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# Center Role of the Oxytocin-Secreting System in Neuroendocrine-Immune Network Revisited

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**Abstract**

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. 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. In this review, we revisit the novel concept: the oxytocin-secreting system is the center structure in the oxytocin neuron-immune network.

**Keywords:** Cytokine; Hormone; Hypothalamus; Immune; Oxytocin; Thymus

## Introduction

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 [1,2]. On the other hand, the autonomic nervous system and neuroendocrine outflow via the pituitary mediate brain modulation of immunologic activities [3]. 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 [4]. These axes function mainly through releasing adenohypophysial hormones and are likely decisive in lymphoid cell homeostasis, self-tolerance, and pathology [4]. Recently, critical roles of hypothalamic oxytocin-secreting system in immune regulation [5] also become clear following the pioneer insight of Dr. Pittman [6]. In this review, we further clarify how the oxytocin-secreting system could be a major part of the neuroendocrine center that regulates immunologic activities.

## 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 [7], 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 [8,9], which have close interactions with the magnocellular oxytocin neurons [10]. In this system, oxytocin neurons can sense changes in synaptic innervations [11], astrocytic activity [12], blood-borne factors [13,14], and self-released chemicals [15,16] as well as the levels of immune cytokines in the local neural circuit [17]. Oxytocin neurons subsequently integrate these signals and regulate immunologic activities by releasing oxytocin into the blood and the brain [18]. Correspondingly, oxytocin receptors (OXTRs) are extensively expressed in central and peripheral tissues [19] including classical immune organs, tissues and cells, such as monocytes and macrophages [20], thymic T-cells [21], and mesenchymal stromal cells of adult bone marrow [22]. 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 [23]. Conversely, oxytocin neurons also express many cytokine receptors, such as interleukin (IL)-6 [24] and receive modulation of immunologic activities [2]. Thus, the oxytocin-secreting system and the immune system form a functional unit in our body's defense system.

In the oxytocin neuron-immune network, the oxytocin-secreting system is considered as a major part of the neuroendocrine center regulating immunologic activity [5], which possesses the following features.

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oxytocin secretion [14]. T is relationship allows positive feedback

of individual cells, tissues and organ systems, oxytocin can strengthen the physical barriers and in turn enhance body's defense ability.

Along with the physical barriers, oxytocin can also exert the defensive functions by using chemical barriers through mobilization of some anti-pathogenic chemicals. For instance, in the respiratory tract epithelium of rats infected with Escherichia coli, oxytocin can activate the protective functions of the epithelial secretory cells by supporting their protein-synthetic and mucin-producing functions, and thus stabilize the protective epithelial mechanisms [74]. By this way, oxytocin helps to limit the number and activity of pathogens that exist on the surface of the physical barriers.

On the other hand, injury can significantly increase oxytocin levels in the brain as shown in rats with acutely induced pancreatitis [75] and in the blood as seen in a chronic inflammatory/nociceptive stress model [76]. Thus, in response to nociceptive stimuli, the oxytocin-secreting system can reactively release more oxytocin into the brain and the circulation, and thus strengthen the surface barriers by maintaining the structural integrity of cells, tissues and body's surface, and by inhibiting bacteria.

**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 [22]. Thus, oxytocin can increase the reserve of immunologic capacity. Conversely, lipopolysaccharide [77] and sepsis [78] can increase plasma oxytocin levels, which in turn decreases TNF-α and IL-1βα

In addition, oxytocin is also involved in anaphylaxis. Anaphylaxis is a

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