

## The immunological function of GABAergic system

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### 1. ABSTRACT

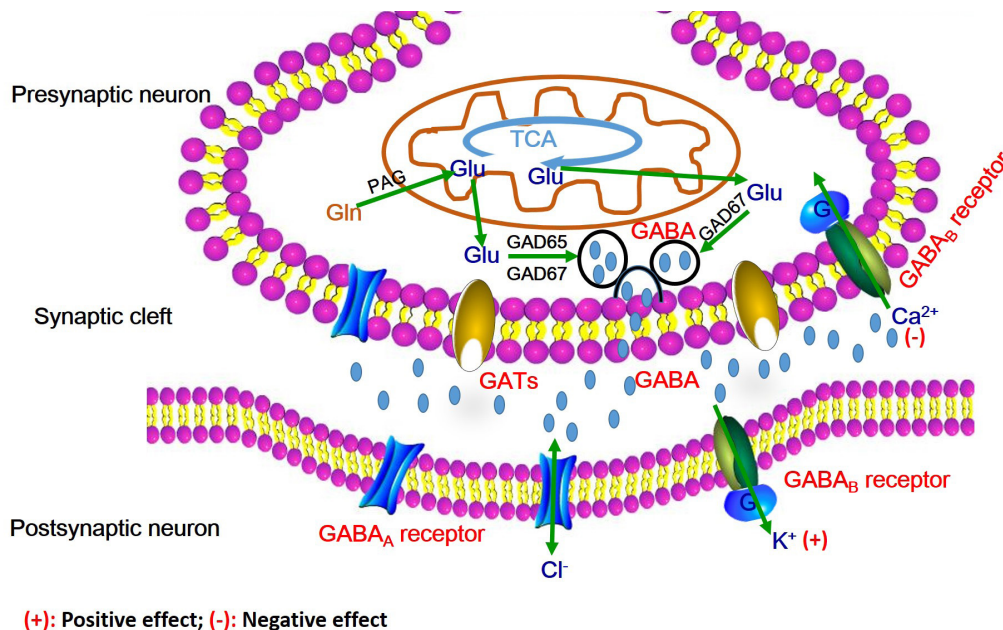
As a well-known inhibitory neurotransmitter in the central nervous system, gamma-aminobutyric acid also has critical roles in immune system. Immune cells (e.g., lymphocytes, macrophages) express the components of GABAergic system, including GABA receptors, GABA transporters, and GABA metabolic enzymes. The functions of immune cells are highly impacted on GABA signaling. GABAergic components negatively regulate the immune responses, particularly the T cell-mediated immunity, via their effects on production of pro-inflammatory cytokines and activation of signal pathways, like mitogen-activated protein kinase and nuclear factor-kappaB pathways. These results may indicate that GABAergic components provide a new therapeutic approach for inflammatory and autoimmune diseases, such as experimental autoimmune encephalomyelitis, multiple sclerosis, and inflammatory bowel diseases.

### 2. INTRODUCTION

Gamma-aminobutyric acid (GABA) is distributed widely among plants and animals. GABA acts as an key inhibitory neurotransmitter in the mammalian cells (1). GABA mainly exists in the central nervous system (CNS). Generally, the concentration of GABA is the highest in the substantia nigra compacta ( $13.8 \pm 0.8 \mu\text{mol g}^{-1}$ ) and the lowest in spinal cord ( $0.8 \pm 0.02 \mu\text{mol g}^{-1}$ ) (2). The process of GABA synthesis from glutamate

needs glutamate decarboxylase (GAD), which includes two isoforms: GAD65 and GAD67 (3). GAD65 and GAD67 differ in gene distribution and have diverse functions (4-6). Upon release, GABA exerts its functions through binding to its receptors, including GABA<sub>A</sub>, GABA<sub>B</sub> and GABA<sub>C</sub> receptors (7). Recently, GABA<sub>C</sub> receptor is regarded as a subclass of GABA<sub>A</sub> receptors by International Union of Pharmacology Committee (8). GABA signaling in synaptic cleft is terminated by the reuptake of excessive GABA via high-affinity GABA transporters (GATs) namely, GAT-1, GAT-2, GAT-3 and betaine-GABA transporter (BGT-1). These transporters exist in presynaptic membranes. After uptake, GABA is catabolized by GABA transaminases (GABA-T) (1,7) (Figure 1). GAT-1 and GAT-3 are abundantly expressed in the CNS, while GAT-2 and BGT-1 are found in tissues such as liver, kidney and intestine (9). Thus, GABAergic system mainly includes GAD, GABA-T, GATs, GABA<sub>A</sub> and GABA<sub>B</sub> receptors.

GABA leads to reduction of blood pressure, reduces stress, and promotes sleep. Levels of GABA correlate with both obesity and multiple necrosis (10-15). Recent research highlights the immunological function of GABA, indicating a crosstalk between nervous system and immune system (16). Indeed, T cells express many neurotransmitter receptors, and their expressions are regulated by T cell receptor (TCR) activation, cytokines, or neurotransmitters themselves



**Figure 1.** The formation and transmission of GABA signaling at the synapse. There are two pathways to synthesize GABA. Pathway 1: GABA is produced from Glu directly which is catalyzed by GAD65 or GAD67. Pathway 2: GABA is synthesized from TCA produced Glu, which is only catalyzed by GAD67. Once GABA released, it exerts its effects through its receptors, mainly GABA<sub>A</sub> and GABA<sub>B</sub> receptors. GABA<sub>A</sub> receptor is ionotropic receptor, which opens its integral Cl<sup>-</sup> channel after binding to GABA, whereas GABA<sub>B</sub> receptor is G protein-coupled metabotropic receptor. GABA<sub>B</sub> receptor negatively acts on presynaptic voltage-activated Ca<sup>2+</sup> channels, but positively acts on postsynaptic inwardly rectifying K<sup>+</sup> channels. GABA signaling in synaptic cleft is terminated by the reuptake of excessive GABA via high-affinity GATs located in presynaptic membrane. Gln: glutamine; Glu: glutamate; PAG: phosphate-activated glutaminase; TCA: tricarboxylic acid cycle; GAT: GABA transporter; GAD: glutamate decarboxylase.

(17). GABA is present in immune cells (i.e., monocytes and macrophages) (18). In addition to GABA, the other components of GABAergic system are found in immune cells. Therefore, effects of GABAergic system on immunological function are discussed in this review with a view focusing on GABA, GABA receptors and GATs.

### 3. THE INTERACTION BETWEEN GATS AND CYTOKINES

GATs are expressed in different immunocytes following immune system activation and cytokine production, presumably leading to increased reuptake of extracellular GABA (7,19) (Table 1). Pro-inflammatory cytokines regulate the expression of GATs (Table 2). GAT-1 and GAT-3 are expressed in neuronal cells and glial cells, respectively, and are mainly involved in the maintenance of extracellular GABA levels and the regulation of GABA<sub>A</sub> receptor-mediated postsynaptic tonic and phasic inhibition in the CNS (20,21). Neuro-inflammation enhances the membrane expression of GAT-3, which is induced by increased level of interleukin (IL)-1 $\beta$  (22). Similarly, IL-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$  up-regulate the expression of GAT-1 and GAT-3 via the mitogen-activated protein kinase (MAPK) (23). Similarly, the occlusion of middle cerebral artery up-regulates the expression of GAT-1 and GAT-3 via IL-1 $\beta$  or TNF- $\alpha$

receptor (24). Indeed, inhibition of IL-1 $\beta$  or TNF- $\alpha$  receptor attenuates the expression of GAT-1 and GAT-3 (23). Interestingly, increased level of IL-6 also up-regulates the expression of GAT-1 and GAT-3 (23). GAT-2 expression in macrophages is induced by interferon (IFN)- $\gamma$  (25).

In addition to re-uptake the excessive GABA from synaptic cleft, GATs still play an important role in production of cytokines. Recently, GATs have been reported to modulate the production of cytokines and proliferation of T cells (26). Thus, GATs can shape the pathogenesis of inflammatory diseases. In mouse model of experimental autoimmune encephalomyelitis (EAE), GAT-1 deficient (GAT-1<sup>-/-</sup>) mice have higher expression of pro-inflammatory cytokines, like IFN- $\gamma$ , IL-23, TNF- $\alpha$ , IL-17, and IL-6, compared to wild type mice (27). CD4<sup>+</sup> T cells from GAT-1<sup>-/-</sup> mice show higher levels of IL-2 than those from wild type mice (28). These results indicate that GAT-1 negatively regulates the expression of pro-inflammatory cytokines in EAE. GAT-2 has a profound effect on accumulation of copper in oysters (29). Excess copper induces the generation of reactive oxygen species (ROS) (30), resulting in tissue damage and production of pro-inflammatory cytokines (31-33). These studies suggest that GAT-2 may be associated with the expression of pro-inflammatory cytokines. Furthermore, the expression of GAT-1 is found in the platelets, which indicates that

**Table 1.** The distribution of GABAergic components in immune cells

| GABAergic components                               | Immunocytes                                                       | Function                                                                                     | References             |
|----------------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------------------------------|------------------------|
| GAD65                                              | DCs <sup>1</sup> (high), Macrophages (low)                        | Modulation of GABA concentration when these immune cells are stimulated                      | (19)                   |
| GAD67                                              | Human peripheral monocytes, Human activated lymphocytes           | Production of plasmatic GABA by peripheral lymphocytes                                       | (7)                    |
| Functional GAT-1 and GAT-2                         | Human activated lymphocytes                                       | GABA transportation                                                                          | (7)                    |
| GAT-1                                              | Antigen-activated T cells                                         | Negative regulation in the activation and survival of T-cells                                | (27)                   |
| GAT-2                                              | Macrophages, T cells, Activated human peripheral monocytes        | Reuptake of GABA from the extracellular space into the cytosol                               | (19)                   |
| GABA-T                                             | Macrophages, CD4 <sup>+</sup> T cells, Peripheral human monocytes | GABA catabolism                                                                              | (19), (27)             |
| Functional GABA <sub>B</sub> receptor              | Neutrophils                                                       | Chemoattractant receptor to induce the migration of neutrophils                              | (56), (57)             |
| Functional GABA <sub>A</sub> receptor              | T cells, Macrophages, DCs                                         | Inhibition in the proliferation immune cells and the production of proinflammatory cytokines | (19), (43), (53), (69) |
| <b>Specific GABA<sub>A</sub> receptor subunits</b> |                                                                   |                                                                                              |                        |
| ε, γ1, α1, α2, α3, β1, β2, β3 <sup>2</sup>         | Macrophages                                                       |                                                                                              | (19), (45), (53), (47) |
| γ1, α1, β2, <sup>2</sup> β3                        | Monocytes                                                         |                                                                                              | (53), (47)             |
| α3, α4, δ, ε, α1, β2, <sup>2</sup> β3              | PBMC                                                              |                                                                                              | (47)                   |
| α1, α2, β1, β2, γ3, δ                              | CD4 <sup>+</sup> T cell (NOD mice)                                |                                                                                              | (69)                   |
| α1, α2, α3, α4, α6, β3, γ1, δ, ρ1, ρ2              | CD4 <sup>+</sup> T cell, CD8 <sup>+</sup> T cell (Wistar rats)    |                                                                                              | (71)                   |
| α1, β2, <sup>2</sup> β3                            | CD8 <sup>+</sup> T cell                                           |                                                                                              | (53), (69), (47)       |
| α1, β2, <sup>2</sup> β3                            | Irradiated B-cells                                                |                                                                                              | (47)                   |

<sup>1</sup>The expression of GAD65 is high in the dendritic cells, but low in the macrophages. <sup>2</sup>β3 subunit is expressed at negligible levels in immune cells. GABA: gamma-aminobutyric acid; GAD: glutamate decarboxylase; GAT: GABA transporter; GABA-T: GABA transaminase; DC: dendritic cell; PBMC: peripheral blood mononuclear cell.

**Table 2.** The regulation of cytokines in the expression of GATs

| Cytokines and cytokine antagonist | GATs            | GAT expression level | Reference  |
|-----------------------------------|-----------------|----------------------|------------|
| IL-1β                             | GAT-1 and GAT-3 | Up-regulation        | (23), (24) |
| IL-6                              | GAT-1 and GAT-3 | Up-regulation        | (23), (24) |
| TNF-α                             | GAT-1 and GAT-3 | Up-regulation        | (23), (24) |
| IFN-γ                             | GAT-2           | Up-regulation        | (25)       |
| IL-1β antagonist                  | GAT-1 and GAT-3 | Down-regulation      | (23), (24) |
| IL-6 antagonist                   | GAT-1 and GAT-3 | No effect            | (23), (24) |
| TNF-α antagonist                  | GAT-1 and GAT-3 | Down-regulation      | (23), (24) |

IL-1β, IL-6 and TNF-α up-regulate the expression of GAT-1 and GAT-3 during inflammation, while IL-1β and TNF-α antagonist down-regulate the expression of GAT-1 and GAT-3. IL-6 antagonist has little effect on the expression of GAT-1 and GAT-3.

BGT-1 regulates the aggregation/anti-aggregation effects of platelets because GABA analogues inhibit signal transduction and thromboxane A2 formation in human platelets (34,35). More detail investigations in the function of BGT-1 in inflammation are needed.

#### 4. GABA RECEPTORS AND IMMUNITY

There mainly are two types of neuronal GABA receptors-GABA<sub>A</sub> receptor and GABA<sub>B</sub> receptor. GABA<sub>A</sub> receptor (ionotropic receptor) is a

ligand-gated ion channel, which opens its integral Cl<sup>-</sup> channel after binding to GABA (8,36-40) (Figure 1). GABA<sub>B</sub> receptor (metabotropic receptor) is G protein-coupled receptor, which negatively acts on presynaptic voltage-activated Ca<sup>2+</sup> channel, but positively acts on postsynaptic inwardly rectifying K<sup>+</sup> channel (8,36-40) (Figure 1). At low concentration of GABA, GABA<sub>A</sub> receptor is recruited to increase acetylcholine releases and propulsive activities. At high concentration of GABA, GABA<sub>B</sub> receptor is activated to decrease acetylcholine releases and peristaltic activities (41).

GABA<sub>A</sub> and GABA<sub>B</sub> receptors play a compelling role in inflammation.

In humans, GABA<sub>A</sub> receptor includes numerous subunit isoforms, including  $\alpha(1-6)$ ,  $\beta(1-3)$ ,  $\gamma(1-3)$ ,  $\delta$ ,  $\epsilon$ ,  $\theta$ ,  $\pi$ , and  $\rho(1-3)$ , however, the most common type of GABA<sub>A</sub> receptor is  $\alpha_1\beta_2\gamma_2$  in the brain(42). These subunits are expressed in different immune cells (Table 1). GABA<sub>A</sub> receptor plays an important role in anti-inflammation via inhibiting the expression of inflammatory cytokines (8). For example, the functional GABA<sub>A</sub> receptor is found in CD4<sup>+</sup> T cells and macrophages, and GABA<sub>A</sub> receptor inhibits the proliferation of antigen-specific T cells and the production of IL-6, IL-12, inducible nitric oxide synthase (iNOS), IL-1 $\beta$ , and TNF- $\alpha$  from CD4<sup>+</sup> T cells and macrophages (43-45). GABA or GABA<sub>A</sub> receptor agonist inhibits the immune responses of immune cells to stimulation, including cytotoxic immune responses, cutaneous delayed-type hypersensitivity (DTH) (19,43,46,47). Honokiol (HNK, a GABA<sub>A</sub> receptor modulator) alleviates the inflammatory arthritis and allergic asthma via its effects on the expression of cytokines (47,48). Endogenous GABA tonically inhibits the plasma level of IL-6 via both GABA<sub>A</sub> and GABA<sub>B</sub> receptors, and plasma level of IL-1 $\beta$  through GABA<sub>A</sub> receptor (49,50). TNF- $\alpha$  induces the endocytosis of GABA<sub>A</sub> receptor in mice and high concentration of TNF- $\alpha$  up-regulates the expression of GABA<sub>A</sub> receptor (51,52). It has been found that GABA<sub>A</sub> receptor is expressed in alveolar macrophages but not in neutrophils, and the activation of GABA<sub>A</sub> receptor inhibits lipopolysaccharide (LPS)-induced release of TNF- $\alpha$  and IL-6 from alveolar macrophages (53). Furthermore, increased GABA<sub>A</sub> receptor and GAD65/67 reduce lung inflammation in LPS-induced lung injury in rats (54).

GABA<sub>B</sub> receptor consists of B1 and B2 subunits, and it is generally accepted that B1a/B2 heterodimer localizes in the presynaptic neurons, while B1b/B2 localizes in the postsynaptic neurons (55). GABA<sub>B</sub> receptor is expressed in neutrophils, and acts as chemoattractant receptor, which has significant roles in inflammatory responses (56). In zymosan-induced arthritis, GABA<sub>B</sub> receptor participates in neutrophil migration to the knee joint, which may attribute to spinal activation of p38 MAPK (57). Likewise, baclofen (GABA<sub>B</sub> receptors agonist) prevents loss of the expression of GABA<sub>B</sub> receptor after acute lung injury, and significantly inhibits the release of TNF- $\alpha$  and IL-1 receptor accessory protein (IL-1R AcP), while concurrently promotes the apoptosis of neutrophils in the bronchoalveolar lavage (58). The up-regulation and functional augmentation of GABA<sub>B</sub> receptor by cytokines and immune activities may serve as a protective factor against the excitotoxic neuroinflammation (59). For example, baclofen exerts anti-inflammatory properties at specific doses through

inhibition in toll-like receptor (TLR) 4-induced activation of nuclear factor-kappaB (NF- $\kappa$ B) and induction of pro-inflammatory cytokines (60). Activation of TLR4 on microglia causes the release of IL-1 $\beta$ , which in turn suppresses the activities of GABAergic system (61). GABA<sub>B</sub> receptor acts as a potential new therapeutic target to treat inflammatory skin diseases (62).

From above discussion, pharmacological modulation of GABA<sub>A</sub> receptor or GABA<sub>B</sub> receptor may provide a new approach to modulate immune responses in inflammatory and autoimmune diseases (43,57).

## 5. EFFECTS OF GABA ON T CELL IMMUNITY AND AUTOIMMUNE DISEASE

### 5.1. GABA-mediated T cell immunity

T cells have key function in the development of many autoimmune diseases (63). The survival and function of T cells not only rely on glucose, but also depend on amino acids (63,64). Indeed, T cells have a functional GABAergic system, which may operate as a modulator of T-cell activation (7). Depletion of glutamine (participates in the synthesis of GABA) in the culture medium blocks the proliferation and cytokine production of T cells (65). GABA is not only an inhibitory neurotransmitter, but also an immunomodulatory. Stimulated mouse macrophages and T cells produce high levels of GABA (19,66). GABA is involved in the proliferation of T cells and the production of cytokines, which inhibits the proinflammatory T cell responses, but increases the regulatory T cell numbers (43,67-70). GABA inhibits TCR-mediated T cell cycle progression *in vitro* (69). Furthermore, GABAergic agents directly affect the function of antigen-presenting cells (APCs) via GABA<sub>A</sub> receptor, and the phosphorylation of MAPK to inhibit the production of inflammatory cytokines from T cells during inflammation (19). GABA inhibits Th1cell-mediated-DTH responses *in vivo* (43).

In addition, there are a lot of reports that GABA is involved in the T cell immunity via GATs, GABA receptors. For example, GAT-1 is only expressed on the activated T cells primed with antigens, and GAT-1 down-regulates the proliferation of CD4<sup>+</sup> T cell has been proved (27,28). These findings indicate that GAT-1 is a critical modulator in T cell-mediated immune responses (27,28). GABA<sub>A</sub> receptor inhibits T cell responses to antigen both *in vitro* and *in vivo* probably through the interference with the TCR/CD3-gated signal pathway and IL-2 gene expression (43). Currently, it has been known that the GABA<sub>A</sub> receptor subunits are expressed in the CD4<sup>+</sup> T cells and the CD8<sup>+</sup> T cells, and this functional channel modulates the proliferation of T cell (71). In turn, activation of T cells increases the expression of at least one GABA<sub>A</sub> receptor subunit (69).

**Table 3.** The distribution and function of GABAergic components in autoimmune diseases

| Autoimmune diseases | Tissue and cells                    | GABAergic components        | Function                                                           | References |
|---------------------|-------------------------------------|-----------------------------|--------------------------------------------------------------------|------------|
| T1D                 | $\beta$ -cells                      | GABA <sub>A</sub> receptors | Formation of autocrine GABA signaling system                       | (81)       |
|                     |                                     | GABA                        | Promotion in the growth and survival of $\beta$ -cell              | (81)       |
|                     |                                     | GAD65/GAD67                 | Destruction of pancreatic $\beta$ cells                            | (78-80)    |
| MS (EAE)            | Plasma                              | GABA, GAD                   | Reduced GABA concentration and GAD activity in blood               | (15)       |
|                     | Spinal cord                         | GAT-1                       | Reduced expression of GAT-1                                        | (27)       |
|                     | Activated T cells                   | GAT-1                       | Regulation in T cell-mediated immune responses in EAE              | (27)       |
|                     | Hippocampus, Sensorimotor cortex    | GABA                        | Correlation with reduced motor function of the contralateral limbs | (74)       |
| T2D                 | Adipocytes, Macrophages and T cells | GABA <sub>A</sub> receptors | Prevention of obesity                                              | (84)       |
| RA                  | DCs                                 | GABA <sub>B</sub> receptors | Inhibition in the secretion of IL-6                                | (85)       |

T1D: type 1 diabetes; MS: multiple sclerosis; EAE: experimental autoimmune encephalomyelitis; T2D: type 2 diabetes; RA: rheumatoid arthritis.

## 5.2. GABA plays an important role in autoimmune diseases

GABA not only plays an inhibitory effect in the nervous system, but also has a parallel inhibition in the immune system, especially in autoimmune diseases. GABA is a pivotal modulator in autoimmune diseases. This review summarizes the roles of GABA in multiple sclerosis (MS), type 1 diabetes (T1D) and the other common autoimmune diseases (Table 3).

MS is a chronic disorder of the CNS that leads to demyelination and neurodegeneration (72). EAE is mediated by autoaggressive MHC class II-restricted antigen-specific CD4<sup>+</sup> effector T cells (Th1 and Th17) (27,73). Its etiology is related to reduced level of plasma GABA, and activities of GAD (15). Reduced level of GABA is found in hippocampus and sensorimotor cortex in patients with secondary progressive MS, and the lower concentration of GABA correlates with reduced motor function of the contralateral limbs (74), suggesting that modulation of GABA neurotransmission may be an important target for neuroprotection in MS. Compared to wild type mice, GAT-1<sup>-/-</sup> mice develop more aggravated EAE because of increased expression of pro-inflammatory cytokines in GAT-1<sup>-/-</sup> mice (27). In T cells, GAT-1 deficiency results in increasing cell cycle entry and reducing apoptosis, and it is also related to greater activation of the NF- $\kappa$ B pathway, which causes the production of pro-inflammatory cytokines (75). These findings indicate that GAT-1 plays negative regulation in T cells and protective roles against EAE.

T1D is a common autoimmune disease characterized by insulinitis, loss of islet  $\beta$ -cells, as well as the increase in autoreactive CD4<sup>+</sup> and CD8<sup>+</sup> T cells (76,77). Pancreatic  $\beta$  cells widely express GAD65/GAD67, which is a target of early T cell autoimmune, leading to the destruction of pancreatic  $\beta$  cells in non-

obese diabetic (NOD) mice (78-80). Pancreatic  $\beta$  cells also express GABA<sub>A</sub> receptor, and secrete GABA to form an autocrine GABA signaling system (81-83). Furthermore, secreted GABA alleviates the disease by causing membrane depolarization in  $\beta$ -cells, which leads to the opening of voltage-dependent calcium channels (VDCCs) and the activation of the Ca<sup>2+</sup>-dependent PI3K/Akt signaling pathway (81). It has been found that GABA induces the proliferation of  $\beta$  cells, and protects the apoptosis of  $\beta$  cells through inactivation of NF- $\kappa$ B in both lymphocytes and islet cells (75,76). Some studies have reported that the treatment with rapamycin and GABA has a protective effect against T1D via two distinct mechanisms-rapamycin induced regulatory T cells and GABA improved islet function (77). Collectively, these results suggest that GABA has an important protective function against T1D.

In addition to T1D, it has been showed that GABA, through activation of its GABA<sub>A</sub> receptor on adipocytes, macrophages and T cells, prevents obesity and alleviates of T2D in clinic application (84). Beyond that, baclofen mitigates collagen-induced arthritis (CIA), which has some features of rheumatoid arthritis (RA), through reducing the number of Th17 cell and the secretion of IL-6 by dendritic cells (DCs) (75,85). Moreover, the therapy through GABA signaling is demonstrated to be beneficial to decrease the inflammation in some dermatitis (62,75,86).

Summarily, all components of GABAergic system are related to autoimmune diseases, and modulation of GABAergic system could regulate the pathogenesis of various proinflammatory diseases and autoimmune diseases.

## 6. CONCLUSION

This review outlines the effects of GABAergic system in immune system, especially about T cell

mediated responses. GABAergic components are not only expressed in the neurons, but also in the immunocytes, such as lymphocytes, macrophages and DCs. GABA signaling is involved in the modulation of immune responses, mainly through negative regulation in the proliferation of T cells and the production of pro-inflammatory cytokines by down-regulation of some relevant signaling pathways (e.g., MAPK and NF- $\kappa$ B pathway). Thus, GABAergic system has great potentials to inhibit inflammatory responses. These findings indicate that the components of GABAergic system have a pharmacological effect and can be a new therapeutic target for inflammatory and autoimmune diseases.

## 7. ACKNOWLEDGMENTS

The authors declare no any conflicts of interests. Our profound admiration and respect go to researchers in this field and in our laboratories, for their dedication and hard work. We apologize to scientists who work in this field if their papers are not cited owing to space limitations. This study is supported by the earmarked fund for China Agriculture Research System (Beef/Yak Cattle, CARS-38), Chongqing Science & Technology Commission (cstc2015shmszx8022).

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**Abbreviations:** APC: antigen-presenting cell; BGT-1: betaine-GABA transporter; CIA: collagen-induced arthritis; CNS: central nervous system; DC: dendritic cell; DTH: delayed-type hypersensitivity; EAE: autoimmune encephalomyelitis; GABA: gamma-aminobutyric acid; GABA-T: GABA transaminase; GAD: glutamate decarboxylase; GAT: GABA transporter; Gln: glutamine; Glu: glutamate; HNK: honokiol; IFN: interferon; iNOS: inducible nitric oxide synthase; IL: interleukin; LPS: lipopolysaccharide; MAPK: mitogen-activated protein kinase; MS: multiple sclerosis; NF- $\kappa$ B: nuclear factor-kappaB; NOD: non-obese diabetic; PAG: phosphate-activated glutaminase; PBMC: peripheral blood mononuclear cell; RA: rheumatoid arthritis; ROS: reactive oxygen species; T1D: type 1 diabetes; T2D: type 2 diabetes; TCA: tricarboxylic acid cycle; TCR: T cell receptor; TLR: toll-like receptor; TNF: tumor necrosis factor; VDCC: voltage-dependent calcium channels.

**Key Words:** GABA, GABA receptors, GABA transporters, Inflammation, Autoimmune diseases, Review

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