochondrial biogenesis [64]. The depletion of growth factors and the activation of caspase 3 and caspase 8 trigger intrinsic apoptotic cell death in neurons [65, 66].

Diabetic polyneuropathy (DNP) is the most common complication of diabetes with a prevalence of 60–70%. DNP represents a heterogeneous group of syndromes with clinical and subclinical disorders and abnormalities such as distal symmetrical polyneuropathy, mononeuropathy, diabetic amyotrophy, autonomic dysfunction, or cranial neuropathies [67]. Hyperglycemia-induced metabolic changes affect tissues and microvascular systems and lead to ischemic pathological changes in the nerve tissue [68]. Erbas *et al.* assessed the neuroprotective and neurorestorative effects of exogenously administered OT on diabetic neuropathy in rats by electrophysiological, biochemical, histological, and immunohistochemical parameters [63]. They demonstrated the potent anti-oxidant and anti-inflammatory effects of different doses of OT on sepsis-induced neuropathy in rats. According to their EMG (electromyography) findings, OT treatment either rescued and/or restored neuromuscular performance in a dose-dependent manner. Following OT treatments, a significant decrease in MDA (malondialdehyde) levels, and a significant increase in GSH

(glutathione) levels were detected. The results showed us OT alleviates the harmful effects of hyperglycemia on peripheral neuronal cells by suppressing inflammation, oxidative and apoptotic pathways [63].

4.4 Rotenone induced Parkinson's disease

The brain is the most complex human organ and is extremely sensitive to the action of external chemicals and/or physical factors during its ontogenesis. Exposure to xenobiotics has raised great concern about the increasing prevalence of neurodevelopmental disorders and the possible unknown developmental neurotoxic effects of certain chemicals and drugs [69, 70].

Rotenone is a commonly used plant-derived pesticide that inhibits mitochondrial complex I of the electron transport chain [71]. Rotenone has been suggested as one of the most important environmental risk factors for Parkinson's Disease (PD) [72, 73]. Clinical and experimental studies have strongly supported that it is not only the SNc (substantia nigra pars compacta) and striatum, but also other regions, such as ventral tegmental area (VTA), have important roles in the pathophysiology of PD [74–76]. Accumulating evidence indicates that OT exerts its cytoprotective effects via anti-oxidative, anti-apoptotic, and anti-inflammatory pathways [44, 77, 78]. In recent years, rotenone-induced PD model in rats is commonly used to study the mechanisms of neuronal degeneration in PD. Erbas *et al.* observed a considerable cytoprotective effect of OT on cell death in dopaminergic neurons due to rotenone toxicity [79]. In the study, immunohistochemical evaluation of the brains showed decreased tyrosine hydroxylase immunoreactivity in saline-treated PD animals whereas OT administration significantly enhanced TH (tyrosine hydroxylase) expression in the striatal neurons. Considering that caspase activities play an important role in rotenone-induced cell death, the results obtained from the study revealed that OT reduces apoptosis by affecting mitochondrial caspase pathways and death signals [79]. *In vivo* and *in vitro* studies demonstrate that OT has a triggering role in cell proliferation and neurogenesis [80, 81].

4.5 Hypoxia

The factors that cause brain damage are varied. These factors include inflammation, birth trauma, tumors, stroke, ischemia, and hypoxia, as well as metabolic and genetic disorders. Hypoxia is the insufficient oxygen supply of the cell. It leads to neurodegeneration by causing mitochondrial dysfunction. Disruption of aerobic respiration mechanism causes different degrees of hypoxia in the tissue. As a result of damage, neurodegeneration, and brain dysfunction accompanied by cognitive impairment are observed [82–84]. Depending on the degree of hypoxia, activation of potassium channels, increase in perivascular PH, elevated blood and tissue concentrations of CO2, variation in intracellular calcium levels may contribute to neurodegeneration [85]. Regardless of neuronal damage, another factor underlying hypoxia-induced neonatal seizures may be a decrease in gamma-aminobutyric acid (GABA) activity [42, 86]. The cerebral cortex, hippocampus, striatum, and cerebellum have been shown to be the primary areas that are significantly affected by hypoxia and these regions have been associated with the resultant long-term cognitive problems in animal models [87]. In 2018, Panaitescu *et al*. reported that OT showed hippocampal neuroprotective effects and reduced the number of cumulative seizures in hypoxia-induced rats [88]. OT suppresses inflammation in the central nervous system and has another vital role that concerns GABA

(gamma-aminobutyric acid; a neurotransmitter in the brain); it alternates the GABAergic neurons from depolarizing to hyperpolarizing in terms of supporting normal anoxia associated with labor and delivery [88–90]. In a study, results showed that OT treatment given in the acute period of hypoxia had ameliorative effects on PTZ (pentylenetetrazol; a GABA(A) receptor antagonist)-induced convulsions in the long term. Also, it was observed significantly decreased TNF-α level in both of the hypoxia groups that were given OT treatment [91]. Possible mechanisms of this effect were hormone suppresses inflammation and reduces hippocampal gliosis, and anticonvulsant effect by increasing GABAergic activity. That conclusion was exemplified by the significantly decreased TNF-α level in both of the hypoxia groups that were given OT treatment. Brain inflammation caused by LPS (lipopolysaccharide) is characterized by neuronal loss and microglial activation. Findings have demonstrated that OT suppressed lipopolysaccharide-induced microglial activation [91, 92]. Studies also have shown that OT reduces the release of cytokines such as TNF-α, IL-6, IL-1β (interleukin 1 beta), IFN-γ (interferon-gamma) by suppressing inflammation [93].

4.6 Stroke

Stroke is a sudden decrease or cessation of blood flow to the brain. It can occur when one of the brain vessels ruptures and blood bleeds into the brain tissue or brain membranes. This is known as "brain hemorrhage". Depending on the affected brain region, speech, muscle strength, coordination-balance, vision, or memory loss occur. Technical advances in neuroimaging and neuropathology have facilitated the understanding of ischemia, infarction, and hemorrhage in the brain [94]. Neuronal injury in stroke is caused by different mechanisms, including excitotoxicity, inflammation, oxidative stress, and apoptosis [95].

Cerebral ischemia induces microglial activation by a strong inflammatory reaction with peripheral leukocyte influx into the cerebral parenchyma. Interruption of cerebral blood flow causes necrotic neuron death by affecting energy metabolism. In addition, different immune responses occur and inflammatory cell activation develops. Inflammatory cells can release a variety of cytotoxic agents including more cytokines, matrix metalloproteinases (MMPs), nitric oxide (NO), and more ROS (**Figure 7**) [95, 96].

One of the dramatic events during ischemia is the increase in intracellular calcium (Ca + 2), which leads to the activation of calpain proteases [97]. A study shows that calpain-1 increases reactive oxygen species levels and inflammatory cytokines [98]. Increased oxidative stress followed by calcium influx, mitochondrial dysfunction, and the loss of cytoskeletal proteins are phenotypes commonly observed in Alzheimer, Huntington, and Parkinson's diseases, as well as amyotrophic lateral sclerosis, stroke, ischemia, spinal cord injury, and TBI (traumatic brain injury) [99].

Neuroprotective effects of OT and the underlying molecular mechanisms are under discussion after different ischemia–reperfusion models [100, 101]. Jankowski *et al* reported that treatment with OT after cardiac ischemic induction in rats can reduce myocardial infarct size and improve heart function [102]. In a study, Etehadi *et al* showed a significant decrease in calpain-1 expression after OT administration in the tMCAO (transient middle cerebral artery occlusion) model. This refers to the neuroprotective role of OT, which could result in the inhibition of calpain [38]. Overall, these findings will add to our knowledge of the positive effects of OT on the outcomes of stroke.

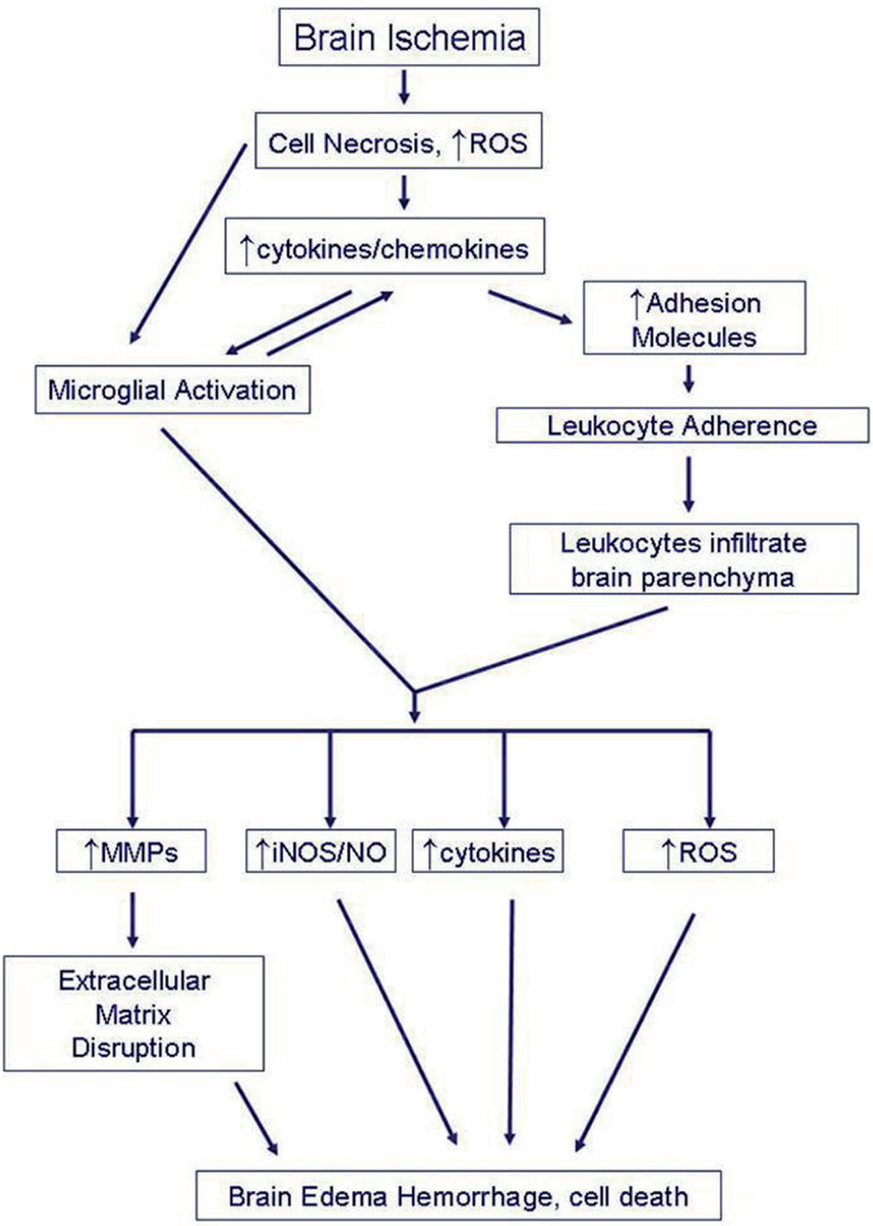

Figure 7.
"Brain ischemia triggers inflammatory responses due to the presence of necrotic cells, generation of reactive oxygen species (ROS), and production of inflammatory cytokines even within neurons" (Wang Q et al. 2007) [95].

5. Summary and discussion

The effect of oxytocin as a neuromodulator is a subject that has been studied in many different ways. It effectively provides nerve regeneration in nerve damage is a known issue. In addition, its anti-epileptic attack or reducing attack power effect in epilepsy models has also been shown in some studies. It plays an important role in the regulation of spinal autonomic functions. Although it regulates urination reflex and uterine motility, it can increase heart rate and renal sympathetic activity. Considering the positive effects of OT on the brain, reproductive system, immune and autonomic nervous system it shows promise as future treatment agents on the spectrum of anxiety, autism, personality disorders, and neurodegenerative disorders. Studies reveal that oxytocin shows its cytoprotective effects through its anti-inflammatory, anti-apoptotic and antioxidant properties. In chronic inflammation, immune cells constantly attack healthy tissues, resulting in

conditions such as obesity, cancer, diabetes, heart disease, autoimmune diseases, Alzheimer's, and some other diseases. Increasing the effectiveness of anti-inflammatory agents such as OT will improve the quality of life by changing the course of many diseases.

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