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Review

β2 Adrenergic receptor on T lymphocytes and its clinical implications

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Abstract

Sustained complex cross-talk between the immune system and the nervous system plays a vital role in retaining homeostasis in a healthy individual. One of the central regulatory mechanisms involved is the existence and functions of β2-adrenergic receptors (β2AR) on T lymphocytes. This article reviews research progress made recently, including the expression of adrenergic receptors on T lymphocytes, the structure and intracellular pathways of β2AR, the activation of β2AR by either endogenous or exogenous agonists, and the effect of β2AR stimulation on T cells which alters T cell proliferation, differentiation, cytokine production and T-helper-mediated antibody production. Furthermore, we discuss the roles of β2AR played in the pathogenesis and treatment of autoimmune diseases.

Keywords: Neuroimmunology; β2-adrenergic receptor; T cell; Autoimmune

1. Introduction

The existence of intense communication between the immune system and the nervous system has been supported by accumulating data over the past 30 years. Today it is generally acknowledged that two different pathways, namely the hypothalamic-pituitary-adrenal-corticotropin-releasing hormone (HPA-CRH) pathway and sympathetic nervous system (SNS) pathway, exist between the brain and the periphery, both of which exercise control over the innate and adaptive immune response through a variety of factors [1].

With the discovery of adrenergic receptors (ARs) on a variety of immune cells involved in the adaptive immune response, currently interest has arisen on the effect of these receptors generated following stimulation with their respective ligands. This article focuses on the effect of AR on T lymphocytes, and briefly discusses its relevance to clinical implications.

2. Structure and intracellular pathways of β2AR

Extensive studies on the structure of β2AR have shown that it is a G protein-coupled seven times transmembrane receptor with three extracellular and three intracellular loops. In the basal state, the receptor oscillates between many conformations, and the role of agonists is to stabilize one or more conformations, leading to subsequent intracellular signal transductions. Upon stimulation, β2AR promotes phosphorylation at serines in the third intracellular loop and the proximal cytoplasmic tail. Adenylyl clyclase (AC) is activated through Gs, which subsequently leads to intracellular cAMP accumulation and protein kinase A (PKA) activation. Furthermore, a family termed G protein-coupled receptor kinases (GRKs) also phosphorylates the receptor at multiple serines and threonines in the cytoplasmic tail.

A special feature of β2AR is the short-term agonist-induced internalization and degradation, while chronic administration causes desensitization. The binding of β-arrestins to the phosphorylated receptor results in uncoupling from Gs, which terminates subsequent signal

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transduction, desensitizes receptor function and promotes receptor internalization. Multiple intracellular pathways have been described, including the c-Src-Ras-RAF-MAPK pathway and Rac-JNK pathway, as well as activation of the intracellular signaling mediators PLC, IP3, protein kinase C (PKC) and Btk, all of which result in activation of various transcription factors and genetic regulation [2]. Ubiquitination via an E3 ligase serves as a further post-translational modification of the β2AR, and is a prerequisite for receptor degradation. Downregulation, or a decrease in receptor expression, is a long-term effect that is due to both transcriptional and protein degradation mechanisms [3]. β2ARs are sensitive to regulation from specific isoforms of PKC, and rapid heterologous desensitization could mediate these protein kinases to decrease maximal adenylyl cyclase stimulation [4]. Upon stimulation of β2AR, receptor-activated Gαs moves into lipid rafts and is internalized from T cell membrane microdomains by distinct endocytic pathways, leading to receptor recycling, receptor desensitization, and downregulation. This is of special interest as physiologically the endocytosis could enable Gαs to traffic into the cellular interior to regulate effectors at multiple cellular sites [5].

3. Expression of adrenergic receptors on T lymphocytes

3.1. Evidence for the existence of AR on T cells

Adrenergic receptors are mainly divided into two types, namely the α- and β-receptor, both of which may be further divided into subtypes based on their molecular characteristics, with the consensus now being nine subsets: α1A, α1B, α1D, α2A, α2B, α2C, β1, β2, and β3 [6]. Early data accumulated through radioligand binding analysis first confirmed the expression of the β-adrenergic receptor on both the human and the murine T cell populations, of which the β2AR subtype is predominant [7]. However, evidence supporting the expression of a high affinity β1 adrenergic receptor or β3 adrenergic receptor (β3AR) on T cells is scarce to date, although there is a report on the function of β1AR in the acute cold- and restraint stress-induced inhibitory action of host resistance to *Listeria monocytogenes* via alternations in cytokine production [8]; and another report on a β3AR agonist that was found to suppress lymphocyte proliferation in diet-induced obese rats [9]. Therefore, the existence of β2AR on T cells has been supported by ample evidence, while the presence of β1AR, β3AR needs to be confirmed.

Due to the divergent cytokine-secreting profiles and regulatory functions of different T cell subtypes, investigations have extended the receptor expression studies to the analysis of AR presence on purified T cell subtypes. The advent of various molecular techniques in separating specific populations of immune cells allowed receptor expression of each cell subtype to be analyzed at the level of protein and gene expression. To date, studies have mainly focused on CD4+ subtypes, while only a few on CD8+ subtypes which include the naïve, Tc1 and Tc2 cells [10]. Shephard et al. showed that expression of CD62L on lymphocytes mediated by β2AR differed in naïve and memory/effector CD8+ subtypes, implying a possibility of differential expression of β2AR on various CD8+ subtype cells [11].

It is well known that the expression of β2AR is different for different specific CD4+ T cell subtypes. Ramer-Quinn et al. observed expression of a functional β2AR on a freshly isolated, sort-purified population of naïve CD4+ T cells stimulated by a β2AR-agonist by pharmacological approaches and PCR, and found that β2AR-agonist stimulated effects were negated following administration of specific blockers, thus providing functional evidence for the existence of β2AR on naïve CD4+ T cells. Unfortunately, they did not perform classic radioligand binding analysis, for an insufficient number of naïve cells were obtained, thus lacking direct visual evidence of the receptor's existence [12].

In Sanders et al.'s study, it was demonstrated that upon stimulation with a β2AR specific agonist, Th1 cells showed an accumulation of cAMP, which is indicative of β2AR activation, thus providing functional evidence for the existence of β2AR receptor on Th1 cells; whereas when using a polyclonal anti-β2AR antibody directed against the cytoplasmic region of the β2AR, they observed that neither resting nor activated clones of murine Th2 cells expressed β2AR [13]. The later studies provided evidence for the presence of β2AR on Th2 cells, which emphasized a direct action of β-agonists on type 2 T cells (IL-13+ T cells including both CD4+ and CD8+ cells) [14,15]. The most recent study revealed that the stimulation of β2AR resulted in increased IL-2 expression, which led to an accumulation of type 2 T cells, with the increase highest at concentrations approximating the dissociation constant of the β-agonist for the β2AR receptor [16].

Concerning the mechanisms responsible for mediating the differential expression of the β2AR on murine Th1 and Th2 cells, it is accepted that epigenetic mechanisms are involved. For example, Viginia et al. reported that DNA methylation particularly occurs in naive CD4+ T cells as they differentiate into effector Th1 and Th2 cells [17]. This result will lead to a further research into the expression of β2AR on Th1 and Th2 cells, especially for β2AR expression. A comparison of β2AR ligation between naïve and memory CD4+/CD8+ T cell subtypes will also be helpful to elucidate its physiological significance and clinical relevance if differential expression is confirmed in the future studies.

3.2. The number of β2AR on T lymphocytes

Early radioligand binding analysis gave an estimate of the absolute number of β2AR on various T cell types, although the exact number differed between studies, most probably due to a variety of factors including different T cell isolation techniques, different types of radiolabels,

pharmacological ligands with differing affinities, and/or radioligand specific activity. The current estimate is that there are approximately 500–2500 β2AR binding sites expressed per CD8+T cell and 200–750 binding sites per CD4+ T cell. However, it should be noted that the level of β2AR expression on a lymphocyte is not static, and can be determined by genetic variations [18], different methods of cell activation, the cytokine environment in which the cell is activated, and/or specific disease states. In an early example, when either fresh or cloned immunocytes were treated with different mitogens, an alternation of the number but not the affinity of β-receptors was observed. Specifically, in various cell lines, ConA increased the number of β2AR per cell, whereas PMA/ionophore or PMA alone decreased it [19]. Another study, however, showed that treatment of murine lymphocytes with ConA prevented a mitogen-induced increase in βAR [20]. Furthermore, it seems that the disease state also markedly affects expression of βAR on T lymphocytes. In a chronic mild stress (CMS) model of depression in mice, catecholamines (epinephrine and norepinephrine) were found to exert an inhibitory effect on mitogen-induced normal T cell proliferation that could be abolished by specific β- and β_2-antagonists, while a significant increase in β2AR density was also observed, without any change in the level of circulating norepinephrine or corticosteroids [21]. The thyroid status also seems to affect βAR density. A decrease or an insignificant increase in βAR number was found on T lymphocytes from hypo- and hyperthyroid mice compared to euthyroid controls [22]. On the other hand, various studies on lymphocytes from multiple sclerosis (MS) donors showed a significant decrease in βAR density and decreased expression of GRK2/3, as well as a low level of agonist-induced cAMP accumulation, demonstrating the close interplay between the systemic inflammatory activity and the β2AR characteristics in patients with MS [23].

It has been found that CD8+ T cells have a higher density of β2AR on their surface, but the exact functions of this receptor is not yet well understood. One study on mice revealed that β2AR activation skewed the CD4+/CD8+ ratio in an age-dependent way, with alternations in immature intermediate T subtypes, and an increase in the frequency of mature CD4-8+ cells [24]. CD8+ cells may be more suspectible than CD4+ to the mechanisms involved in β2AR stimulation, perhaps due to the relative abundance in receptor number [10]. Up to now, β2AR-mediated regulation of CD8+ T cells has not been well understood, and further research into this area should be encouraged as it may be of clinical importance, especially in the area of enhancing cytotoxicity against tumor cells.

From above all, we know that the expression of β2AR on T lymphocytes is regulated by a number of factors including mode of activation, disease states and cytokine milieu, leading to different states of sensitivity of T lymphocytes to adrenergic regulation.

4. Effect of β2AR stimulation on T cells

Early studies primarily used unfractionated T cell populations in assessing the regulatory actions of β2AR on the immune system. With the discovery of subtype-related differential β2AR expression, purified populations of naïve CD4 T cells and effector Th1 and Th2 cells were examined to determine if stimulation of β2AR affects each CD4 T cell subtype similarly, in terms of proliferation, differentiation and cytokine production. In the following, we discuss each issue in detail.

4.1. Proliferation and differentiation

Under Th-1 polarizing conditions, stimulation of the β2AR on purified naïve T cell population generated Th1 cells that produced 2- to 4-fold more IFN-γ in the presence of IL-12. The effect was blocked by a β-antagonist, while α-antagonists exhibited no effect. This increase was the result of more IFN-γ produced per cell instead of more IFN-γ-secreting cells, thus stimulation of β2AR did not affect either the ability of the naïve T cell to develop into a Th1 cell or the number of Th1 cells that subsequently develop. As IL-2 promotes naïve T cell proliferation, this result is in line with rapid densensitization of IL-2 decrease [25].

Further research led to the discovery that β2AR activation preferentially enhanced type 2 T cell survival and accumulation, through increased IL-2-induced accumulation of human type 2 T cells. However, this effect is dependent on the mitogen used for activation, and the increase is often obscured by concomitant and antimitogenic PKA activation [26]. However, studies with human cord blood T cells and adult peripheral blood T cells did not completely give the same results. In cord blood T cells, chronic β2-agonist exposure predisposed differentiation of T lymphocytes towards Th2 while that of Th1 was relatively suppressed, which parallels results obtained from murine naïve T cells, perhaps due to their similarities [27]. But this trend was not observed in adult peripheral blood T cells. Studies using proteases derived from *Aspergillus* species as antigens have also yielded peripheral evidence in that decrease in IL-12/IL-12R secretion primed T cells towards Th2 development [28].

The direct actions of the β2AR-induced differentiation on CD8+ T cells have not been described to date. However, it has been noted that β2AR may propitiate CTLs towards the CT2 subtype (CD8+CD4-CD30+ CD40L+) through the indirect action of increased IL-10 expression [29].

4.2. Cytokine production

The effects of β2AR regarding cytokine production of CD4+ T cells seem to be dependent on the stage of maturity and the method of stimulation. Studies on murine splenocytes indicated that naïve CD4+ T cells produced a 2- to 4-fold increase in IFN-γ upon stimulation with

norepinephrine [25]; while a decrease in IL-2 secretion was noted [30]. The increase in IFN-γ could be synergistically induced by T-bet and Hlx, and DNA demethylation may also be involved as increased IFN-γ was found in DNA methyltransferase knockout mice [31,32].

The case with Th0 cells, however, is not so clear cut. Using a βAR-agonist, it was noted that the effects of stimulation on Th0 cells varied depending on the mode of T cell activation; IL-2 production decreased, and IL-4 and IL-5 production varied, indicating that the latter two cytokines may have a different regulatory mechanism [33,34]. In murine Th1 cells, an increase in intracellular cAMP decreased the level of IL-2 and IFN-γ production [35], while exposure to a β2AR agonist seemed to be dependent on the time of activation compared to the time of β2AR stimulation. Stimulation before TCR activation led to a decrease in both IL-2 and IFN-γ, while stimulation at the time of or after cell activation either induced a small increase or did not affect IFN-γ production, although IL-2 levels were also decreased in a concentration-dependent manner [36]. This differential effect points to the fact that cAMP accumulation may be dependent on the mode of activation, which plays diverse roles during different stages of T cell activation.

The effects of β2AR stimulation on regulating Th2 cells are less clear, as a functional β2AR does not appear to exist. Some studies point to the fact that the expression of IL-4, a Th2 cytokine, is negatively regulated by the cAMP-PKA-dependent signaling pathway by transcriptional and posttranscriptional mechanisms, and is dependent on costimulatory signals [37]. Others, however, yield contrarily results, in which an increase in cAMP was found to not affect, inhibit, or enhance the level of IL-4 and IL-5 produced by Th2 cells [38]. Although the precise function of β2AR on differentiated Th2 cells is still open to debate, it is clear that the adrenoceptors play a major part in shifting the immune response to the cytokine profile of a Th2 response [39], as was illustrated in human peripheral mononuclear cells. Furthermore, variable enhancement of type-1/type-2 immune deviation occurred depending upon when the stimulation occurred, and was dependent on other costimulatory factors, such as corticosteroids [40].

Early research indicates that β2AR stimulation seems to affect Th2 by augmenting the development of a Th2 response rather than by influencing effector T cell development. This fact is mostly in agreement with the observation that β2AR was not found to be present on Th2 cells. However, the above theory is beginning to unravel due to the contradictory results of a study conducted by Loza et al., who found that Type 2 IL-13+ T cells (CD4+ and CD8+) in human peripheral blood lymphocytes respond directly to β-agonists, with subsequent effects including the induction of PKA activity and associated inhibition of CD3-stimulated CD25 expression; CD3-stimulated IL-13, IFN-γ and IL-2 production; and p38 mitogen-activated protein kinase (MAPK) phosphorylation [15]. A different view states that pro-Th2 cytokine development is indirectly mediated by a direct effect of β2AR stimulation on various types of antigen presenting cells (APCs), such as macrophages or dentritic cells (DCs). For example, in short-term exposure of bone marrow-derived DCs to norepinephrine (NE), at the beginning of the stimulation IL-12 production was hampered while IL-10 release increased, thus limiting their Th1 polarizing properties [41].

5. The effects of β2AR stimulation on antibody production

The most significant function of a Th cell is to aid B cells in producing antibody, and research shows that β2AR stimulation alters this process. Upon stimulation, a β2AR-dependent increase in the ability of a CD40 ligand/interleukin-4-activated B cell to respond to IL-4 was noted, and this may work synergistically with a B cell receptor to up-regulate CD86, leading to further increases in the amount of IgG1 and IgE produced per cell by increasing the rate of mature IgG1 transcription [42,43]. The upregulation of CD86 is dependent on a number of intracellular pathways including protein tyrosine kinase-, protein kinase A-, protein kinase C-, and mitogen-activated protein kinase-dependent mechanisms, and increased B cell-associated B7-2 expression is mediated by increased B7-2 mRNA stability, NF-κ B nuclear binding, and NF-κ B-dependent gene transcription [44].

The regulatory actions of β2AR on IgE production seemed to depend on a different mechanism from IgG1. Stimulation of βAR *in vitro* directly increased the level of IgE on a per cell basis without an effect on the class switch recombination, and appeared to be regulated by NE in a p38 MAPK- and CD23-dependent manner [45]. Although β2AR-mediated IgE secretion is supported by a vast amount of phenotypic research, elucidation of precise mechanisms calls for in-depth investigation.

6. Clinical relevance

Interaction between the sympathetic nervous system and the immune system concomitantly regulates the immune response, as a change in β2AR number and/or function may induce a change in immune cell type, number, cytokine production, and may even predispose the response to that of a Th1 or Th2 profile. Thus, in the *in vitro* study of immune function, it should be practical to introduce NE or other endogenous β2AR agonists to the system, in order to more accurately reflect the immune response as it is *in vivo*.

To date, a number of illnesses can be associated to β2AR dysfunction, especially in the cases of autoimmune diseases, e.g. systemic lupus erythematosus [46], multiple sclerosis [47,48], rheumatoid arthritis [49], Grave's disease [50], asthma [51], insulin-dependent diabetes mellitus [52], chronic heart failure [53], vaccine responses [54], HIV pathogenesis [55], protection against septic shock [56,57]. Perhaps the best clinical example of β2AR's effect on the immune system is illustrated by its role in mediating auto-

immune diseases [58]. From a long-term standpoint, chronic stress may increase sympathetic activity, resulting in an increased susceptibility or exacerbation to autoimmune diseases. One of the most intensely researched is rheumatoid arthritis patients who demonstrate an impaired inhibitory effect of catecholamines on IFN-γ production together with a failure to induce a shift of T cell cytokine responses toward a Th2-like profile, including a decrease in IL-4 production. This modification generates a cytokine environment that perpetuates inflammation, and thus might be a contributing factor to pathogenesis [59]. Furthermore, β2 AR gene single nucleotide polymorphisms are associated with rheumatoid arthritis in a northern Swedish population [60], while the genes *FCRL3* and *SEC8L1* are biomarkers for RA in the Japanese population [61]. This implies that a change in the β2AR structure may augment different levels of sensitivity of a T lymphocyte to β2AR stimulation, providing a basis for a genetic predisposition to RA [62].

A study with murine spleen cells has also shown a bimodal role of the sympathetic nervous system, with proimflamatory actions during the asymptomatic phase of arthritis, and inhibitory actions during the chronic symptomatic phase, establishing the idea that the effect of β2AR stimulation is time-dependent, and may play an important role in the treatment of bone destruction in AR [63,64]. Thus, β2AR activity is implicated in the generation, progression and treatment of RA, and this complex relationship has been mimicked by a variety of other autoimmune diseases as listed above. Drugs targeting the sympathetic nervous system, particularly the β2AR, could provide a novel direction in the treatment of autoimmune diseases, although it should be kept in mind that the time and mode of drug administration could influence its therapeutic effects.

7. Conclusion

In the past 30 years, increased evidence has accumulated in emphasizing complex functional interconnections between the system immune and the nervous system, and how impediment of this cross-talk may generate a variety of neurological and immunological diseases [65]. The focus of this paper is mainly on the existence and function of β2AR on T lymphocytes, activation-induced intracellular pathways and related cross-talk between intracellular messengers, and a brief overview of the many cytokines that may be involved. The progress made in this area may implicate that (1) the design of *in vitro* immunological experiments where the influence of β2AR needs to be considered should better reflect *in vivo* reactions; (2) clarification of the etiology and development in autoimmune diseases and several neurological diseases should be further studied; and (3) the novel neuro-immunoregulatory drugs and their respective specific time-dependent administration method should be developed for the clinical applications.

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