

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

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Received date: Dec 06, 2015; Accepted date: Feb 11, 2016; Published date: Feb 15, 2016

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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 adenohipophysial 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.

The oxytocin-secreting system is essential for the development and functioning of major immune organs; that is the thymus and bone marrow. For example, after removal of the pituitary in chicken, the key link between the oxytocin-secreting system and the immune system, the thymic cortical and medullary compartments diminished markedly in size [25]. Consistently, oxytocin can also increase bone mass [26] and the production of hematopoietic progenitor cells [27]. Thus, oxytocin could be a critical factor for the development of the immune system.

The oxytocin-secreting system is also essential for immune regulation. Neurointermediate pituitary lobectomy blocks the secretion of neurohypophysial hormones and significantly reduces hormone and cell-mediated immune responses to pathological challenges in rats [28,29]. Blocking OXTRs inhibits T-cell differentiation in the thymus [30] and activates transcription factor NF-kappaB p65, prostaglandin synthesis and the expression and excretion of the inflammatory cytokines, IL-6 and CCL5 [31].

Oxytocin extensively modulates the functions of the immune system via multiple approaches. As revealed in rodents, oxytocin treatment results in a reduction of endotoxin-induced increases in plasma adrenocorticotropin hormone, cortisol, tumor necrosis factor- α (TNF- α), IL-1, IL-4, IL-6, macrophage inflammatory protein-1 α and 1 β , monocyte chemoattractant protein-1, interferon-inducible protein 10, and vascular endothelial growth factor [32]. Thus, oxytocin cannot only act on immune cells directly through OXTRs, but also change immune functions through other immune-regulating axes indirectly.

In the immunologic regulation, oxytocin neurons themselves are a source of immune cytokines, such as IL-1 β [17]. Thus, changes in oxytocin neuron activity will influence neural structures innervated by oxytocin neurons through co-released cytokines with oxytocin. Moreover, intracerebroventricular administration of IL-1 β can activate corticotropin-releasing hormone neurons, magnocellular oxytocin neurons, and the spinal cord-projecting PVN neurons; the activation of these neural structures sequentially activates vagal output and sympathetic outflows according to the polyvagal theory [33]. In this efferent approach, the PVN has been previously considered as an integrative center for immunomodulation since intracerebroventricular administration of IL-1 β activates the corticotropin-releasing hormone neurons, magnocellular oxytocin neurons and PVN-spinal cord sympathetic neural pathway [34] that innervated the thymus [35]. By modulating the activity of the HPA axis and PVN neurons [36], oxytocin can also change HPA axis-modulated sympathetic activity following immunologic challenges [24] and in turn alter thymic activities.

Oxytocin neurons are the target of immunologic activities. Under immunologic challenges, oxytocin neuron activity is modulated by cytokines, inflammatory cells, microglia, and pathogens [37]. Afferent pathway of immune challenges to oxytocin neurons involves vagal nerve, medullary dorsal vagal complex in the caudal brainstem [38], catecholaminergic projections [39], histaminergic neurons in hypothalamic ventral tuberomammillary nucleus [40], and the PVN [41]. Certainly, the supraoptic nucleus is also a direct target of immune cytokines, such as IL-1 β [42,43] and IL-6 [24]. Obviously, the oxytocin-secreting system can receive feedback regulation of immunologic activities to adjust its influence on immune system accurately.

As a whole, the oxytocin-secreting system and the immune system have bidirectional communications under both physiological

conditions and immunologic challenges, and constitute the oxytocin neuron-immune network.

Challenges to the central role of the oxytocin-secreting system in the neuroendocrine regulation of immunologic activities.

To establish the central position of the oxytocin-secreting system in the neuroendocrine regulation of immunologic activities, it is essential to clarify the following questions.

What is the relationship between the oxytocin-secreting system and other hypothalamic-pituitary-endocrine gland axes? The HPA axis has been considered as the central link of the neuroendocrine-immune network [3] and can suppress immunologic activities by counteracting adrenergic pro-inflammatory actions, prime the immune system, and potentiate acute defensive responses [44]. In fact, glucocorticoids secreted in response to stress activation of the HPA axis can exert feedback influences onto the hypothalamus to suppress neuroendocrine activation rapidly, including oxytocin secretion [45]. Conversely, oxytocin inhibits the activity of HPA axis, which depends on the site of intracerebral oxytocin release and the stressors exposed to the animals [36]. Moreover, there are synergistic actions of the two systems, such as the anti-inflammatory actions of corticosteroids and oxytocin. Thus, the HPA axis and the oxytocin-secreting system form a negative feedback loop in the central levels while functioning as collaborating partners in responses to immunologic challenges.

Thyrotropin-releasing hormone is another hypothalamic hormone and regulates immune activity by acting on immune cells directly and by promoting the release of thyroid hormones. Immune cells express thyrotropin-releasing hormone receptor, the activation of which promotes the development of the immune system and participates in the inflammatory process with specific relevance to the "cytokine-induced sickness behavior" paradigm [46]. However, the major carrier of the immune functions of the hypothalamic-pituitary-thyroid axis is thyroid hormones. In hyperthyroid mice, lymphocytes display higher T- and B-cell mitogen-induced proliferation; those from hypothyroid mice display lower T- and B-cell mitogen-induced proliferation. Triiodothyronine administration can reverse the latter effect [47]. There is also mutual interaction between the oxytocin-secreting system and hypothalamic-pituitary-thyroid axis. The oxytocin gene promoter has a composite hormone response element, which can respond to steroid/thyroid hormone. High doses of triiodothyronine elevates oxytocin mRNA levels in the PVN [48] and hyperthyroidism elevates the release of neurohypophysial oxytocin as shown in rats [49]. In contrast, oxytocin exerts an inhibitory role in thyroid hormone actions [50]. This likely serves as a compensatory measure to alleviate high fever in inflammatory diseases.

The third one is gonadotropin-releasing hormone that contributes to the sex-dependent changes in immune responsiveness during the estrous-menstrual cycle as well as pregnancy [51]. Oxytocin stimulates gonadotropin-releasing hormone secretion from hypothalamic explants whereas central administration of oxytocin antiserum abolishes the pro-estrous luteinizing hormone surge. This is associated with direct innervations of supraoptic oxytocin neurons on OXTR-bearing medial preoptic gonadotropin-releasing hormone neurons [52]. Conversely, the oxytocin-secreting system also receives modulation of sex steroid hormones in the hypothalamic-pituitary-gonad axis. For instance, allopregnanolone induces opioid inhibition over magnocellular oxytocin neurons and then inhibits oxytocin secretion in response to immune challenge [13]. Estrogen receptor- β activation increases oxytocin peptide transcription and promotes

oxytocin secretion [14]. This relationship allows positive feedback interactions between the two systems around ovulation while weakening oxytocin influence during pregnancy [43].

Collectively, in the neuroendocrine-immune network, oxytocin is a common regulator of other immune-regulating neuroendocrine axes while receiving feedback regulation by the activity of these axes. By this way, the oxytocin-secreting system subtly controls the neuroendocrine reactions to fit the defense requirement of the immune system.

The second question is whether the vasopressin-secreting system exerts the same effects as that of the oxytocin-secreting system on the immune system? Vasopressin presents in parallel with oxytocin in the hypothalamus; hypophysectomy [25] and the neurointermediate lobectomy [28,29] also involve the vasopressin secretion channel. Thus, it is possible that the vasopressin-secreting system is also responsible for the immunologic influences in the absence of the pituitary.

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 [44]. In murine thymus, OTXR presents in all T-cell subsets, much broader than the presence of vasopressin receptors [53]. Neutralizing oxytocin but not vasopressin using specific antibodies induces a marked increase in IL-6 and leukemia inhibitory factor secretion in cell cultures [54]. Relative to the clear immunologic effect that blocking OXTRs significantly inhibits the productions of cytokines IL-1 β and IL-6 elicited by anti-CD3 treatment of human whole blood cell cultures [55], 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.

Why there is no report of dramatic immune deficiency in oxytocin knockout mice? It seems quite straightforward to believe that the oxytocin or its receptor knockout would greatly delay the development of immune organs and result in immune deficiency or severe infectious diseases. However, among several hundred pieces of related publications, no one indicates such a phenomenon. Can this fact negate all experimental findings presented above? How should we interpret this obvious contradiction?

The first explanation is that the compensatory effects of some neurohormones could partially replace the functions of the oxytocin-secreting system, thereby masking the potential consequence of oxytocin deficiency. One clue is from the observation that the chronic absence of oxytocin in oxytocin-null mice leads to an increase in OXTR responsiveness as shown by the augmented grooming activity elicited by centrally administered oxytocin [56]. Supporting evidence is that despite the essential role of oxytocin in the regulation of parturition and maternal behaviors in wild-type animals [57], oxytocin knockout female mice are able to deliver their litters and maintain maternal behaviors once initiated [58]. One of such compensatory molecules could be vasopressin that has the ability to cross-activate OXTRs [19], the secretion of which become more sensitive to environmental changes in oxytocin-deficient animals [59]. Additionally, vasopressin does have some immune functions, such as promoting T-cell differentiation [53] that could become stronger in the absence of oxytocin. Certainly, the overlapping of the immunologic functions of HPA-, hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonad-axes with that of oxytocin could substitute some functions of the oxytocin-secreting system in the knockout mice.

On the other hand, it is possible that previous observations of these knockout mice did not thoroughly examine impacts of oxytocin deficiency on the immunologic activities. In the absence of oxytocin, there is a heightened response of the HPA axis to certain stressors such as overnight food or water deprivation in male mice [60]. Since intense stimulation of the HPA-axis and the ensuing increased levels of glucocorticoids can cause thymic atrophy [61], the lack of oxytocin is likely to decrease immune functions due to the increased HPA-axis reacting activity. It remains to examine if this is the case in the ontogenesis and functioning of the immune system in oxytocin deficiency.

Taken together, the integrative abilities of the oxytocin-secreting system in its regulating immunologic activities and the lack of integrative role of individual immune organs support the central position of the oxytocin-secreting system in the oxytocin neuron-immune network. Moreover, the coordinative ability of the oxytocin-secreting system over the activities of other well-established immune regulatory axes and autonomic nervous system highlights its dominant position in the neuroendocrine regulation of the immune system. Thus, we tentatively believe that the oxytocin-secreting system plays a central role in the neuroendocrine-immune network.

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. 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 [62]. Moreover, local application of oxytocin increases the efficacy of ciprofloxacin in treating septic wounds [63]. 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 [64], 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 [65,66]. Subcutaneous application of oxytocin cannot only reduce burn-induced skin damage but also alleviate gastric [65] and ileal [66] inflammation and damage by reducing tissue neutrophil infiltration and TNF- α release. Moreover, oxytocin can strengthen the intestine mucosa barrier by inducing prostaglandin E2 release [67]. In addition, oxytocin can also maintain the structural integrity of cells and tissues against ischemic injury as shown in rats' kidney [68], liver [69], skeletal muscle [70], ovary [71], and heart [72]. Similarly, intraperitoneal oxytocin administration accelerates functional, histological, and electrophysiological recovery after different sciatic injury models in rats [73]. 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.

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-1 β levels in the macrophages [78] and reduces superoxide production in OXTR-bearing monocytes and macrophages [20]. Oxytocin also suppresses endotoxin-induced increases in plasma adrenocorticotropin hormone, TNF- α , IL-1, IL-6, and other cytokines [32]. In the anti-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 [79]. Although oxytocin could also exert proinflammatory effect at uterus, specifically at human labor [80], it mainly plays immunologic homeostatic roles in response to immunologic challenges.

Adaptive immune system: If pathogens successfully break the non-specific immunity of the surface barriers and the innate immune defense, the adaptive immune system becomes active. Septic shock, for example, results from an excessively defensive and inflammatory response through releasing immune cytokines into the circulation by activated immune cells. These cytokines reach the supraoptic nucleus and increase the release of oxytocin and other hormones directly or through the release of intermediates such as prostaglandins, catecholamines and nitric oxide [81]. Oxytocin in turn regulates the specific immunity. For instance, oxytocin stimulates murine immature T cells and promotes interactions between thymic stromal cells and developing T cells, thereby promoting thymic T-cell differentiation [82]. Gut microbiome-triggered oxytocin release can activate host CD4+Foxp3+CD25+ immune T regulatory cells to facilitate wound healing [83]. In women infected with HIV, oxytocin can improve their health status through increasing CD4+ cell counts [84]. The effect of oxytocin on the acquired immunity can also be achieved through its promoting the release of prolactin [85]. Prolactin can increase CD4+

cells and the ratio of CD4+ versus CD8+ cells derived from inguinal lymph nodes [86]. Collectively, oxytocin can exert defensive functions through regulating the acquired immunity.

An important aspect of this acquired immunity is its differentiating the pathogen from self-antigens. Thymic epithelial and nurse cells synthesize oxytocin, the dominant peptide of the neurohypophysial family expressed by thymic epithelial and nurse cells in various species [87]. Thymic oxytocin is not secreted but is integrated within the plasma membrane of thymic epithelial cells after translocation of a hybrid neurophysin/MHC class I protein, thus allowing its presentation to pre-T cells [54]. Hence, oxytocin can serve as the self-antigen of the neurohypophysial family while being a source of signals to interact with OXTRs expressed by target pre-T cells.

Functional Implications

The critical position of the oxytocin-secreting system in the immune regulation allows it to regulate the cytotoxic and humoral immune processes extensively based on its participation of the immune defense, homeostasis and surveillance [5].

Restraining inflammatory responses to immune challenges: There is an increase in plasma oxytocin levels in the early phase of sepsis [78], which can decrease nitrite, TNF- α and IL-1 β levels in the macrophages of humans and animals [88]. Oxytocin decreases the cytokine activation caused by bacterial endotoxin in men [32] and decreases the elevation of serum lactate dehydrogenase and TNF- α levels in acetic acid-induced colitis [89]. Thus, oxytocin increase in the plasma can limit excessive inflammatory reactions, thereby reducing immunologic damages in infectious diseases.

Involvement in autoimmune diseases: The thymus can prevent autoimmunity through self-tolerance of T cells in the immune system. Oxytocin is one of the self-antigens predominantly expressed in thymic epithelium and is presented to thymus T cells for educating them to tolerate other antigens related to them [87,90]. Autoantibodies in sera from patients with multiple sclerosis are reactive with oxytocin neurons in rat and swine brains [91], which reduces the number of oxytocin neurons [92]. Thus, oxytocin is an important factor preventing autoimmune occurrence; impairing the oxytocin-secreting system is involved in the development of autoimmune diseases.

Transplantation: The immune-regulating function of oxytocin also presents in the transplantation of mesenchymal stem cells. Oxytocin-treated 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 [93]. The oxytocin pretreatment also increases mesenchymal stem cells engraftment and connexin 43 expression in infarcted myocardium and cardiac contractility in rats [94], which along with the inhibitory effect of oxytocin on inflammatory cytokine release [32] would facilitate the success of cell transplantation.

Immundeficiency: 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 [95]; through increasing CD4+ cell counts, oxytocin can improve the health status of women infected with HIV [84].

Others: As recently reviewed, the oxytocin-secreting system has the potential to suppress inflammation, increase the sensitivity of antibiotics, promote wound healing, and cure mental disturbance [5].

In addition, oxytocin is also involved in anaphylaxis. Anaphylaxis is a quite rare side effect of oxytocin in comparison with the hypotension and tachycardia observed in the induction, augmentation of labor and preventing postpartum hemorrhage [96]. However, it does occur in delivering women with latex allergy and bronchial asthma [97]. The fact again raises the necessity to use oxytocin in clinical trials with caution in the parturition-associated conditions.

Closing Remarks

Taken together, the interactions between the oxytocin-secreting system and the immune system have the following features. 1) The oxytocin-secreting system, immune and neural activities are parts of an integrative network that underlies many physiological processes and diseases, in which oxytocin neurons function as an immune-regulating organ participating in immune responses. 2) This network can synthesize and release neurotransmitters, neuropeptides, growth factors, neuroendocrine hormones and cytokines; shared ligands and receptors mediate the communication between oxytocin neurons and immune systems. 3) Information transmission from the immune system to oxytocin neurons runs through cytokines and vagus. Both the neuroendocrine and autonomic nervous systems convey efferent signals from the oxytocin-secreting system to the immune system. 4) This network is active when proinflammatory cytokines interrupt the function of a variety of hormones; the increased activity of this system can coordinate neural and humoral responses. 5) This system maintains the homeostasis of the internal environment during immunologic challenges through coordinating the interactions between cytokines, neural activity, oxytocin and other neurohormones. We believe that the better understandings of how this system synchronizes the activity of whole neuroendocrine-immune network, particularly effects of acutely removing oxytocin actions on various immune functions, will further highlight therapeutic potentials of the oxytocin-secreting system in immunologic diseases.

Acknowledgement

This work is sponsored by the National Natural Science Foundation of China (grant No. 31471113), and the higher education talents funds of Heilongjiang province (grant No. 002000154).

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