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Review article

Oxytocin-secreting system: A major part of the neuroendocrine center regulating immunologic activity

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ABSTRACT

Interactions between the nervous system and immune system have been studied extensively. However, the mechanisms underlying the neural regulation of immune activity, particularly the neuroendocrine regulation of immunologic functions, remain elusive. In this review, we provide a comprehensive examination of current evidence on interactions between the immune system and hypothalamic oxytocin-secreting system. We highlight the fact that oxytocin may have significant effects in the body, beyond its classical functions in lactation and parturition. Similar to the hypothalamo–pituitary–adrenal axis, the oxytocin-secreting system closely interacts with classical immune system, integrating both neurochemical and immunologic signals in the central nervous system and in turn affects immunologic defense, homeostasis, and surveillance. Lastly, this review explores therapeutic potentials of oxytocin in treating immunologic disorders.

Contents

1. Introduction

Neuroendocrinoimmunology is a multidisciplinary field integrating neurology, endocrinology, and immunology. It is a major branch of neuroimmunology focusing on the interactions between neural and

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immune processes. This concept emerged gradually over past decades and expanded rapidly to include almost all aspects of neurology, endocrinology and immunology, particularly their interactions during responses to adverse challenges (Kelley et al., 2007). In this review, we discuss an important neuroendocrine mechanism regulating immunologic activities that have received much less attention than the hypothalamic–pituitary–adrenal (HPA) axis, i.e., the involvement in the hypothalamic oxytocin-secreting system.

2. Oxytocin-secreting system

Oxytocin is a mammalian neuropeptide and an essential humoral factor in lactation and parturition (Burbach et al., 2001). In the central nervous system, genes encoding oxytocin and its carrier protein, neurophysin I are expressed in the magnocellular neurons of hypothalamic supraoptic (SON), paraventricular (PVN) nuclei and several accessory nuclei (Knobloch and Grinevich, 2014). In these larger neuroendocrine cells, oxytocin and neurophysin I are mainly co-transported along axons, stored in posterior pituitary and released into circulation to (classically) affect lactation and parturition. In the parvocellular portion of the PVN, oxytocin neurons with smaller cell bodies (parvocellular) provide axonal projections to widespread parts of the brain and spinal cord (Pittman et al., 1984; Landgraf et al., 1990a; Knobloch et al., 2012). Oxytocin receptors (OXTRs) are found extensively distributed throughout central and peripheral tissues (Gimpl and Fahrenholz, 2001). Thus, oxytocin can broadly modulate the activity of centrally controlled autonomic function and a variety of social and nonsocial behaviors (Yang et al., 2013; Veening and Olivier, 2013) that will not be discussed here. While the presence of OXTRs in mammary and uterine smooth muscle and a variety of other peripheral tissues has long been known, it is now appreciated that cells of the immune system also contain OXTRs that are accessible to circulating oxytocin.

Oxytocin neuron activity and oxytocin release are modulated by neurochemicals in extracellular space immediately surrounding oxytocin neurons through synaptic innervations, astrocytic activity, blood-borne factors, metabolic products, and auto-regulation. Oxytocin neurons receive synaptic innervations originating from both peripheral and central loci, and function to integrate various neurochemical events and serve as an outlet of neural activities that regulate oxytocin-associated life processes (Brown et al., 2013). The responses of oxytocin neurons to neural and humoral factors mainly depend on the functional states of their adjacent astrocytes (Wang and Zhu, 2014). For instance, disabling astrocytic functions can disrupt the pulsatile secretion pattern of oxytocin during lactation (Wang and Hatton, 2009). Oxytocin can also be released from somatodendritic sites of oxytocin neurons to auto-regulate their own activity (Ludwig et al., 2002; Hirasawa et al., 2004; Wang et al., 2006). Blood-borne factors, such as cholecystokinin (Yamashita et al., 2013; Katoh et al., 2014) and cytokines like interleukin (IL)-1β (Brunton et al., 2006) contribute to oxytocin neuron activity as well. Nevertheless, effects of extracellular neurochemical cannot be actualized until synergistic reactions occur in intracellular signaling processes (Hatton and Wang, 2008; Makani et al., 2013). Lastly, genomic processes determine long-term morphological properties and functional features of oxytocin neurons (Yue et al., 2008). Clearly, the activity of the oxytocin-secreting system reflects integrative neurochemical processes at multiple levels while being a mediator of neural modulation of other systems including the immune system.

3. Immunologic functions of the oxytocin-secreting system

In neuroendocrinoimmunology, the modulatory effect of the oxytocin-secreting system on the activity of immune system has come to gain the attention of many neuroendocrinologists and immunologists. The interaction between oxytocin-secreting and immune systems is highlighted as an important component in this discipline (Pittman, 2011). For instance, oxytocin secretion from oxytocin neurons is directly modulated by prostaglandins, endocannabinoids and nitric oxide (Carnio et al., 2006; De Laurentiis et al., 2010) and by various classical immune cytokines, such as IL-1β (Landgraf et al., 1995; Landgraf et al., 1995; Summy-Long and Hu, 2009). Inhibiting the production or action of these mediators also blocks modulatory effects of many neurochemicals. The use of indomathecin to inhibit the production of prostaglandins can also block the excitatory effect of oxytocin on oxytocin neurons (Wang and Hatton, 2006). Importantly, oxytocin itself carries a variety of immune functions, including immunologic defense, homeostasis and surveillance as further reviewed below.

Oxytocin has dramatic regulatory roles in immunologic defense and homeostasis. Septic shock can result from an excessively defensive and inflammatory response by releasing cytokines into the circulation from activated immune cells. These cytokines reach neuroendocrine organs, acting either directly by themselves or through the release of intermediates such as prostaglandins, catecholamine and nitric oxide, which affect the release of oxytocin and other hormones (Carnio et al., 2006). Thus, an increase in oxytocin levels can serve as a potential biomarker of an infectious process, while contributing to the overall host response to infection by decreasing the proinflammatory response and oxidative stress. It was observed that in the early phase of sepsis (4–6 h), there is an increased level of oxytocin in plasma, which decreases nitrite, tumor necrosis factor-α (TNF-α) and IL-1β levels in the macrophages (Oliveira-Pelegrin et al., 2013). This effect is seen in both humans and animals to minimize immunologic damages (Ross et al., 2013; Wang et al., 2013). Thus, oxytocin can attenuate immunologic disturbances and exert protective effects by restoring the host homeostasis. This view is in agreement with evidence that released oxytocin acts both within the brain and in the periphery to maintain cardiovascular and metabolic homeostasis, and to limit the rise in body temperature, which allows the organism to successfully endure immunologic challenges (Pittman, 2011).

In immune surveillance, effects of oxytocin are even more complex than in immunologic defense and homeostasis. In infectious diseases, the serum level of oxytocin increases significantly. Besides serving as an infectious biomarker, oxytocin can also respond to pathogen threats and elicit a variety of adaptive behavioral responses to suppress complications. For instance, oxytocin is involved in olfactory bulb-mediated social recognition and response to environmental threats; evidence from rodents indicates that oxytocin may be important for signaling animals to avoid infected individuals through odorant clues (Kavaliers and Choleris, 2011). Oxytocin and the immune system communicate closely to monitor and modulate carcinogenesis (Imanieh et al., 2014) although the underlying mechanism is unknown. Mravec et al. reported that cancer at its advanced stage could activate Fos expression in oxytocin neurons of hypothalamic PVN, SON and accessory nuclei (Mravec et al., 2009). In normal human lungs, OXTR is co-localized with vascular endothelial cells of the lung and is not expressed by lung cells of epithelial nature; however, OXTRs are expressed in 86% of small cell lung carcinoma biopsies and 50% of non-small cell lung cancer biopsies (Pequeux et al., 2005). Gene expression of OXTRs can accurately distinguish 136 liver metastases of small bowel and pancreas neuroendocrine tumors with 94.1% accuracy (Sherman et al., 2014). As illustrated above, oxytocin plays critical roles in monitoring tumorigenesis, and can serve as a potential diagnostic and therapeutic target in different malignancies.

Oxytocin can prevent some tumorigenesis through identification, destruction and prompt elimination of mutant cells. A typical example is its inhibitory effects on breast cancer. Breast cancer increases pituitary release of oxytocin by inhibiting insulin-regulated aminopeptidase (an oxytocinase) and decreasing hypothalamic catabolism of oxytocin (Carrera-Gonzalez et al., 2011). However, activity of this oxytocinase increases significantly in human breast cancer tissue (Pilar Carrera et al., 2006), which decreases oxytocin levels in mammary tissues. Since oxytocin can inhibit the proliferation of breast cancer, as shown in MCF7 estrogen-dependent human breast cancer cells (Cassoni et al., 2002), a reduction of oxytocin in the mammary tissue can partially account for