

## Paraneoplastic Encephalomyelitis Opinion and Treatment Encephalitis is a Seditious Condition of the Brain with Numerous Etiologies

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### Abstract

The neuroendocrine system has close interactions with the immune system. Their bidirectional communications emerged decades ago. On the one hand, there is a flow of information from the activated immune system to the hypothalamus. Antigenic stimulation changes the electrical activity of the hypothalamus and major endocrine responses; following thymectomy, hypothalamic cells degenerate extensively, appearing losses of nuclei or shrunk markedly. On the other hand, the autonomic nervous system and neuroendocrine outflow via the pituitary mediate brain modulation of immunologic activities. Thus, there is a neuroendocrine-immune network in the living organisms. In this network, the hypothalamus is the higher neuroendocrine center that regulates immunologic activities, and the target of immunologic activities. The immune-regulating ability of the hypothalamic center is represented by the hypothalamic-pituitary-adrenal (HPA) axis, the hypothalamic-pituitary-thyroid axis, and the hypothalamic-pituitary-gonad axis [1]. These axes function mainly through releasing Aden hypophysial hormones and are likely decisive in lymphoid cell homeostasis, self-tolerance, and pathology. Recently, critical roles of hypothalamic oxytocin-secreting system in immune regulation also become clear following the pioneer insight of Dr. Pittman. In this review, we further clarify how the oxytocin secreting system could be a major part of the neuroendocrine center that regulates immunologic activities.

**Keywords:** Cytokine; Hypothalamus; Oxytocin

### Introduction

The hypothalamic neuroendocrine system has extensive and bidirectional interactions with immune system. In parallel with the hypothalamic-pituitary-adrenal axis, the oxytocin-secreting system composed of hypothalamic oxytocin neurons and their associated neural tissues has also emerged as a major part of the neuroendocrine center that regulates immunologic activities of living organisms [2]. This oxytocin neuron-immune network can synthesize and release many cytokines and oxytocin while being the target of both oxytocin and cytokines by the mediation of corresponding receptors. Pathogens and cytokines along with the humoral and neural activities induced by them provide afferent input onto oxytocin neurons while oxytocin, cytokines and autonomic nervous systems convey efferent signals from the oxytocin-secreting system to the immune system. Serving as an integrative organelle, the oxytocin-secreting system coordinates all neural, humoral, and immunologic signals to change immunologic activities through releasing oxytocin into the brain and blood to minimize pathological injury and secure the functional stability of our body. Oxytocin exerts these effects through strengthening surface barriers and maintaining immunologic homeostasis involving both humoral immunity and cellular immunity [3]. In this review, we revisit the novel concept: the oxytocin-secreting system is the center structure in the oxytocin neuron-immune network.

### Oxytocin role in postpartum

It plays a vital role in labour and delivery. The hormone is produced in the hypothalamus and is secreted from the paraventricular nucleus to the posterior pituitary where it is stored. It is then released in pulses during childbirth to induce uterine contractions. The concentration of oxytocin receptors on the myometrium increases significantly during pregnancy and reaches a peak in early labor. Activation of oxytocin receptors on the myometrium triggers a downstream cascade that leads to increased intracellular calcium in uterine myofibrils which strengthens and increases the frequency of uterine contractions. In humans, most hormones are regulated by negative feedback; however, oxytocin is one of the few that is regulated by positive feedback. The

head of the fetus pushing on the cervix signals the release of oxytocin from the posterior pituitary of the mother. Oxytocin then travels to the uterus where it stimulates uterine contractions. The elicited uterine contractions will then stimulate the release of increasing amounts of oxytocin. This positive feedback loop will continue until parturition. Since exogenously administered and endogenously secreted oxytocin result in the same effects on the female reproductive system, synthetic oxytocin may be used in specific instances during the antepartum and postpartum period to induce or improve uterine contractions.

### The oxytocin neuron-immune network

The oxytocin-secreting system is mainly composed of magnocellular oxytocin neurons in the supraoptic nucleus, paraventricular (PVN) nuclei and several hypothalamic accessory nuclei, the posterior pituitary harboring their axonal terminals, their associated glial cells and presynaptic neurons that directly regulate oxytocin neuron activities. The parvocellular paraventricular oxytocin neurons are another branch of the oxytocin-secreting system and the major source of brain and spinal cord oxytocin, which have close interactions with the magnocellular oxytocin neurons [4]. In this system, oxytocin neurons can sense changes in synaptic innervations, astrocytic activity, blood-borne factors, and self-released chemicals as well as the levels of immune cytokines in the local neural circuit. Oxytocin neurons subsequently integrate these signals and regulate

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immunologic activities by releasing oxytocin into the blood and the brain. Correspondingly, oxytocin receptors (OXTRs) are extensively expressed in central and peripheral tissues including classical immune organs, tissues and cells, such as monocytes and macrophages, thymic T-cells, and mesenchymal stromal cells of adult bone marrow. Thus, oxytocin can modulate activities of both the innate and acquired immune systems while exerting broad effects on the activity of central and peripheral tissues. Conversely, oxytocin neurons also express many cytokine receptors, such as interleukin (IL)-6 and receive modulation of immunologic activities. Thus, the oxytocin-secreting system and the immune system form a functional unit in our body's defense system.

Relative to oxytocin, the known association of vasopressin with immune system is mostly indirect and limited. The immunologic regulatory role of vasopressin is likely due to its promotion of adrenocorticotropin hormone release. In murine thymus, OXTR presents in all T-cell subsets, much broader than the presence of vasopressin receptors. Neutralizing oxytocin but not vasopressin using specific antibodies induces a marked increase in IL-6 and leukemia inhibitory factor secretion in cell cultures. Relative to the clear immunologic effect that blocking OXTRs significantly inhibits the productions of cytokines IL-1 $\beta$  and IL-6 elicited by anti-CD3 treatment of human whole blood cell cultures, the immunologic functions of vasopressin were largely not verified. Thus, we tentatively believe that the oxytocin- but not vasopressin-secreting system is the major carrier in neuroendocrine regulation of immunologic activities via the neurohypophysis [5].

### Participation of the oxytocin-secreting system in layered immunologic defenses

The immune system protects the body against diseases through detecting pathogens, preventing their invasion/diffusion, reducing their injury effects and eradicating them from the body. The oxytocin-secreting system executes these functions through three layered defenses with increasing specificity that include the surface barriers, the innate and the adaptive immune processes.

**Surface barriers:** The most primary form of immune defense system is the surface barriers that include the physical and chemical barriers. The physical barriers can prevent pathogens such as bacteria and viruses from entering the organism. A prerequisite of executing this function is the structural integrity of the barriers like the skin, blood-brain barrier, and intestinal mucus as well as individual cells and tissues. Oxytocin involves this layer of defense at first by its antibiotic ability and wound-healing effect [6]. It has been reported that in patients with diabetes mellitus, oxytocin inhibits the focal microflora of pyo-inflammatory processes and leads to a more rapid elimination of microorganisms from the pyo-inflammatory focus. Moreover, local application of oxytocin increases the efficacy of ciprofloxacin in treating septic wounds. Through enhancing the function of classical antibiotics and direct antimicrobial effect, oxytocin can accelerate wound closure by promoting vasculogenesis and proliferation of endotheliocytes and histiocytes, and thus increase skin resistance to pathogen infections. That locally applied oxytocin promotes the barrier functions is also associated with its antisecretory and antiulcer effects. Subcutaneous application of oxytocin cannot only reduce burn-induced skin damage but also alleviate gastric and ileal inflammation and damage by reducing tissue neutrophil infiltration and TNF- $\alpha$  release. Moreover, oxytocin can strengthen the intestine mucosa barrier by inducing prostaglandin E2 release. In addition, oxytocin can also maintain the structural integrity of cellular and tissues against ischemic injury as shown in rats' kidney, liver, skeletal muscle,

ovary and heart. Similarly, intraperitoneal oxytocin administration accelerates functional, histological, and electrophysiological recovery after different sciatic injury models in rats. By maintaining the integrity of individual cells, tissues and organ systems, oxytocin can strengthen the physical barriers and in turn enhance body's defense ability [7].

**Innate immune system:** If a pathogen breaches the surface barriers and gets into the body, the innate immune system can provide an immediate response by releasing antibacterial molecules and mobilizing immune cells. Different from the actions of other immunologic modulators, the effect of oxytocin on the innate immunity is at mobilizing the immune defense potential while suppressing pathogenic injury due to over-reactions of the innate immunity. As reported, oxytocin acts on mesenchymal stromal cells of adult bone marrow to promote bone formation and all blood lineages. Thus, oxytocin can increase the reserve of immunologic capacity. Conversely, lipopolysaccharide and sepsis can increase plasma oxytocin levels, which in turn decreases TNF- $\alpha$  and IL-1 $\beta$  levels in the macrophages and reduces superoxide production in OXTR-bearing monocytes and macrophages [8-10]. Oxytocin also suppresses endotoxin-induced increases in plasma adrenocorticotropin hormone TNF- $\alpha$ , IL-1, IL-6, and other cytokines. In the ant ischemic injury effect, oxytocin diminishes cell apoptosis and fibrotic deposits in the remote myocardium while suppressing inflammation by reduction of neutrophils, macrophages and T-lymphocytes. Although oxytocin could also exert proinflammatory effect at uterus, specifically at human labor, it mainly plays immunologic homeostatic roles in response to immunologic challenges. The immune-regulating function of oxytocin also presents in the transplantation of mesenchymal stem cells. Oxytocintreated umbilical cord derived- mesenchymal stem cells show a decrease in tube formation but a drastic increase in transwell migration activity. This effect is associated with the increased transcription level of matrix metalloproteinase-2. The oxytocin pretreatment also increases mesenchymal stem cells engraftment and connexin expression in infarcted myocardium and cardiac contractility in rats, which along with the inhibitory effect of oxytocin on inflammatory cytokine release would facilitate the success of cell transplantation. Immunodeficiency: Oxytocin can be beneficial to the treatment of human immunodeficiency. For instance, in ADIS patients, the number of oxytocin neurons reduces significantly in the PVN; through increasing CD4+ cell counts, oxytocin can improve the health status of women infected with HIV.

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