

## Adrenergic modulation of immune cells: an update

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**Abstract** Sympathoadrenergic pathways are crucial to the communication between the nervous system and the immune system. The present review addresses emerging issues in the adrenergic modulation of immune cells, including: the specific pattern of adrenoceptor expression on immune cells and their role and changes upon cell differentiation and activation; the production and utilization of noradrenaline and adrenaline by immune cells themselves; the dysregulation of adrenergic immune mechanisms in disease and their potential as novel therapeutic targets. A wide array of sympthoadrenergic therapeutics is currently used for non-immune indications, and could represent an attractive source of non-conventional immunomodulating agents.

**Keywords** Noradrenaline · Adrenaline · Adrenoceptors · Immune cells · Human disease

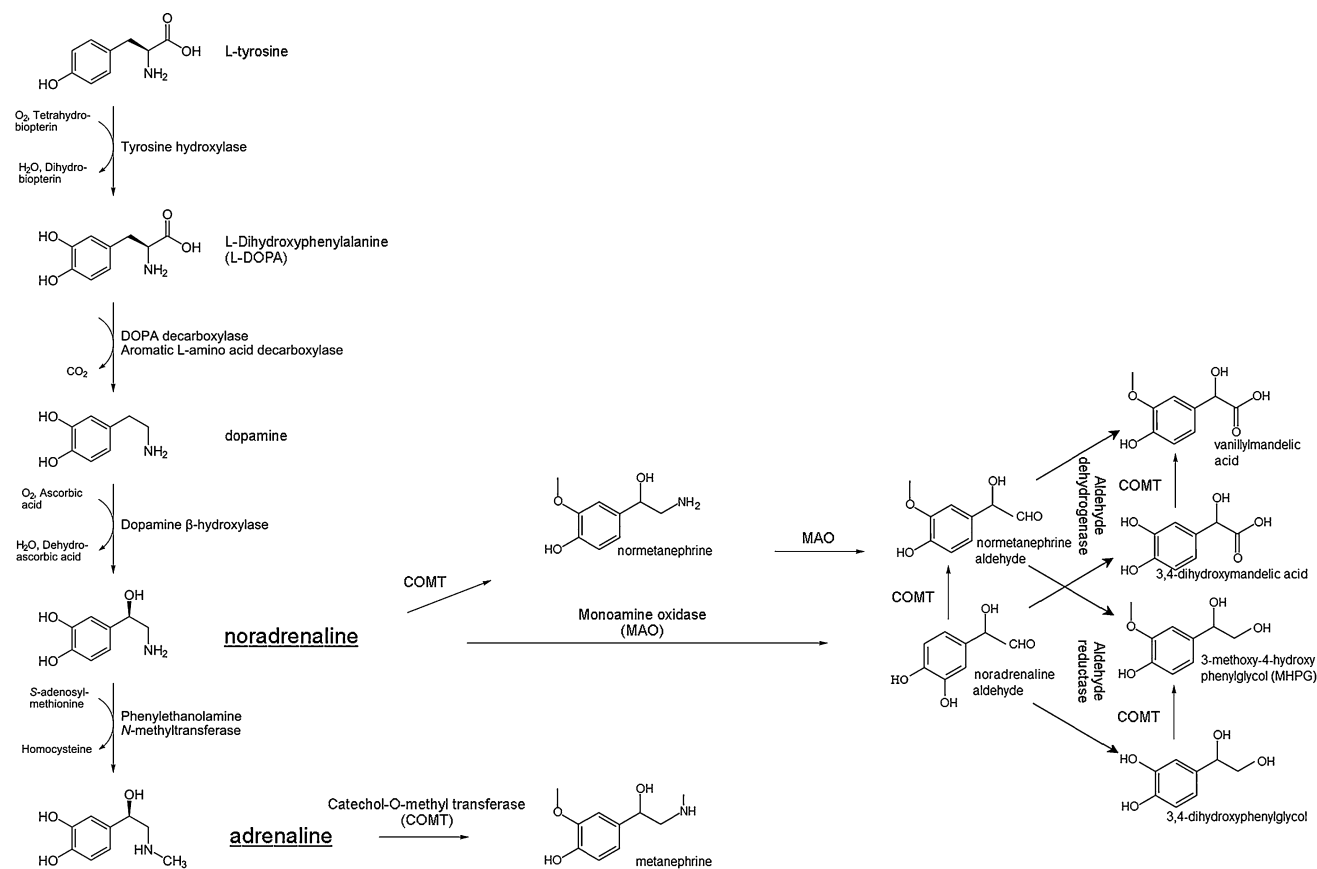
### Physiopharmacology of noradrenaline and adrenaline

Noradrenaline and adrenaline are catecholamines, i.e. chemical compounds with a 3,4-dihydroxyphenyl group (catechol) and an amine function. Together with dopamine, they represent the main catecholamines in humans and are all produced from the non-essential amino acid tyrosine. The enzyme dopamine  $\beta$ -hydroxylase synthesizes noradrenaline from dopamine, and phenylethanolamine *N*-methyltransferase converts noradrenaline to adrenaline (Fig. 1). The

natural stereoisomers are L-(-)-(R)-noradrenaline and adrenaline. Adrenaline was isolated as pure crystalline base in 1900 by Jokichi Takamine, while noradrenaline was synthesized a few years later (the prefix 'nor' is the acronym of *nitrogen ohne radikal*, indicating the absence of a methyl group) and in 1949 it was proved by Ulf von Euler in Stockholm to be the main sympathomimetic neurotransmitter in humans (Sneader 2005).

Noradrenaline and, to a lesser extent, adrenaline act as neurotransmitters in the central and peripheral nervous systems, and as neurohormones in chromaffin cells in medulla of adrenal glands. The most important noradrenergic nucleus in the central nervous system is the *locus coeruleus* (LC), which axons project rostrally to hippocampus, septum, hypothalamus and thalamus, cortex and amygdala, dorsally to cerebellum, and caudally to spinal cord, affecting attention, arousal and vigilance to salient and relevant external stimuli, and regulating hunger and feeding behavior. Adrenaline in the central nervous system acts as neurotransmitter in the medullary reticular formation, possibly contributing to coordination of eating and in visceral activities such as blood pressure regulation. Outside the central nervous system, noradrenaline is the main transmitter of most autonomic sympathetic postganglionic fibers. Peripheral actions of noradrenaline and adrenaline include: contraction of certain smooth muscles (blood vessels supplying skin, kidney, and mucous membranes), stimulation of exocrine glands (e.g., salivary and sweat glands), relaxation of certain other smooth muscles (gut wall, bronchi, blood vessels supplying skeletal muscle), increases of heart rate and force of contraction, metabolic actions (increased glycogenolysis in liver and muscle, lipolysis in adipose tissue), and endocrine actions (e.g., modulation of the secretion of insulin and renin). Detailed discussion of noradrenaline and adrenaline neurochemistry,

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**Fig. 1** Biosynthesis and degradation of adrenaline and noradrenaline. The responsible enzymes are shown close to each *arrow*

anatomy and physiology can be found in Feldman et al. (1997).

The effects of noradrenaline and adrenaline are mediated by adrenergic receptors or ‘adrenoceptors’ (ARs), 7-transmembrane G protein-coupled receptors expressed in the central nervous system and in virtually all peripheral tissues (Table 1). ARs involved in the control of blood pressure, myocardial contractile rate and force, airway reactivity, as well as a variety of metabolic and central nervous system functions. ARs include three major types— $\alpha_1$ ,  $\alpha_2$  and  $\beta$ —each further divided into three subtypes (Bylund et al. 2011). ARs can be either pre- or postsynaptic. Presynaptic ARs are mainly of the  $\alpha_2$  type and mediate inhibition of neurotransmitter release, while postsynaptic receptors include all AR types. In peripheral tissues,  $\alpha$ -ARs are expressed in smooth muscle cells and usually mediate contraction, while  $\beta$ -ARs can be found in heart (mainly  $\beta_1$ , which mediate contraction), in smooth muscle cells (mainly  $\beta_2$ , inducing relaxation), and in skeletal muscle ( $\beta_2$ , possibly inducing hypertrophy). Virtually all normal human cells express  $\beta_2$ -ARs. Usually,  $\alpha_1$ - and  $\beta_1$ -ARs are located nearby sympathoadrenergic terminals and are therefore the main target of noradrenaline released upon nerve stimulation. On the contrary,  $\alpha_2$ - and

$\beta_2$ -ARs are preferentially extrajunctional receptors and are acted upon by circulating noradrenaline and adrenaline. ARs are also widely distributed in the brain. AR agonists and antagonists are currently used to treat a variety of diseases, including hypertension, angina pectoris, congestive heart failure, asthma, depression, benign prostatic hypertrophy, and glaucoma. Additional conditions where these agents proved useful include shock, premature labor and opioid withdrawal, and as adjunct medications in general anesthesia.

Both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid organs are innervated mainly by sympathoadrenergic nerve fibers. Together with the hypothalamic–pituitary–adrenal axis, the sympathetic nervous system represents the major pathway involved in the cross-talk between the brain and the immune system (reviewed in Elenkov et al. 2000). The origin, pattern of distribution and targets of sympathetic nerves in lymphoid organs, and their neurochemical signaling have been the subject of several excellent reviews (see e.g. Felten 1991; Straub 2004), as well as the occurrence of age-induced changes in sympathetic-immune interactions (Bellinger et al. 1992; Friedman and Irwin 1997; Madden et al. 1998) and the consequences of dysregulated sympathetic nervous

**Table 1** Classification of ARs

Receptor	Transduction mechanisms (effectors)	Tissue distribution	Physiological functions
$\alpha_{1A}$	G <sub>q</sub> /G <sub>11</sub> (phospholipase C stimulation, calcium channel) Phospholipase D stimulation Protein kinase C	Human heart, liver, cerebellum, cerebral cortex, predominant subtype in human prostate and urethra	Contraction of urethral smooth muscle, contraction of skeletal muscle resistance arteries
$\alpha_{1B}$	Mitogen activated protein kinases	Human spleen and kidney, human somatic arteries and veins	Contraction of arteries and veins
$\alpha_{1D}$		Human aorta, blood vessels of human prostate, human bladder	Constriction of arteries, urethral contraction, contraction of corpus cavernosum
$\alpha_{2A}$	G <sub>i</sub> /G <sub>o</sub> (adenylate cyclase inhibition, potassium channel, calcium channel, phospholipase A2 stimulation)	Human brain > spleen > kidney > aorta = lung = skeletal muscle > heart = liver	Presynaptic inhibition of noradrenaline release, hypotension, sedation, analgesia, hypothermia
$\alpha_{2B}$	G <sub>s</sub> (adenylate cyclase stimulation)	Human kidney $\gg$ liver > brain = lung = heart = skeletal muscle (also reported in aorta and spleen)	Vasoconstriction
$\alpha_{2C}$		Human brain $\geq$ kidney (also reported in spleen, aorta, heart, liver, lung, skeletal muscle)	Presynaptic inhibition of noradrenaline release
$\beta_1$	G <sub>s</sub> (adenylate cyclase stimulation) G <sub>i</sub> /G <sub>o</sub> (guanylate cyclase stimulation)	Pineal gland, skeletal muscle, liver, superior cervical ganglion, heart, lung, adrenal cortex, cardiac myocytes, brain	Increase of cardiac output (heart rate, contractility, automaticity, conduction), renin release from juxtaglomerular cells, lipolysis in adipose tissue
$\beta_2$		Lung, lymphocytes, skin, liver, heart	Smooth muscle relaxation, striated muscle tremor and glycogenolysis, increase of cardiac output, increase of aqueous humor production in eye, glycogenolysis and gluconeogenesis in liver, insulin secretion
$\beta_3$		Adipose, gall bladder > small intestine > stomach, prostate > left atrium > bladder	Lipolysis, thermogenesis, relaxation of miometrium and colonic smooth muscle cells, vasodilatation of coronary arteries, negative cardiac inotropic effect

system in stress responses (Irwin 1994; Sloan et al. 2008) and in the development and progression of immune-mediated diseases (Madden et al. 1995; Friedman and Irwin 1997; Marshall and Agarwal 2000; Frohman et al. 2001; Wrona 2006; Straub et al. 2006; Bellinger et al. 2008; Benarroch 2009).

### Adrenergic modulation of immune cells

Usually,  $\beta_2$ -ARs are the most expressed on immune cells and as a consequence they are regarded as the main mediators of the immune effects of noradrenaline and adrenaline. Evidence is, however, increasing regarding the occurrence of other ARs, in particular the  $\alpha_1$ -AR subtype (reviewed by Kavelaars 2002). Different immune cell populations express distinct patterns of ARs, which in turn undergo up/downregulation upon cell development and/or response to activating stimuli. Hereafter, current knowledge will be summarized regarding ARs on well-defined

cell types (and not, e.g., peripheral blood mononuclear cell preparations), with particular regard to results obtained in human samples. Several reviews have been dedicated to the sympathoadrenergic modulation of the immune response (e.g., Elenkov et al. 2000; Kohm and Sanders 2001; Nance and Sanders 2007; Flierl et al. 2008) and to the sympathoadrenergic control of thymic function (Leposavić et al. 2008).

### T and B lymphocytes

It is well established that T cells express less  $\beta$ -AR than B cells (Bidart et al. 1983; Paietta and Schwarzmeier 1983). Among T cells, Khan et al. (1986) reported the following rank order of  $\beta$ -AR (likely  $\beta_2$ -AR) density: T suppressor > T cytolytic > T helper. Karaszewski et al. (1990) confirmed that B lymphocytes had the greatest number of  $\beta$ -ARs ( $12.1 \pm 1.8$  fmol/ $10^6$ ) cells, followed by CD8<sup>+</sup> T lymphocytes ( $3.4 \pm 0.4$  fmol/ $10^6$ ) and CD4<sup>+</sup> T lymphocytes ( $1.2 \pm 0.1$  fmol/ $10^6$ ), and subsequently reported that

CD8<sup>+</sup>CD28<sup>-</sup> (suppressor) T cells express more ( $2.8 \pm 0.3$  fmol/10<sup>6</sup> cells) than CD8<sup>+</sup>CD28<sup>+</sup> (cytotoxic) T cells ( $1.4 \pm 0.4$  fmol/10<sup>6</sup> cells) (Karaszewski et al. 1991). Human CD4<sup>+</sup>CD25<sup>+</sup> regulatory T lymphocytes express mRNA not only for  $\beta_2$ - but also for  $\beta_1$ -ARs (Cosentino et al. 2007), and it was recently suggested that these receptors may mediate the effects of stress on T regulatory cells (Freier et al. 2010). Expression of  $\beta_3$ -AR mRNA was reported in only one study in concanavalin A (Con A)-stimulated human T lymphocytes, however, without correlations with specific functional responses (Borger et al. 1998). Only a few data exist regarding  $\alpha$ -ARs. Ligand binding studies suggest the occurrence of  $\alpha_2$ -ARs in human CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes, as well as their upregulation after in vivo administration of adrenaline (Jetschmann et al. 1997), while it was shown that the T lymphocyte-preferring mitogen phytohaemagglutinin (PHA) can induce  $\alpha_1$ -ARs in stimulated peripheral blood mononuclear cells, suggesting that their expression may occur in particular on activated T cells (Roupe van der Voort et al. 2000). The density and functional responsiveness of  $\beta_2$ -ARs on human T lymphocytes is increased by interleukin-2 (IL-2) and after activation with PHA (Korichneva and Tkachuk 1990; Carlson et al. 1994). IL-2 upregulates  $\beta_2$ -AR expression CD8<sup>+</sup> T lymphocytes, but not on CD4<sup>+</sup> T cells, while IL-1 $\beta$  has no effect (Wahle et al. 2001b). In vivo, the expression of  $\beta_2$ -ARs is increased in both T and B cells after physical stress and returns to normal after 30 min rest (Ratge et al. 1988).

Stimulation of  $\beta$ -ARs usually inhibits lymphocyte responses, e.g. IL-2 receptor expression (Feldman et al. 1987), proliferation of T lymphocytes (Elliott et al. 1992) as well as of CD4<sup>+</sup>, CD8<sup>+</sup>, or CD45RO<sup>+</sup> lymphocyte subsets and production of IL-2 (Bartik et al. 1993), IFN- $\gamma$ , GM-CSF, and IL-3 (Borger et al. 1998). Polarized T helper (Th) cells, however, may be less sensitive to  $\beta_2$ -AR-induced inhibition of both Th1 (IFN- $\gamma$ ) and Th2 (IL-4, IL-5) cytokine production (Heijink et al. 2003).

Activation of  $\beta$ -ARs on human lymphocytes may also result in stimulation of immunity (Sanders et al. 1997; Kohm and Sanders 1999). Noradrenaline may indeed promote IL-12-mediated differentiation of naive CD4<sup>+</sup> T cells into Th1 effector cells, and increase the amount of IFN- $\gamma$  produced by Th1 cells (Swanson et al. 2001). With regard to B lymphocytes, IgG1 and IgE production increases when noradrenaline is added either during antigen processing or within the first 12 h of culture with Th2 cells (Kasprowicz et al. 2000), while in plasma cells noradrenaline decreases antibody production (Melmon et al. 1974).

#### Natural killer cells

Binding assays in lymphocyte subsets showed that CD16<sup>+</sup>CD56<sup>+</sup> natural killer cells express the highest

number of  $\beta$ -ARs ( $1,934 \pm 122$  sites/cell), which after physical exercise increased (to  $2,617 \pm 289$  sites/cell) (Maisel et al. 1990). Activation of  $\beta$ -AR (likely  $\beta_2$ -AR) pathways decrease NK cell cytotoxicity (Whalen and Bankhurst 1990; Takamoto et al. 1991) and reduce adhesion to endothelial cells (Benschop et al. 1994, 1997). In human subjects, infusion of either adrenaline or noradrenaline modulates the migratory capacity of human NK cells via  $\beta_2$ -AR mechanism (Schedlowski et al. 1996; Benschop et al. 1997).

Human NK cells express also  $\alpha$ -ARs. In CD16<sup>+</sup> lymphocytes, ligand binding studies indeed showed the presence of  $\beta_2$ -,  $\alpha_1$ -,  $\alpha_2$ - but not  $\beta_1$ -AR, and infusion of adrenaline (but not noradrenaline) significantly decreased their numbers (Jetschmann et al. 1997). The functional relevance of  $\alpha$ -AR pathways in human NK cells, however, still awaits investigation.

#### Monocytes/macrophages

In classical binding experiments,  $\beta$ -AR density on human circulating monocytes was about 2,400 binding sites/cell, thus higher than that in lymphocytes, and further increased to 3,220 binding sites/cell after physical exercise (Ratge et al. 1988). Changes in receptor number can be, however, regulated with different states of cell maturation and function (Radojcic et al. 1991). Indeed, during the maturation of human monocytes to macrophages in vitro  $\beta$ -AR responsiveness may be lost (Baker and Fuller 1995), thus these cells may become insensitive to the inhibitory effects of  $\beta$ -AR agonists (Ezeamuzie et al. 2011). Activation of  $\beta$ -ARs (possibly,  $\beta_2$ -ARs) on human monocytes usually result in anti-inflammatory effects, e.g. inhibition of oxygen radicals production (Schopf and Lemmel 1983), upregulation of TNF receptors and inhibition of TNF (Guirao et al. 1997), reduction of the phagocytosis of *C. albicans* (Borda et al. 1998), and inhibition of LPS-induced macrophage inflammatory protein-1  $\alpha$  (MIP-1  $\alpha$ ), which has an important role in the development of inflammatory responses during infection by regulating leukocyte trafficking and function (Li et al. 2003). Selective activation of  $\beta_2$ -ARs may down-regulate IL-18-induced intercellular adhesion molecule (ICAM)-1 expression and IL-12, TNF- $\alpha$  and IFN- $\gamma$  production (Takahashi et al. 2003) as well as LPS-induced IL-18 and IL-12 production in human monocytes, an effect which might be beneficial in the treatment of sepsis (Mizuno et al. 2005).

Evidence exists, however, that under certain conditions, monocyte  $\beta$ -AR stimulation may lead to proinflammatory responses. Indeed,  $\beta_2$ -AR activation in unstimulated monocytes may increase the production of IL-18 (Takahashi et al. 2004), while in LPS- or IL-1-stimulated cells it increased the production not only of the antiinflammatory

cytokine IL-10 but also of the pro-inflammatory chemokine IL-8 (Kavelaars et al. 1997). In vitro, adrenaline may upregulate the surface expression of L-selectin on human monocytes possibly through a partial contribution of  $\beta$ -ARs (Rainer et al. 1999), and noradrenaline and adrenaline, possibly through the activation of  $\beta_2$ -ARs, up-regulate MMP-1 and potentiate LPS-induced expression of MMP-1 in peripheral blood monocytes and monocyte-derived macrophages (Speidl et al. 2004). Isoprenaline treatment was reported to increase phorbol ester-induced production of TNF- $\alpha$ , IL-12, and nitric oxide, while it decreased inflammatory mediator production in combination with LPS stimulation (Szelenyi et al. 2006). Isoprenaline also increased LPS-induced production of IL-1 $\beta$  in human monocytes, however, this effect—according to pharmacological evidence—was due to the activation of  $\beta_1$ -ARs, which were directly observed in the monocytic cell line THP-1 by immunoblot techniques as well as by radioligand binding studies (Grisanti et al. 2010).

Under certain circumstances, human monocytes may also express functional  $\alpha$ -ARs, e.g. after culture with dexamethasone or the  $\beta_2$ -AR agonist terbutaline, when both  $\alpha_{1B}$ - and  $\alpha_{1D}$ -AR mRNA can be detected (Roupe van der Voort et al. 1999). In the human THP-1 monocytic cell line,  $\alpha_{1B}$ - and  $\alpha_{1D}$ -AR mRNA are, respectively, upregulated and reduced by the proinflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$  (but not by IL-6 or IL-8) (Heijnen et al. 2002). With regard to the functional relevance of  $\alpha$ -AR in human monocytes, in a recent study it was shown that the selective  $\alpha_1$ -AR agonist phenylephrine synergistically increased LPS-induced IL-1 $\beta$  production and this effect was blocked in the presence of a selective  $\alpha_1$ -AR antagonist as well as of inhibitors of protein kinase C (PKC) (Grisanti et al. 2011). Pharmacological evidence might also suggest the occurrence of  $\alpha_2$ -AR-mediated effects in human monocytes (Maes et al. 2000); however, the actual expression of functional  $\alpha_2$ -ARs on these cells remains to be established.

#### Dendritic cells

Extensive evidence exists for the presence and the functional relevance on murine dendritic cells (DCs) of ARs, which mediate sympathetic nervous system influence on DC-T cell interactions thus contributing to the shaping of the appropriate adaptive immune response (Maestroni 2005, 2006; Manni and Maestroni 2008; Yanagawa et al. 2010; Manni et al. 2011). On the contrary, very few information is available regarding human DCs. Activation of  $\beta_2$ -ARs in human dendritic cells stimulated via CD40 results in inhibited IL-12 production via increased cAMP, finally blunting Th1 and promoting Th2 differentiation (Panina-Bordignon et al. 1997), while in human DCs obtained by differentiating human cord blood CD34<sup>+</sup>

precursor cells  $\beta_2$ -ARs inhibit LPS-stimulated production of IL-23, IL-12 p40, TNF- $\alpha$  and IL-6 (Goyarts et al. 2008). This response pattern is similar to that obtained in mouse skin DCs (Maestroni 2005, 2006), thus suggesting that noradrenaline may regulate human skin DC function resulting in decreased Th1 differentiation of CD4<sup>+</sup> T cells.

#### Granulocytes

Expression of  $\beta$ -ARs on human polymorphonuclear cells (PMN) has been investigated only by means of ligand binding assays, which indicated the existence on average of 1,700–2,200 binding sites per cell (Pohl et al. 1991; Schwab et al. 1993) or 39–61 fmol/mg of protein (Boreus et al. 1986; Gurguis et al. 1999). In one study, the possible existence of  $\alpha_2$ -AR was excluded based on both ligand binding and functional experiments in either PMN and differentiated HL-60 cells, a promyelocytic cell line frequently used as a model for neutrophils (Musgrave and Seifert 1994). The functional relevance of  $\beta$ -AR on human PMN is a matter of debate. Low concentration of the  $\beta$ -AR agonist isoprenaline inhibited the respiratory burst induced by various stimuli (Nielson 1987), however, in another study adrenaline reduced only slightly and only at very high concentrations PMN production of IL-8 and expression of the adhesion molecules CD15, CD44, and CD54. It should be, however, considered that  $\beta$ -AR desensitization has been reported after activation of PMN respiratory burst (Vago et al. 1990).

Expression of  $\beta$ -AR on circulating PMN was found decreased in essential hypertension (Corradi et al. 1981), juvenile type I diabetes mellitus (Schwab et al. 1993), and increased in post-traumatic stress disorder (Gurguis et al. 1999a). Physical exercise may decrease PMN  $\beta$ -AR, however, only after acute heavy resistance exercises (Ratge et al. 1988; Fragala et al. 2011).

#### Microglia

In the central nervous system (CNS), microglial cells are involved in phagocytosis and neuroinflammatory responses, triggering or amplifying both innate and acquired immune responses and in particular contributing to T-cell activation within the CNS. Microglia are therefore usually considered the CNS mononuclear phagocytes (Ghorpade et al. 2008). Adrenergic mechanisms in microglia have been so far investigated only in non-human cells. Hertz et al. (2010) showed the occurrence in murine microglia of  $\beta_2$ -ARs and possibly of  $\beta_1$ -ARs and  $\alpha_{2A}$ -ARs. Activation of  $\beta$ -ARs in these cells results in increased IL-1 $\beta$ , TNF- $\alpha$  and IL-6 expression through signal transduction mechanisms involving cAMP and cAMP-dependent protein kinase (Tomozawa et al. 1995) as well as ERK1/2 and P38 MAPK



(Wang et al. 2010). Interestingly, however, noradrenaline acting on  $\beta$ -ARs has been shown to induce also IL-1ra and IL-1 type II receptor expression in murine microglia enriched cultures and to protect cortical neurons against IL-1  $\beta$ -induced neurotoxicity (McNamee et al. 2010). In agreement with these observations, exposure to both  $\beta$ 1- and  $\beta$ 2-AR agonists decreased the levels of secreted TNF- $\alpha$ , IL-6 and monocyte chemoattractant protein-1, prevented microglia activation and was antiinflammatory and neuroprotective in LPS-treated murine hippocampal slices (Markus et al. 2010). Notably, it has been recently shown that, in a rat model of monoarthritis, spinal glia, as well as dorsal root ganglion primary afferent neurons, express  $\alpha$ <sub>2</sub>-AR and the  $\alpha$ <sub>2</sub>-AR agonist dexmedetomidine exerted analgesic effects involving the blockade of spinal glial activation (Xu et al. 2010).

### Astrocytes

Astrocytes provide mechanical and functional support for neurons, there is, however, also evidence that they contribute to neuroinflammation upon severe challenges by releasing pro-inflammatory molecules (e.g., TNF- $\alpha$ , IL-1, IL-6) and possibly by contributing to antigen presentation under autoimmune response, although this latter function needs further investigation (Jana et al. 2008). Human astrocytes express mainly  $\beta$ <sub>2</sub>-AR, which play a key role in glycogen metabolism, regulation of immune responses, release of neurotrophic factors, as well as in the astrogliosis that occurs in response to neuronal injury. Accordingly, downregulation of the astrocytic  $\beta$ <sub>2</sub>-AR-pathway might be involved in a number of neurological conditions such as multiple sclerosis, Alzheimer's disease, human immunodeficiency virus encephalitis, stroke and hepatic encephalopathy (reviewed in Hertz et al. 2004 and Laureys et al. 2010). Stimulation of  $\beta$ -ARs together with TNF-receptor triggering in astrocytes can, however, also induce synergistic expression of IL-6, which may be involved in neurodegeneration and glioma development (Spooren et al. 2011). Circumstantial evidence also exists regarding the occurrence of  $\alpha$ <sub>1</sub>-AR, e.g. in astrocytes from human optic nerves (Mantyh et al. 1995).

### Production and utilization of endogenous noradrenaline and adrenaline by immune cells

Traditional criteria to assess the role of a substance as neurotransmitter in the nervous system usually include (Purves et al. 2001): (a) presence of the substance within the cell (either synthesized by the cell or taken up from other cells that release it); (b) stimulus-dependent release; (c) mechanisms for removal (i.e., by degradation or

reuptake); and (d) action on target cells through specific receptors (effects mimicked by exogenous application of the substance in appropriate amounts). Evidence for the presence and the functional relevance of ARs on immune cells has been already discussed (see previous section).

### Presence and synthesis

Consistent amounts of noradrenaline and adrenaline (as well as dopamine, the direct precursor of noradrenaline, and of their major metabolites) can be found in murine lymphocytes (Josefsson et al. 1996), peritoneal macrophages (Spengler et al. 1994), bone marrow-derived mast cells (Freeman et al. 2001), human PBMC (Musso et al. 1996; Bergquist and Silberring 1998; Marino et al. 1999; Cosentino et al. 2002a), various lymphocyte subsets (Bergquist et al. 1994; Cosentino et al. 2000), including CD4<sup>+</sup>CD25<sup>+</sup> regulatory T lymphocytes (Cosentino et al. 2007), granulocytes (Cosentino et al. 1999), as well as in hematopoietic cell lines (Cosentino et al. 2000). Intracellular levels of noradrenaline and adrenaline (as well as of dopamine) sharply increase in human stimulated PBMC (Cosentino et al. 2002a). Similar results have been published also in rodent lymphocytes, and by use of immunohistochemistry it was shown that TH-positive cells in rodent lymphoid organs have highest density in lymph nodes and lowest density in thymus (Qiu et al. 2004). Mitogen-stimulated increase of intracellular catecholamines is in line with the reported upregulation of ARs occurring in lymphocytes following mitogen, glucocorticoid or proinflammatory cytokine treatment (see e.g. Zoukos et al. 1994; Rouppe van der Voort et al. 2000a) and suggests a preferential involvement of intracellular catecholamine-operated pathways in activated immune cells. According to pharmacological evidence, endogenous synthesis of catecholamines occurs through protein kinase C (PKC) activation and the contribution of intracellular Ca<sup>2+</sup>-dependent mechanisms (Cosentino et al. 2002a).

The existence of a classical pathway (Fig. 1) for the synthesis of noradrenaline and adrenaline in immune cells is suggested by the expression of the enzyme tyrosine hydroxylase (TH, EC 1.14.16.2), the first and rate-limiting enzyme in the synthesis of catecholamines, which undergoes upregulation following cell stimulation, as well as by the ability of the TH inhibitor  $\alpha$ -methyl-*p*-tyrosine to prevent intracellular enhancement of catecholamine levels (Cosentino et al. 2002a, b; Reguzzoni et al. 2002). Circumstantial evidence also exists regarding the presence in immune cells of phenylethanolamine *N*-methyltransferase (Andreassi et al. 1998; Ziegler et al. 2002) as well as of dopamine  $\beta$ -hydroxylase (Giubilei et al. 2004).

In human PBMC stimulated in vitro with PHA, TH mRNA expression and catecholamine production occur

only in T and B lymphocytes (but not in monocytes) and are reduced by dopamine (but not by noradrenaline or adrenaline) acting through dopaminergic D1-like receptors (Ferrari et al. 2004), and by the proinflammatory cytokine IFN- $\gamma$ , which in turn is counteracted by IFN- $\beta$  (Cosentino et al. 2005). TH expression and catecholamine production are on the contrary enhanced by agents which induce catecholamine release (see next section).

#### Storage and release

In human lymphocytes, catecholamines are stored in reserpine-sensitive compartments (Marino et al. 1999; Cosentino et al. 2000, 2007), possibly through vesicular monoamine transporters (VMAT) similar to those expressed in neural and neuroendocrine cells (Henry et al. 1994). VMAT-1 and 2 indeed have been reported in rat thymus and spleen (Mignini et al. 2009) and possibly also in human peripheral blood lymphocytes (Amenta et al. 2001). In human activated lymphocytes, catecholamine release can be effectively induced by biological agents such as IFN- $\beta$  (Cosentino et al. 2005) or by physiological stimuli such as elevation of extracellular  $K^+$  concentrations ( $[K^+]_e$ ) (Cosentino et al. 2003). High  $[K^+]_e$  is characteristic of various pathological conditions and is per se a sufficient stimulus to activate integrin-mediated adhesion and migration of T cells (reviewed in Levite 2001). An excess  $[K^+]_e$  may thus both assist the recruitment of lymphocytes to an injured tissue and lead to local increase of catecholamines, which in turn may act upon lymphocytes themselves and/or upon neighboring cells. Release of catecholamines is usually associated with increased TH mRNA levels and catecholamine production (Cosentino et al. 2000, 2005).

#### Mechanisms for removal

Signal termination of noradrenaline and adrenaline as neurotransmitters and hormones is the result of reuptake through specific membrane transporters and/or of degradation, mainly through monoamine oxidase (MAO)- and catechol-*O*-methyl transferase (COMT)-mediated pathways (Fig. 1). In the synapse of noradrenergic neurons, termination of the action of noradrenaline is brought about by NET (norepinephrine transporter) (see e.g. Mandela and Ordway 2006). In immune cells, however, only few indirect evidence exists for the presence of NET (Audus and Gordon 1982). More convincing evidence, however, for the expression and the functional relevance of DAT (dopamine transporter) (reviewed in Marazziti et al. 2010), which has for noradrenaline the same affinity as NET (see e.g. PDSP  $K_i$  database—<http://pdsp.med.unc.edu/pdsp.php>). Incubation of human PBMC with the NET inhibitor desipramine

or with the DAT inhibitor GBR 12909 increases the extracellular levels of both dopamine and noradrenaline (Marino et al. 1999), an observation which is compatible with the occurrence of both transporters on the human lymphocyte membrane. Whether the immunomodulating effects of monoamine uptake inhibitors (see e.g. Berkeley et al. 1994) can be attributed to a direct effect on NET and/or DAT remain, however, to be established.

Occurrence in human immune cells of both MAO and COMT is supported by functional assays and pharmacological experiments. Investigations on COMT activity were so far very limited (Bidart et al. 1981) and its eventual connections with modulation of immune response were never examined. On the contrary, MAO expression and activity in immune cells has received significantly more attention, not only as a marker of neurodegenerative and neuropsychiatric disease (Tsavaris et al. 1995; Jiang et al. 2006). MAO activity occurs in both human granulocytes and lymphocytes and it is predominantly of the B type (Pintar and Breakefield 1982; Thorpe et al. 1987; Balsa et al. 1989), and the MAO inhibitor pargyline leads to increased catecholamine levels in concanavalin A-stimulated rodent lymphocytes (Qiu et al. 2005) as well as in human peripheral blood mononuclear cells (Marino et al. 1999) and granulocytes (Cosentino et al. 1999). Recently, evidence has been provided that MAO type A is expressed in human monocytes in particular after incubation with IL-4, and it may contribute to switch naive monocytes into a resolving phenotype (Chaitidis et al. 2004, 2005).

#### Functional relevance

Possible strategies to study the role and the functional relevance of endogenous noradrenaline and adrenaline production in immune cells include: effect of AR antagonists; interference with synthesis/degradation; and interference with intracellular storage/release/uptake. The first evidence that endogenous noradrenaline and adrenaline may subserve autocrine/paracrine regulatory loops in immune cells was obtained by Spengler et al. (1994), who showed that in mouse peritoneal macrophages stimulated with LPS, the  $\beta$ -AR selective antagonist propranolol increased and the  $\alpha_2$ -AR selective antagonist idazoxan decreased TNF- $\alpha$  production, which—together with the presence of intracellular noradrenaline in these cells—was taken as an evidence of the existence of an adrenergic autocrine loop, even more pronounced in macrophages obtained from rats with streptococcal cell wall-induced arthritis (Chou et al. 1998).

Involvement of endogenous catecholamines and  $\alpha_2$ -ARs in the regulation of innate immunity was further demonstrated showing that exposure of rodent phagocytes to LPS led to catecholamine release together with induction of

catecholamine-generating and degrading enzymes, and blockade of  $\alpha_2$ -ARs or pharmacological inhibition of catecholamine synthesis suppressed (while  $\alpha_2$ -AR agonism or inhibition of catecholamine-degrading enzymes enhanced) lung inflammation in two rodent models of acute lung injury (Flierl et al. 2007, 2009).

Experimental evidence for the functional relevance of endogenous noradrenaline and adrenaline also exists in rodent lymphocytes. Qiu et al. (2004, 2005) reported that stimulation with concanavalin A markedly increased both TH expression and catecholamine content in lymphocytes and that inhibition of TH with  $\alpha$ -methyl-*p*-tyrosine significantly facilitated concanavalin A-induced IL-2 production and proliferation.

In human immune cells, indirect evidence for a functional role of endogenous noradrenaline and adrenaline was provided by Knudsen et al. (1996), who showed that their intracellular levels in circulating lymphocytes from healthy subjects were strongly correlated with both basal and isoprenaline-stimulated cAMP. More direct evidence came a few years later from studies in human PBMC, where stimulation with PHA induces the synthesis of catecholamines through induction of TH and its pharmacological inhibition with  $\alpha$ -methyl-*p*-tyrosine results in decreased activation-induced apoptosis (Cosentino et al. 2002a). Similar findings were subsequently obtained in rodent lymphocytes activated with concanavalin A (Jiang et al. 2007). In separate experiments, by use of a pharmacological approach, it was shown that the effects of pargyline-increased endogenous catecholamine levels on rodent lymphocyte apoptosis were mediated by cAMP–PKA- and PLC–PKC-linked CREB–Smac/DIABLO pathways coupled to  $\alpha_1$ - and  $\beta_2$ -ARs (Jiang et al. 2009).

## Relevance for immune-mediated disease

### Multiple sclerosis

Multiple sclerosis (MS) is an organ-specific autoimmune disorder characterized by inflammation, demyelination and axonal loss in the CNS (Noseworthy et al. 2000; Frohman et al. 2006). Several lines of evidence indicate that adrenergic pathways contribute to MS in immune system cells as well as in glial cells. Indeed, membrane expression of  $\beta_2$ -ARs in PBMC is upregulated in MS (Arnason et al. 1988; Karaszewski et al. 1990, 1993; Zoukos et al. 1992) possibly in relation to disease activity (Zoukos et al. 1994). Increased expression of  $\beta_2$ -ARs seems specific for CD8<sup>+</sup>CD28-T lymphocytes (Karaszewski et al. 1990, 1993). In circulating PBMC, gene expression of  $\beta_2$ -ARs (and of other G protein-coupled receptors like dopaminergic receptors D5) and responsiveness to the  $\beta$ -AR

agonist isoprenaline are on the contrary downregulated in untreated patients (suggesting the occurrence of receptor uncoupling) but restored in IFN- $\beta$ -treated subjects (Giorelli et al. 2004). Intracellular levels of catecholamines are also affected in lymphocytes of MS patients. Peripheral blood lymphocyte levels of adrenaline may be higher in first-attack MS whilst noradrenaline levels are lower during remissions (Rajda et al. 2002). In stimulated lymphocytes from MS patients, no difference was observed in noradrenaline or adrenaline levels in comparison to cells from healthy controls, however, cells from patients with chronic-progressive MS or relapsing-remitting MS in relapse produced less dopamine (Cosentino et al. 2002a). In view of the role of stimulation-induced increase of endogenous catecholamines in activation-induced apoptosis of lymphocytes (Cosentino et al. 2002a), this finding was tentatively linked to the occurrence of impaired apoptotic mechanisms, which in MS can contribute to survival of autoreactive cells (Pender 1998; Macchi et al. 1999; Comi et al. 2000; Sharief et al. 2002).

Additional evidence for the relevance of adrenergic (and dopaminergic) lymphocyte-related mechanisms come from the observation that *in vitro* IFN- $\beta$  increases lymphocyte production and release of catecholamines and, while IFN- $\gamma$  profoundly decreases catecholamines production as well as TH mRNA expression, and cocubation with both IFNs prevents the inhibitory effect of IFN- $\gamma$ , as well as the enhancing/releasing effect of IFN- $\beta$  (Cosentino et al. 2005), and in MS patients IFN- $\beta$  treatment enhances the ability of lymphocytes to produce CA, and restores the efficiency of  $\beta_2$ -AR- (and dopaminergic receptor-) operated pathways (Zaffaroni et al. 2008), which could result in reduced T-cell proliferation and IFN- $\gamma$  secretion (Giorelli et al. 2004).

With regard to glial cells, consistent evidence indicates that astrocytes of MS patients are deficient in  $\beta_2$ -AR, both in normal-appearing white matter as well as in chronic active and inactive plaques (De Keyser et al. 1999; Zeinstra et al. 2000), resulting in failure of  $\beta_2$ -AR-mediated suppression of class II major histocompatibility complex molecules and subsequent enhancement of antigen-presenting functions of these cells in MS (De Keyser et al. 2003). Astrocyte  $\beta_2$ -AR dysregulation, however, may contribute to MS pathogenesis and progression through several other mechanisms, including: deficient suppression of nitric oxide and proinflammatory cytokine production and glutamate uptake, deficient glycogenolysis and production of trophic factors (De Keyser et al. 2004) and reduced perfusion of normal-appearing white matter (De Keyser et al. 2008).

Astrocytes as therapeutic targets in MS were recently challenged in a proof of concept study in MS subjects by use of fluoxetine, which activates protein kinase (PK) A in



astrocytes. PKA is physiologically activated by  $\beta_2$ -AR-mediated cAMP increase and in turn suppresses coactivator class II transactivator (CIITA), which regulates major histocompatibility (MHC) class II molecule transcription (De Keyser et al. 2010). Direct activation of PKA could in principle bypass the functional deficiency of  $\beta_2$ -ARs in astrocytes, however, preliminary results need to be confirmed and extended in larger, randomized studies.

Indeed,  $\beta_2$ -ARs have been already regarded as a promising target in the pharmacotherapy of MS and in particular salbutamol has been proposed as add-on therapy in patients with MS (Makhlouf et al. 2002). In-depth understanding of the complex (dys)regulation of  $\beta_2$ -AR pathways in lymphocytes as well in the central nervous system in MS patients also in relation to treatment with immunomodulating agents could allow better exploitation of the potential benefits of drugs acting on  $\beta_2$ -ARs.

### Rheumatoid arthritis

Several studies over the last two decades reported decreased density and affinity of  $\beta_2$ -ARs on PBMC from rheumatoid arthritis (RA) patients, in particular on CD8<sup>+</sup> T lymphocytes and in CD19<sup>+</sup> B lymphocytes, showing negative correlation with disease activity (Baerwald et al. 1992, 1997; Wahle et al. 2001a) and serum IL-2R levels (Krause et al. 1992). Reduction of  $\beta_2$ -ARs may be even more pronounced in synovial fluid lymphocytes, with impairment of the suppressive effect of catecholamines on anti-CD3-induced lymphocyte proliferation (Baerwald et al. 1997, 1999). In RA patients with high disease activity, a shift to  $\alpha_1$ -AR-mediated catecholamine effects on PBMC reactivity could also be observed (Wahle et al. 1999). Indeed, noradrenaline and adrenaline fail to shift anti-CD3/anti-CD28-induced T-cell cytokine responses toward a Th2 profile and in particular CD8<sup>+</sup> T cells are responsible for the impaired adrenergic control of IFN- $\gamma$  production (Wahle et al. 2006). At least one study, however, found no changes in  $\beta_2$ -ARs on RA lymphocytes, while showing a significant decrease in G protein-coupled receptor kinase (GRK) activity, with reduced protein expression of GRK-2 and GRK-6, possibly as a result of increased cell exposure to proinflammatory cytokines. RA lymphocytes showed a significantly increased cAMP production and inhibition of TNF- $\alpha$  production after  $\beta_2$ -AR stimulation (Lombardi et al. 1999).

Evidence for dysregulated sympathoadrenergic modulation of the immune response is available also in juvenile RA (JRA), a subset of arthritis occurring in children, which may be transient or chronic. Patients with JRA have an altered function of the autonomic nervous system associated with increased central noradrenergic outflow and decreased  $\beta_2$ -AR response of leukocytes (Kuis et al. 1996). Exposure of

JRA patients (but not healthy controls) to a noradrenergic stressor results in enhanced LPS-induced IL-6 production by peripheral blood cells. In addition, PBMC of patients with JRA express mRNA encoding  $\alpha_1$ -ARs, predominantly of the  $\alpha_{1D}$ -AR subtype, which on the contrary are undetectable in cells from healthy subjects (Roupe van der Voort et al. 2000) and which mediate noradrenaline-induced production of the proinflammatory cytokine IL-6 (Heijnen et al. 1996).

Dysregulation of the sympathoadrenergic tuning of the immune response in RA occurs also at the local level, in synovial tissue, where sympathetic innervation is reduced while sensory innervation is increased (Miller et al. 2000). Local noradrenaline production is maintained by TH<sup>+</sup> cells, mainly synovial macrophages, in direct correlation with the degree of inflammation and with spontaneous secretion of IL-6, IL-8, and MMP-3 (Miller et al. 2002). In vitro, in human synoviocytes noradrenaline inhibits IL-8 and TNF production (Miller et al. 2002), as well as the production of the proinflammatory bactericidal alpha-defensins human neutrophil peptides 1-3 (HNP1-3) (Riepl et al. 2010), suggesting that the loss of sympathetic nerve fibers with low resting noradrenaline levels is crucial for the development of the inflammatory process, possibly through a shift from  $\beta$ -to- $\alpha$  adrenergic signaling ( $\beta$ -to- $\alpha$  adrenergic shift) (reviewed by Straub and Härle 2005). Noradrenaline secreted by TH<sup>+</sup> cells occurring in synovial tissue during RA would thus represent an antiinflammatory mechanism acting together with systemic secretion of cortisol to counteract local inflammation (Straub et al. 2002a), while on the contrary systemic infusion of adrenaline (e.g. during a typical stress reaction) may result in lowered endogenous cortisol production and consequently increased inflammation (Straub et al. 2002b). Increased catecholamine release induced after blockade of vesicular monoamine transporter 2 (VMAT2) results in strong reduction of TNF and amelioration of inflammation in an animal model of RA (Capellino et al. 2010). Local catecholamine-producing cells may thus represent a novel target for the pharmacotherapy of RA, possibly in the context of neuroimmunopharmacological strategies aimed at restoring the global autonomic balance (Koopman et al. 2011).

In summary, extensive experimental and clinical evidence support the occurrence of dysregulated immune system responses to the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system in RA, and targeting the neuroimmune network is increasingly regarded as an attractive therapeutic strategy (Baerwald et al. 2000; Wahle et al. 2002; Lorton et al. 2003; Straub et al. 2005).

### Cancer

In animal models, activation of the sympathoadrenergic system through either stressful events or direct stimulation

of  $\beta$ -ARs usually leads to compromised resistance to tumor development and metastasis (Stefanski and Ben-Eliyahu 1996; Shakhar and Ben-Eliyahu 1998). Enhancement of tumor progression is usually ascribed to  $\beta$ -AR-mediated decrease of NK activity (Shakhar and Ben-Eliyahu 1998; Ben-Eliyahu et al. 2000), although several lines of evidence suggest that noradrenaline and adrenaline may also directly affect tumor proliferation, angiogenesis, invasion, migration and metastasis (reviewed by Chakroborty et al. 2009; Li and Cho 2011). Impairment of NK activity and reduced antitumor resistance following stress and  $\beta$ -AR stimulation seem to be affected by age (Page and Ben-Eliyahu 2000) as well as by gender (Page et al. 2008). Recently, the prophylactic use of pharmacological blockade of  $\beta$ -ARs in association with type-C CpG oligodeoxynucleotides and COX inhibition has been proposed as a potential approach to limit postoperative immunosuppression and metastatic progression through enhancement of NK activity (Goldfarb et al. 2011).

AR modulation of immune response may be relevant also to cancer vaccine strategies. Indeed, Botta and Maestroni (2008) found that  $\beta_2$ -AR antagonism along with TLR2 activation at the site of intradermal cancer vaccination may either enhance the resulting antitumor response or be tolerogenic in dependence of the maturation state of the transferred DCs, suggesting that manipulation of  $\beta_2$ -ARs expressed in the site of DCs inoculation may influence the efficacy of the antitumor response.

Epidemiological studies support the hypothesis that exposure to  $\beta_2$ -AR antagonists (beta blockers) may indeed reduce cancer progression and mortality, e.g. in melanoma (De Giorgi et al. 2011) and in breast cancer (Powe et al. 2010; Barron et al. 2011), although conflicting results have also been reported (Shah et al. 2011). Larger epidemiological studies as well as well-designed randomised clinical trials are needed for several cancer types to establish the potential of AR manipulation as antitumor therapy.

A role for ARs has been proposed long time ago also in the proliferation of hematological malignancies. Very low  $\beta$ -AR density and loss of adenylate cyclase activity are well-characterized features of pathologic cells from acute and chronic lymphocytic leukemia (CLL) (Sheppard et al. 1977; Paietta and Schwarzmeier 1983). Impaired  $\beta$ -AR expression in circulating cells from patients with CLL was shown to be specific for  $\beta_2$ -ARs and to be associated with disease progression (Kamp et al. 1997). Whether activation of  $\beta$ -ARs may represent a therapeutic strategy in leukemias remains, however, to be established. Indeed, although accumulation of cAMP has been shown to increase the chemosensitivity of CLL cells, the proapoptotic effect of the long acting  $\beta_2$ -AR agonists salmeterol and formoterol in these cells has been shown to be independent from  $\beta_2$ -AR activation (Mamani-Matsuda et al. 2004). On the

other side, endogenous adrenaline together with prostaglandins has been recently shown to mediate the promoting effects of stress on leukemia progression at least in animal models through suppression of NK activity, thus providing the rationale to explore the therapeutic potential of  $\beta$ -AR blockers and COX inhibitors also in hematological malignancies (Inbar et al. 2011).

#### Other diseases

The density of  $\beta_2$ -ARs on circulating lymphocytes is decreased in several other chronic inflammatory and autoimmune diseases, including *Crohn's disease* (Krause et al. 1992), *systemic lupus erythematosus* (del Rey and Besedovsky 2008), and *myasthenia gravis* (Xu et al. 1998). In lymphocytes from *Alzheimer's disease* (AD) subjects, isoprenaline-induced cAMP increase may be reduced (Garlind et al. 1997) and GRK2 expression may be increased (Leosco et al. 2007), and  $\alpha_2$ -AR gene expression is altered (Kálmán et al. 2005). Lymphocytes of patients with *asthma* as well have reduced  $\beta$ -AR binding capacity (Hataoka et al. 1993), however, sympathoadrenergic modulation of immunity in asthma and allergy received so far limited attention, despite extensive evidence on the role of neuroimmune mechanisms in such conditions (Marshall 2004).

Reduced lymphocyte  $\beta$ -AR density has been reported in patients with *cardiac disease* such as: congestive ischemic disease and coronary artery bypass grafting (Chello et al. 1995) and chronic severe heart failure of various origins (Townend et al. 1993; Wu et al. 1996; Dzimir et al. 1995). Reduced  $\beta$ -AR on lymphocytes during cardiac disease results in impaired  $\beta$ -adrenergic control of lymphocyte activation (Werner et al. 2001), and should be addressed in the light of chronic low-intensity inflammation occurring in critical heart disease (see e.g. Barnes and Ackland 2010; Arslan et al. 2011).

Noradrenaline and adrenaline exert extensive effects on innate immunity which may be highly relevant for *bacterial infections and sepsis* (reviewed by Flierl et al. 2008). The therapeutic potential of  $\alpha_2$ -AR antagonism or pharmacological inhibition of catecholamine synthesis in rodent models of acute lung injury, as well as the beneficial effects of the  $\beta$ -AR antagonist propranolol in reducing the risk of opportunistic infections in severely burned patients have been already discussed (see previous section). *Viral infections* (e.g., herpes simplex virus type-1, cytomegalovirus and varicella zoster virus) can be promoted by stressful life events through activation of the sympathetic nervous system (Prösch et al. 2000). Noradrenaline may also accelerate human immunodeficiency virus (HIV) replication in infected lymphocytes via  $\beta$ -ARs (Cole et al. 1998), while in the central nervous system, HIV coat

protein gp120 may disrupt  $\beta$ -AR-mediated regulation of astrocytes and microglia eventually promoting neuroinflammation (Levi et al. 1993).

Finally, decreased  $\beta$ -ARs on circulating lymphocytes have been reported in subjects with psychic disturbances, including *depression* (reviewed by Werstiuk et al. 1990), *panic disorder* (Brown et al. 1988), and even in normal subjects with *increased tension and anxiety* traits (Yu et al. 1999). The significance of these findings should be, however, assessed in the context of dysregulated immunity occurring in depression (reviewed by Blume et al. 2011).

## Concluding remarks

Sympathoadrenergic mechanisms represent the main channel of communication between the nervous system and the immune system, however, much remains to be elucidated before AR-mediated pathways can be fully exploited as pharmacotherapeutic targets. Open issues include: (1) the existence of multiple subtypes of ARs which are expressed on immune cells with specific patterns in each cell subset, where each of them is involved in the control of well-defined functions; (2) receptor dysregulations occurring in disease states is not only specific for the receptor type but also for the cell subset(s); (3) receptors may be acted upon not only by exogenous but also by endogenous catecholamines directly produced by immune cells; (4) dynamic changes occur to receptor expression and responsiveness (and to endogenous catecholamine production) during treatment with immunomodulatory drugs. A wide array of sympathoadrenergic agents is currently used for various indications with a usually favorable therapeutic index, and represent therefore an attractive source of potentially novel immunomodulating agents with significant therapeutic potential.

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

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