In recent years, it has become clear that there is an extensive cross-talk between the nervous and the immune system. Somewhat surprisingly, the immune cells themselves do express components of the neuronal neurotransmitters systems. What role the neurotransmitters, their ion channels, receptors and transporters have in immune function and regulation is an emerging field of study.

Several recent studies have shown that the immune system is capable of synthesizing and releasing the classical neurotransmitter GABA (γ-aminobutyric acid). GABA has a number of effects on the immune cells such as activation or suppression of cytokine secretion, modification of cell proliferation and GABA can even affect migration of the cells. The immune cells encounter GABA when released by the immune cells themselves or when the immune cells enter the brain. In addition, GABA can also be found in tissues like the lymph nodes, the islets of Langerhans and GABA is in high enough concentration in blood to activate, e.g., GABA-A channels. GABA appears to have a role in autoimmune diseases like multiple sclerosis, type 1 diabetes, and rheumatoid arthritis and may modulate the immune response to infections. In the near future, it will be important to work out what specific effects GABA has on the function of the different types of immune cells and determine the underlying mechanisms. In this review, we discuss some of the recent findings revealing the role of GABA as an immunomodulator.

**Keywords**  GABA · GABA-A · Neurotransmitter · Immunomodulation · Autoimmune disease · Immune cells

**Introduction**

The role of GABA in a physiological process is best studied in the brain where GABA is the main inhibitory neurotransmitter. GABA is made and released by neurons and it activates GABA-A ion channels and the GABA-B receptor in the neuronal plasma membrane. Activation of the channels and receptor generally results in decreased neuronal excitability in mature neurons. The low extracellular GABA concentration is maintained by reuptake of GABA into the neurons and astrocytes by sodium-dependent GABA cotransporters.

GABA is produced by decarboxylation of the amino acid glutamate by the enzyme glutamic acid decarboxylase (GAD) that exists in two isoforms GAD65 and GAD67. The two GAD isoforms have different subcellular location with GAD67 distributed evenly throughout the neuronal cytoplasm whereas the GAD65 is associated with synaptic vesicles (Buddhala et al. 2009). GABA is metabolized into succinic semialdehyde by the action of the enzyme GABA transaminase (GABA-T).

The GABA-A ion channels are pentameric chloride channels and normally contain three types of subunits: 2zs, 2βs and a third type of subunit. To date, 19 different mammalian GABA-A subunits have been cloned (α1–6, β1–3, γ1–3, δ, ε, π, θ, ρ1–3) (Olsen and Sieghart 2009). Evidence for the existence of a multitude of GABA-A channel subtypes comes from pharmacological studies. It has been shown that, e.g., benzodiazepine-site ligands can differentiate between GABA-A channel subtypes based on the type of α and γ subunits in the channel complex (Olsen and Sieghart 2009).
The components of the GABA signaling machinery expressed in immune cells

The neuronal GABAergic system is composed of four primary parts: the GABA-A channels, the GABA-B receptor, the GABA transporters and the enzymes that make or degrade GABA (Fig. 1). So far, there are relatively few studies that have looked at the GABA system in immune cells (Table 1).

The enzymes responsible for GABA synthesis have been detected in T cells, macrophages and dendritic cells (Bhat et al. 2010; Dionisio et al. 2011). GAD65 was present in dendritic cells and macrophages (Bhat et al. 2010) from encephalomyelitis (EAE) mice whereas GAD67 was detected in human peripheral monocytes (Dionisio et al. 2011). GABA secretion from stimulated mouse macrophages and T cells has been reported (Bhat et al. 2010; Soltani et al. 2011) and GABA was detected in extracts from human peripheral blood macrophages (Stuckey et al. 2005). GABA-T has been detected in macrophages, CD4+ T cells and peripheral human monocytes (Bhat et al. 2010; Dionisio et al. 2011). In immune cells only one study, so far, has examined the expression of the transporter that transport GABA into synaptic vesicles (vesicular inhibitory amino acid transporter (VIAAT)). In peripheral human monocytes, gene transcripts were detected for VIAAT and then additionally verified by immunohistochemistry (Dionisio et al. 2011).

Gene transcripts encoding the GABA-A channel subunits have been detected in several types of immune cells but which subunits were present varied. Tian et al. (2004) identified the α1, α2, β1, β2, γ3 and δ subunits in CD4+ T cells from NOD (non-obese diabetic) mice, a mouse model for type 1 diabetes, whereas Bhat et al. (2010) did not identify any of the four subunits (α1, β1, γ1, γ2) they examined in CD4+ T cells from EAE mice, the animal model for multiple sclerosis (MS). Only in two studies was the expression of all 19 different GABA-A channel subunits examined; in an EAE cell line, the α1, α4, β2, β3, γ1 and δ subunits were detected (Bjurstrom et al. 2008) and in CD4+ and CD8+ T cells from Wistar rats the α1, α2, α3, α4, x6, β3, γ1, δ, ρ1 and ρ2 subunits identified out of the 19 subunits (Mendu et al. 2011). It is therefore possible that more subunits types can be detected in T cells from the mouse models or alternatively, the expression of the GABA-A subunits may be regulated depending on, e.g., the state of activation of the cells or the species. Clearly the T cells express the GABA-A channel subunits but what determines the specific channel subtypes in the cells remains to be determined. Similarly, the α1, α2, β3 and δ subunits have been detected in cultured peritoneal macrophages and the β1 and ε subunits in macrophages isolated from the EAE mouse model (Bhat et al. 2010).
Human peripheral monocytes expressed the α1, α3, β2 and the δ subunits (Alam et al. 2006). So far, other immune cells like dendritic cells or natural killer cells have not been reported to express GABA-A channels subunits. Together these results demonstrate that immune cells from rats, mice and humans do have the necessary building blocks to form GABA-A ion channels. Whether the GABA-B receptor is of importance for the immunological effect of GABA on immune cells is not known today.

There have been four plasma membrane GABA co-transporters identified (GAT1-4) in neurons. All of these cotransporters mediate ion-coupled secondary active transport of GABA across the plasma membrane. Only two of these cotransporters have, so far, been detected in immune cells. Gene transcripts for the GAT-1 or GAT-2 have been identified in human peripheral lymphocytes (Dionisio et al. 2011) and in T cells from EAE mice but the results differ in whether a transcript is detected in resting (Bhat et al. 2010) or in activated cells (Wang et al. 2008). Interestingly, both Wang et al. (2008) and Bath et al. (2010) isolated macrophages from the EAE mouse model but only Bath et al. (2010) detected GABA cotransporter in these cells and then only in stimulated macrophages.

The components of the GABA signaling system appear to be dynamically regulated in immune cells as is reflected by the variability in results from the few studies published to date. Whether the results also depend on the species (humans, rats and mice), strains of animals or animal models, state of activation of the cells or classes of cells or different subtypes of GABA-A ion channels and GABA transporters expressed in the cells remains to be examined.

Effects of GABA on immune cells

Bergeret et al. (1998) reported that GABA modulated cytotoxicity of immunocompetent cells expressing GABA-A ion channel subunits. GABA activated GABA-A ion channel currents in T cells and macrophages (Bjurstom et al. 2008; Bhat et al. 2010; Mendu et al. 2011) and GABA application resulted in decreased cytokine secretion and T cells proliferation (Tian et al. 2004; Bjurstom et al. 2008; Mendu et al. 2011) or had no effects on these properties of the cells (Bhat and Steinman 2009). In lymphocytes, exposure to GABA reduced but did not abolish the transient increase in the intracellular calcium concentration that was associated with activation of the cells (Alam et al. 2006). Drugs that mimic GABA (e.g. muscimol) or increase the ambient GABA concentration in the brain (e.g. vigabatin, gabaculine) decreased cytokine production in macrophages (Reyes-García et al. 2007; Bhat et al. 2010).

The GABA transporters have also been reported to modulate cytokine production and T cell proliferation. In GAT-1 knock-out mice both cell proliferation and IFN-γ production are increased in T cells from these animals relative to T cells from wild-type mice (Wang et al. 2008). Finally, in classical immunological chemotaxis and phagocytotic assays, pharmacological modulation of human peripheral monocytes with drugs acting at the GABA-A channels impaired the function of the cells (Wheeler et al. 2011).

The GABA signaling system is clearly active in the immune cells and can affect a variety of functional properties of the cells like cytokine secretion, cell proliferation, phagocytic activity and chemotaxis. Nevertheless, much remains to be discovered, as we know relatively little about how these processes are linked to GABA and the GABA signalling system in the cells.

Role of GABA in immune and autoimmune diseases

GABA is decreased in the serum of MS patients (Dem-akova et al. 2003). Oral GABA treatment down-regulated inflammatory responses in a mouse model of rheumatoid arthritis and in a mouse model of obesity (Tian et al. 2011a,
| Species                  | Origin/cell type                  | GABA signalling system component | Function                                                                 | References                  |
|-------------------------|-----------------------------------|----------------------------------|--------------------------------------------------------------------------|-----------------------------|
| Human                   | Monocyte                          | GABA-A α1 mRNA                  | GABA decreases [Ca^{2+}]                                               | Alam et al. (2006)          |
| CD4+ T cell             |                                   | GABA-A α1, α3, β2 mRNA, α1 protein |                                                                           |                             |
| CD8+ T cell             |                                   | GABA-A β2 mRNA                  |                                                                           |                             |
| CD8+ T cell             |                                   | GABA-A α1, α3, β2 mRNA, α1 protein |                                                                           |                             |
| Irradiated B cell       |                                   | GABA-A α1, α3, β2 mRNA, α1 protein |                                                                           |                             |
| PBMC                    |                                   | GABA-A α1 mRNA                  | GABA decreases [Ca^{2+}]                                               | Shiratsuchi et al. (2009)   |
| PBMC                    |                                   | GABA-A α1, α3, β2 mRNA, α1 mRNA, α1 protein | Blocking of GABA-A channels prevents pressure-induced macrophage phagocytosis |                             |
| Human peripheral blood  | Macrophage                        | GABA-A x mRNA                   |                                                                           | Stuckey et al. (2005)       |
| T lymphocyte            |                                   | GABA-A x mRNA                   |                                                                           |                             |
| Psoriatic skin/macrophage, lymphocyte, neutrophil | [{GABA}] present (macrophage and lymphocytes) | GABA decreases T cell proliferation | Dionisio et al. (2011)       |
| Human peripheral T      | GAD67, VIAAT, GABA-T              | GABA decreases T cell proliferation |                                                                           |                             |
| T lymphocyte            | GAT1 (50% of resting cell)        | GABA decreases T cell proliferation |                                                                           |                             |
| Human monocyte          | GABA-A β2 mRNA                   | GABA decreases T cell proliferation |                                                                           |                             |
| Human PBMC              |                                   | GABA-B receptor protein          | GABA-B receptor agonist baclofen increases neutrophil chemotaxis by anaesthetics | Duthey et al. (2010)        |
| Human neutrophil        | GABA-B protein                    | GABA-B receptor agonist baclofen increases neutrophil chemotaxis |                                                                           | Rane et al. (2005)          |
| Rat                     | CD4+ or CD8+ T cell               | GABA-A α1, α2 mRNA, x2, α3, α4, α6, α7, β3, δ, δ, β2 mRNA                   | 100 mM GABA decreases T cell proliferation | Mendu et al. (2011)        |
| Species | Original cell type | GABA signalling protein component | Function |
|---------|------------------|---------------------------------|----------|
| Mouse | Cells from spleen or lymph nodes from NOD mice | Functional GABA-A channels | GABA decreases proliferation and IL-2 production in stimulated T cells |
|       | CD4+ T cell | | |
| Tian and Chau et al. (1999) | Tian and Chau et al. (1999) | |
| CD4+ T cell | Functional GABA-A channels | GABA decreases proliferation and IL-2 production in stimulated T cells |
| Tian et al. (2004) | Tian et al. (2004) | |
| CD4+ T cell from NOD mice | GABA-A a1, a2, b1, b2, d mRNA | |
| GABA-A protein | |
| Functional GABA-A channels | |
| GABA decreases both T cell autoreactivity and ADCC activity |
| Peritoneal macrophage (non-stimulated and stimulated) | GABA-A a1, a2, b1, b2, d mRNA | |
| GABA decreases IL-6 and IL-12 production in macrophages |
| Reyes-Garcia et al. (2007) | Reyes-Garcia et al. (2007) | |
| Spleen cells from GAT1+/− and -/- mice | GABA-A a1, a2, a5, b1, b2, d, c1, c3 mRNA | |
| GAT-1 deficiency increases T cell proliferation and cytokine production from APCs and ameliorates EAE |
| Wang et al. (2008) | Wang et al. (2008) | |
| Human CD4+ T cell line | Functional GABA-A channels | Blocking of GABA-A channel increases pressure-induced macrophage phagocytosis |
| Bhat et al. (2010) | Bhat et al. (2010) | |
| Human CD4+ T cell line | GABA-A a1, a2, b1, a5 mRNA | |
| GABA decreases T cell-dependent cytotoxicity |
| Bergeret et al. (1998) | Bergeret et al. (1998) | |
| Human CD4+ T cell line | Functional GABA-A channels | Blocking of GABA-A channel reverses the inhibition of monocyte migration by anesthetics |
| Alam et al. (2006) | Alam et al. (2006) | |
| Human monocytic cell line THP-1 | Blocking of GABA-A channels reverses the inhibition of monocyte migration by anesthetics |
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Disregulation of the GABA metabolism preceded pancreatic islets autoimmunity in children who later progressed to type 1 diabetes (Oresic et al. 2008) and GAD is a major autoantigen in type 1 diabetes (Lernmark et al. 1978). What role the GABA system has in these diseases remains to be clarified. The realization that extrasynaptic GABA-A ion channels in immune cells can be fully activated by submicromolar GABA concentrations makes GABA a potential effector molecule in many parts of the body including blood, pancreatic islets, cerebrospinal fluid and, of course, in the brain where the ambient GABA concentration is in the submicromolar range (Tosson et al. 1986; de Groote and Linthorst 2007). Tian et al. (2004) showed that increasing the systemic GABA concentration delayed the onset and incidence of type 1 diabetes in NOD/scid mice. Similarly, Bath et al. (2010) showed that increasing the ambient CNS GABA concentration ameliorated ongoing paralysis in EAE mice, by inhibiting onset of inflammation. GABA has also been proposed to have a role in rheumatoid arthritis (Kelley et al. 2008; Tian et al. 2011b) and psoriasis (Nigam et al. 2011b). The cross-talk between the immune cells and the affected tissues is complex but the relatively few studies published to date imply that GABA and the GABA signaling system components are an important part of the disease environment.

Conclusion

In recent years, it has become evident that cells of the immune system are capable of synthesizing and releasing the classical neurotransmitter GABA and they do often express proteins that are parts of the neuronal GABA signaling system. Immune cells from rats, mice and humans do have the necessary building blocks to form GABA-A ion channels. The absence of a presynaptic terminal defines these channels in the immune cells as extrasynaptic-like channels. Physiologically this seems reasonable as the cells will not encounter the same high millimolar concentrations of GABA as in the neuronal synapses but rather will be exposed to submicromolar GABA concentrations as they travel in the blood, enter the brain or the pancreatic islets. When GABA opens the GABA-A channels in the plasma membrane of immune cells, the membrane potential changes and thereby a number of cellular processes may be affected such as, e.g., calcium entry into the cell. Despite the limited number of studies to date, there are significant differences between the results such as what GABA-A channel subunits and therefore what channel subtypes are expressed in the immune cells. How easily the channels change the membrane potential is related to the GABA-A channel subtype. The subtypes differ in terms of efficiency of ion conduction as the single-channel conductance and kinetic properties vary (Lindquist and Birnir 2006; Olsen and Sieghart 2009). Furthermore, properties like the affinity for GABA and modulation by drugs such as the benzodiazepines and steroids is determined by the specific subunit composition of the GABA-A ion channel subtype (Lindquist and Birnir 2006; Olsen and Sieghart 2009). It is, therefore, of great importance to know what subunits do form the channel and how their composition is determined and regulated in the immune cells. The discrepancies in results between studies may reflect difference between species (humans, rats and mice) or some experimental condition such as different strains of animals or animal models, different state of activation of the immune cells or classes of cells and in some cases, limited number of subunits being examined.

GABA appears to have a role in autoimmune diseases like MS, type 1 diabetes and rheumatoid arthritis and may modulate the immune response to infections (Bhat et al. 2010; Mendu et al. 2011; Soltani et al. 2011; Tian et al. 2011b; Wheeler et al. 2011). Neuroinflammation is involved in epileptogenic process in the brain (Vezzani et al. 2008) and has even a role in Alzheimer disease, stroke and traumatic brain injury (Popovich and Longbrake 2008; Schwartz and Shechter 2010). Clearly there is an extensive cross-talk between the immune and the nervous system and one of the molecules participating in the exchange between the two systems is GABA. Despite the few studies, it is apparent that the GABA signaling system is an important and integral part of the immune system. In the near future, it will be important to work out what determines whether components of the GABA system are expressed or not in an immune cell and then, what cellular processes are affected when GABA activates GABA-A channels, GABA transporters and the GABA-B receptor in the plasma membrane of the cells. Identifying the GABA-A channel subtypes expressed in the immune cells may be of great clinical significance as a number of drugs modulating functional properties of GABA-A channels are widely used in clinical settings.

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Conflict of interest The authors declare that they have no conflict of interest.

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GABA is an effective immunomodulatory molecule

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