Cardiovascular Action of Oxytocin

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Editorial

Oxytocin, a neuropeptide that participates in mammalian birth and lactation, is produced primarily in the hypothalamus. Oxytocin, acting in the central nervous system, plays an important role in a variety of complex social behaviors in mammals. Recent studies have suggested that oxytocin is endowed with plerotropic effects on cardiovascular system, intrinsic oxytocin system is critical for maintenance of cardiovascular homeostasis [1,2]. It has also been proposed that oxytocin may work directly on vascular cells to slow the progression of pathophysiological processes involved in cardiovascular diseases [3].

Oxytocin is synthesized and released in the heart and the vasculature of rats [4,5]. The intrinsic oxytocin in the heart stimulates the local release of atrial natriuretic peptide (ANP) that slows the heart rate and decreases cardiac contractility [6]. Oxytocin action of cardiovascular system is mediated by oxytocin receptors, which are present in both the heart and large vessels [5]. Oxytocin receptors are members of a subclass of G-protein-coupled receptor and activation of the receptor transducer signaling via Gαq and Gαi subunits to activate phospholipase Cβ and mitogen-activated protein kinase, resulting in increased intracellular calcium concentration [7]. The expression of oxytocin and its receptor is eminent in postnatal cardiomyocytes, and decreases with age to low levels in adults [8]. However, oxytocin receptors develop in the endothelial cells at postnatal and achieve a plateau in adult rats, indicating a dynamic regulation of oxytocin system in the heart rather than constitutive expression [8]. Interestingly, the cardiac oxytocin expression in the fetal heart was upregulated by retinoic acid, a well-recognized major cardiomyogen. An oxytocin antagonist inhibited retinoic acid-mediated cardiomyocyte differentiation of embryonic stem cells, suggesting that cardiac oxytocin system play the role in retinoic acid-induced cardiomyogenesis [8].

The homeostatic functions of the intrinsic cardiovascular oxytocin system are beginning to be understood. It has been proposed that balance between nitric oxide (NO) and oxidative stress is critical for maintenance of cardiovascular homeostasis [9]. NO is an important protective molecule in cardiovascular system. NO, an endogenous vasodilator, inhibits proliferation of vascular smooth muscle and aggregation of platelet and has anti-inflammatory and anti-atherogenic effects [10]. We recently demonstrated that oxytocin dose-dependently increased eNOS phosphorylation in HUVECs in vitro as well as in the aorta of rat ex vivo (ATVB). In the rat with myocardial infarct (MI) oxytocin reduced MI size and improved cardiac function and remodeling with increased eNOS expression in the scar area [11]. In the context of ischemia-reperfusion injury, pretreatment with oxytocin protected against ischemia-reperfusion-induced myocardial injury and ventricular arrhythmia, which appeared to be mediated by stimulation of NO and ANP synthesis/release, because the protective effects of oxytocin were diminished by either eNOS inhibitor L-NNAME or ANP receptor blocker [12]. In addition, Menaouar et al [1] demonstrated that in cultured newborn and adult rat myocardocyte oxytocin significantly attenuated angiotensin II- or endothelin-1-induced myocardocyte hypertrophy. The anti-hypertrophic effects of oxytocin were also attenuated by L-NNAME or ANP receptor blocker, suggesting involvement of NO and ANP-cGMP pathway.

Increased vascular oxidative stress and inflammation play a critical role in the pathogenesis of hypertension and cardiovascular diseases [13,14]. Oxytocin receptors are expressed in human endothelial cells and THP1 monocyte and macrophage, oxytocin decreased both superoxide production and release of proinflammatory cytokine from these cells [3]. Oxytocin inhibition of inflammatory cytokines has also been demonstrated in both humans and animals in vivo and ex vivo, which may be mediated by stimulation of the cholinergic anti-inflammatory pathways [15,16]. It has been shown that oxytocin abolished the sepsis-induced increase in tumor necrosis factor α, and protected against multiple organ damage [17]. The anti-inflammatory effects of oxytocin are implicated in its regression of atherosclerosis [2,16]. Chronic administration of oxytocin attenuated aortic atherosclerotic lesion development with reduced secretion of the pro-inflammatory cytokine IL-6 in visceral adipose tissue in social isolated apo-E knockout mice and decreased plasma C-reactive protein level in Watanale Heritble Hyperlipidemic rabbits [12,16]. Clinical and experimental studies have shown that emotion-social stress increases cardiovascular and atherosclerotic diseases [18]. It is well established that oxytocin acts centrally to facilitate a variety of prosocial behaviors, affiliative social behaviors and warm contact stimuli are associated with elevations in plasma oxytocin [19,20]. Therefore, the plerotropic effects of oxytocin on cardiovascular system and decreased psychological-social stress suggests a potentially larger role in maintenance of cardiovascular homeostasis and attenuation of the diseases.

Several lines of evidences suggest that oxytocin may act as a central neurotransmitter or cardiovascular hormone to participate in the regulation of blood pressure [21]. First, oxytocinergic neurons innervate brain regions that control cardiovascular activities, such as nucleus tractus solitaries, nucleus ambiguous and dorsal motor nucleus of the vagus [21]. The microinjection of oxytocin into the rostral ventrolateral medulla produced a marked elevation of blood pressure [21]. Peripheral injection of oxytocin also affected blood pressure, although the responses were variable, with evidence for both pressor and depressor responses [22]. Second, baroreflex function, controlled by brainstem pathways, is modulated by oxytocinergic input. Higa and coworkers [23] reported that oxytocin and its antagonists injected into the nucleus of the solitary tract and dorsal motor nucleus of the vagus of conscious rats produced opposite effects on baroreflex activity, accentuation or inhibition, respectively. Third, studies on mice with genetic modification of oxytocin gene showed that mice with a deficient oxytocin exhibited a slightly reduced...
baseline blood pressure, an enhanced baroreflex gain and an enhanced pressor response to oxytocin [24], while overexpression of oxytocin receptors in the hypothalamic paraventricular nucleus increased baroreceptor reflex sensitivity and buffers blood pressure variability in conscious rats [25], suggesting that endogenous oxytocin in central neural system functions as a vasopressor peptide to enhance pressor response in normal condition. However, oxytocin knockout mice also exhibited an increased pressor response to chronic stress, suggesting that oxytocin has an inhibitory effect of stress-induced pressor response [26], because it has been proposed that oxytocin may act as an anti-stress hormone with regards to the cardiovascular axis [27]. Inhibitory effects of pressor response to chronic stress may be related to anti-stress effect of oxytocin. Blood volume is essential for blood pressure, particular for long-term regulation of blood pressure. It has been observed that isotonic volume expansion by intra-atrial injection of isotonic saline induced a rapid increase in plasma oxytocin and release of ANP from atria. It has been hypothesized that volume-ANP concentrations and a concomitant decrease in plasma pressure, particular for long-term regulation of blood pressure. It has been proposed that vascular oxytocin regulates vascular tone as well as vascular regrowth and remodeling [29]. Oxytocin can directly induce vasoconstriction or relaxation dependent on the vascular beds [21]. The cultured human vascular endothelial cells and aortic smooth muscle cells express oxytocin receptors [3]. Stimulation of these cells by oxytocin produced an increase in intracellular calcium, release of nitric oxide, and a protein kinase C-dependent cellular proliferative response [29,30].

In summary, oxytocin, a neuropeptide which is traditionally associated with female reproduction, has been implicated in several important cardiovascular functions including antioxidant, anti-inflammation, blood pressure and body volume regulation, stimulation/release of cardiovascular protective molecules including ANP and NO [1,12]. It has also been demonstrated that oxytocin may have a therapeutic beneficial effect on atherosclerosis and decreases stress-induced pressor response. Research has shed light that oxytocin may function as a cardiovascular protective molecule to play the role in maintenance of cardiovascular homeostasis and attenuation of the diseases. However, exploration in this area has only just begun, the findings warrant to be further investigated.

References


