

# Nerve Driven Immunity: Noradrenaline and Adrenaline

# 2

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## 2.1 Noradrenaline and Adrenaline as Classical Neurotransmitters and Neurohormones

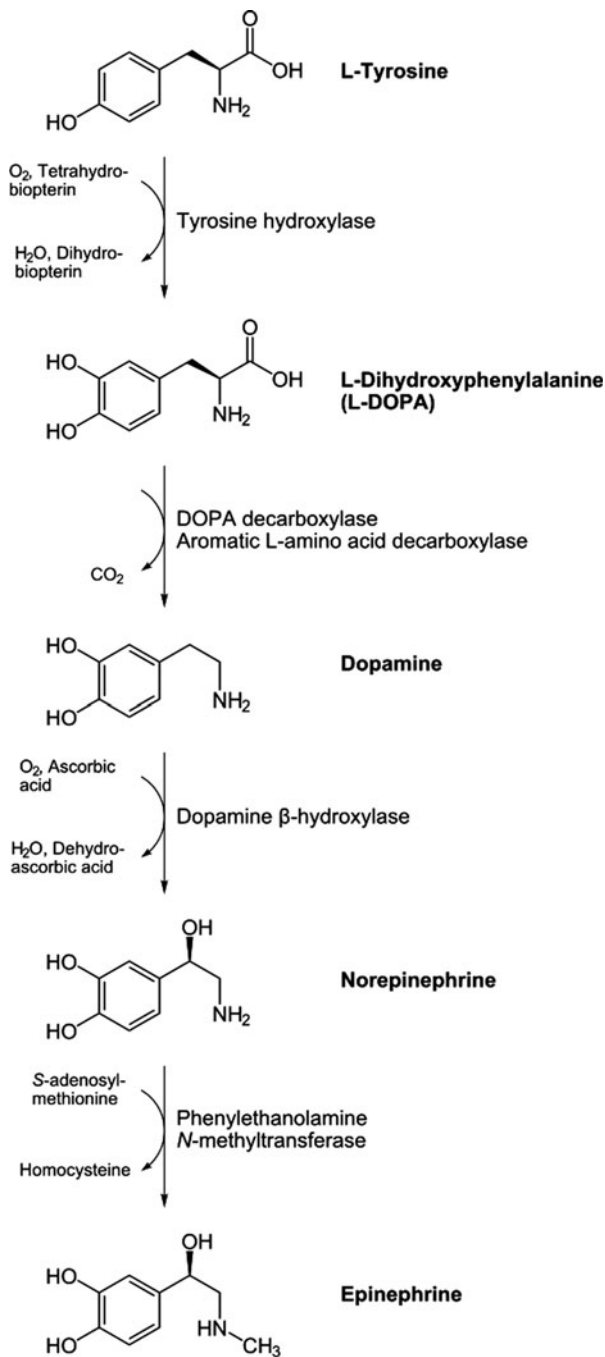
Noradrenaline and adrenaline belong to catecholamines, a family of chemical compounds containing a catechol or 3,4-dihydroxyphenyl group and an amine function. Together with dopamine, they are the most abundant and important catecholamines in the human body and are all produced from tyrosine, a non-essential amino acid which is both obtained from dietary proteins or in turn synthesized from the essential amino acid phenylalanine by the enzyme phenylalanine hydroxylase. Noradrenaline is synthesized from dopamine by dopamine  $\beta$ -hydroxylase and is converted to adrenaline by phenylethanolamine *N*-methyltransferase (Fig. 2.1). The natural stereoisomers are L-(-)-(R)-noradrenaline and adrenaline.

Adrenaline was the first hormone to be isolated in a pure state. After Georg Oliver's empirical observation in 1893 of the effect of an extract of sheep's adrenal gland on human blood vessels, John Abel obtained the impure form of the active principle in 1897 and named it as "epinephrine" (from the Greek roots *epi* and *nephros*, i.e. "on the kidney"), but it was Jokichi Takamine in 1900 the first to isolate adrenaline as pure crystalline base. He immediately patented the process for isolating the hormone, which was then marketed under the proprietary name of Adrenalin<sup>®</sup> ("near the kidney", from Latin roots *ad* and *renes*). Noradrenaline was synthesized a few years later (the prefix "nor" is the acronym of *nitrogen ohne radikal*, indicating the absence of a methyl group), but it was only in 1949 that this molecule was proved by Ulf von Euler in Stockholm to be the main sympathomimetic neurotransmitter in humans (Sneader 2005).

Adrenaline (and, as a consequence, noradrenaline) was introduced as the British Approved Names (BAN) in the United Kingdom and British Commonwealth, while in the US epinephrine (and norepinephrine) was adopted as the United States Approved Name (USAN). Epinephrine and norepinephrine later became also the World Health Organization Recommended International Nonproprietary Names (rINN) for these compounds. Although the use of rINN is now mandatory in the European Union, adrenaline and noradrenaline represent the sole exception to the rule and retain their BAN on grounds of safety (Sneader 2005).

Noradrenaline and, to a lesser extent, adrenaline act as neurotransmitters in the central and peripheral nervous systems. Chromaffin cells in medulla of adrenal glands also produce adrenaline (~80% in humans) and noradrenaline (~20%), which are directly released into the blood upon stimulation by the sympathetic nervous system through preganglionic fibers originating in the thoracic spinal cord. In the central nervous system, the *locus coeruleus* (LC) is the most important noradrenergic nucleus, its axons projecting rostrally to hippocampus, septum, hypothalamus and thalamus, cortex and amygdala, dorsally to cerebellum, and caudally to spinal cord. Noradrenaline in LC neurons plays an important role in attention, arousal and vigilance to salient and relevant external stimuli, and regulates hunger and feeding behavior exerting a stimulatory effect on feeding possibly acting directly on the hypothalamus. Adrenaline-containing neurons in the central nervous system are mainly localized in the medullary reticular formation and their axons project both rostrally and caudally, possibly participating in the

**Fig. 2.1** Biosynthesis of the catecholamines adrenaline (epinephrine) and noradrenaline (norepinephrine). The synthesizing enzymes are shown to the *right* of each arrow, while enzyme cofactors are shown to the *left* (reproduced from the Wikimedia Commons – <http://commons.wikimedia.org>)



coordination of eating and in visceral activities such as blood pressure regulation. In the peripheral nervous system, noradrenaline is the principal transmitter of most autonomic sympathetic postganglionic fibers. Main peripheral actions of noradrenaline and adrenaline include: contraction of certain types of smooth muscle (blood vessels supplying skin, kidney, and mucous membranes), stimulation of exocrine glands (e.g. salivary and sweat glands), relaxation of certain other types of smooth muscle (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), endocrine actions (e.g. modulation of the secretion of insulin and renin). An extensive discussion of noradrenaline and adrenaline neurochemistry, anatomy and physiology can be found in Feldman et al. (1997).

### 2.1.1 Adrenoceptors

Noradrenaline and adrenaline exert their effects by acting on 7-transmembrane, G-protein coupled receptors called “adrenergic receptors” or “adrenoceptors” (ARs). ARs are expressed in virtually all peripheral tissues and within the central nervous system and are 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. 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.

ARs were first divided into  $\alpha$  and  $\beta$ , based on the rank order of potency of selected agonists, and subsequently, both the  $\alpha$  and  $\beta$  types were further divided into  $\alpha_1$ ,  $\alpha_2$ ,  $\beta_1$  and  $\beta_2$  subtypes (Bylund et al. 1994). Current classification is based on both pharmacological and molecular evidence and includes three major types –  $\alpha_1$ ,  $\alpha_2$  and  $\beta$  – each further divided into three subtypes. 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, in particular in the vasculature, and usually mediate contraction, while  $\beta$ -ARs can be found in heart ( $\beta_1$  and to a minor extent  $\beta_2$ , which mediate contraction), in smooth muscle cells (mainly  $\beta_2$ , inducing relaxation), and in skeletal muscle ( $\beta_2$ , possibly inducing hypertrophy). Indeed,  $\beta_2$ -ARs are expressed in virtually all normal human cell types. Usually,  $\alpha_1$ - and  $\beta_1$ -ARs are located in the immediate proximity of sympathoadrenergic terminals and are therefore the main target of noradrenaline released upon nerve stimulation. On the contrary,  $\alpha_2$ - and  $\beta_2$ -ARs may be located far from nerve terminals (extrajunctional receptors) and may represent the preferential target of circulating noradrenaline and adrenaline. ARs are also widely distributed in the brain. AR physiology and pharmacology is summarized in Table 2.1, while detailed and continuously updated information is provided in Bylund et al. (2011).

**Table 2.1** Classification, nomenclature, molecular and cellular physiopharmacology of adrenoceptors (based on Bylund et.al. 2011)

Name	Previous and unofficial names	Agonists <sup>a</sup> (affinity) <sup>b</sup>	Antagonists <sup>a</sup> (affinity) <sup>b</sup>	Transduction mechanisms (effectors)	Tissue distribution	Physiological functions
$\alpha_{1A}$	$\alpha_{1a}$	(-)-Adrenaline (6.3)	Tamsulosin (10.0–10.4)	$G_q/G_{11}$ (phospholipase C stimulation, calcium channel)	Human heart, liver, cerebellum, cerebral cortex, predominant subtype in human prostate and urethra	Contraction of urethral smooth muscle, contraction of skeletal muscle resistance arteries
	$\alpha_{1c}$	Noradrenaline (5.8–6.0)	Silodosin (10.4)			
	Adrenergic receptor	Oxymetazoline (8.0–8.2)	Prazosin <sup>c</sup> (9.5)	Phospholipase D stimulation		
		Phenylephrine (5.2–5.4)		Protein kinase C		
		Methoxamine (5.0–5.2)				
$\alpha_{1B}$	$\alpha_{1b}$	(-)-Adrenaline (6.5)	Prazosin <sup>c</sup> (9.6–9.9)	Mitogen activated protein kinases	Human spleen and kidney, human somatic arteries and veins	Contraction of arteries and veins
		(-)-Noradrenaline (6.2)	Tamsulosin (9.5)			
		Oxymetazoline (6.5)				
		Phenylephrine (pIC <sub>50</sub> : 6.3–7.5)				
		Methoxamine (4.0)				
$\alpha_{1D}$	$\alpha_{1a/d}$	(-)-Noradrenaline (7.4)	Tamsulosin (9.8–10.1)		Human aorta, blood vessels of human prostate, human bladder	Constriction of arteries, urethral contraction, contraction of corpus cavernosum
	$\alpha_{1A}$					
	Adrenergic receptor	(-)-Adrenaline (7.2)	Prazosin <sup>c</sup> (9.5–10.2)			
		Oxymetazoline (6.1–6.4)				
		Xylometazoline (6.0)				
		Phenylephrine (5.9)				

(continued)

Table 2.1 (continued)

Name	Previous and unofficial names	Agonists <sup>a</sup> (affinity) <sup>b</sup>	Antagonists <sup>a</sup> (affinity) <sup>b</sup>	Transduction mechanisms (effectors)	Tissue distribution	Physiological functions
$\alpha_{2A}$	RG20	(±)-Adrenaline (5.6–8.3)	Lisuride (10.3)	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
		Noradrenaline (5.6–8.4)	Phentolamine (8.4)			
		Oxymetazoline <sup>d</sup> (8.0)				
		Guanfacine <sup>d</sup> (7.3)				
		Clonidine <sup>d</sup> (7.2–9.2)				
$\alpha_{2B}$	RNG	Noradrenaline <sup>d</sup> (5.6–9.1)	Lisuride (9.9)	G <sub>s</sub> (adenylate cyclase stimulation)	Human kidney >> liver > brain = lung = heart = skeletal muscle (also reported in aorta and spleen)	Vasoconstriction
		(±)-Adrenaline <sup>d</sup> (5.2–6.2)	Phentolamine (8.2)			
		Clonidine <sup>d</sup> (6.7–9.5)	Yohimbine (7.9–8.9)			
		Guanfacine (5.8–6.5)				
		Oxymetazoline (5.5–6.2)				
		Noradrenaline (5.9–8.7)	Lisuride (9.9)			
		(±)-Adrenaline (5.8–6.2)	Rauwolscine (9.1)			
$\alpha_{2C}$	$\alpha_2$ -C4	Oxymetazoline <sup>d</sup> (6.7)	Yohimbine (8.5–9.5)		Human brain ≥ kidney (also reported in spleen, aorta, heart, liver, lung, skeletal muscle)	Presynaptic inhibition of noradrenaline release
		Clonidine <sup>d</sup> (6.0–7.8)				
		Brimonidine <sup>d</sup> (5.7–7.6)				

$\beta_1$	( $\pm$ )-Adrenaline (6.0)	Carvedilol (9.5) Betaxolol (8.8)	$G_s$ (adenylate 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			
	Noradrenaline (6.0)	(-)- Propranolol (8.2–8.9)						
	Isoprenaline (6.6–7.0)							
	Denopamine <sup>d</sup> (5.8)							
	Dobutamine <sup>d</sup> (5.5)							
$\beta_2$	( $\pm$ )-Adrenaline (6.2)	Timolol (9.7) Carvedilol (9.4–9.9)	$G_i/G_o$ (guanylate cyclase stimulation)	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			
	Noradrenaline (5.4)							
	Salmeterol (8.8)	Propranolol (9.1–9.5)						
	Isoprenaline (6.4)							
	Dobutamine <sup>d</sup> (6.2)							
	$\beta_3$	Atypical $\beta$ adrenoceptor				Carvedilol (9.4)	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
		( $\pm$ )-Adrenaline (3.9–4.7)				Propranolol (6.3–7.2)		
		BRL 37344 (6.4–7.0)				Nadolol (6.3)		
		Isoprenaline (5.1–6.2)						
		SR58611A (5.2)						

<sup>a</sup> Besides adrenaline and noradrenaline, representative agonists and antagonists were selected on the basis of higher affinity, with preference for drugs approved for therapeutic use. For investigational agents as well as for comparative affinity profiles see Bylund et al. (2011).

<sup>b</sup> Unless otherwise specified, affinity (i.e., a measure of how strongly the ligand binds to the receptor) is expressed in terms of pK, that is the negative logarithm to base 10 of the equilibrium dissociation constant, K in molar concentration units (Neubig et al. 2003).

<sup>c</sup> Inverse agonist.

<sup>d</sup> Partial agonist.

### 2.1.2 Sympathoadrenergic Innervation of Lymphoid Organs

Both primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid organs are innervated by autonomic efferent nerve fibers which are mainly sympathoadrenergic. Indeed, the sympathetic nervous system represents, together with the hypothalamic-pituitary-adrenal axis, the major pathway involved in the cross-talk between the brain and the immune system (reviewed in Elenkov et al. 2000). ARs expressed on immune cells are usually located far from noradrenergic varicosities of sympathetic nerves, thus representing a prominent example of extrajunctional receptors and possibly also of volume transmission mode of intercellular communication (Agnati et al. 2010). Several excellent reviews addressed over the years the origin, pattern of distribution and targets of sympathetic nerves in lymphoid organs, their neurochemical signaling (Felten et al. 1985; Felten and Felten 1988; Felten 1991; Straub 2004), as well as the functional and clinical significance of age-induced changes in sympathetic-immune interactions (Bellinger et al. 1992; Madden et al. 1995, 1997, 1998; Friedman and Irwin 1997) and the consequences of dysregulated sympathetic nervous system in stress responses (Irwin 1994; Nagatomi et al. 2000; Marshall and Agarwal 2000; Sloan et al. 2008) and in the development and progression of immune-mediated diseases (Bellinger et al. 1992, 2008; Madden et al. 1995; Friedman and Irwin 1997; Marshall and Agarwal 2000; Frohman et al. 2001; Wrona 2006; Straub et al. 2006; del Rey and Besedovsky 2008; Benarroch 2009).

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## 2.2 Expression of ARs and Effects of Noradrenaline and Adrenaline on Immune Cells

In the study of nervous system-immune system interactions, sympathoadrenergic pathways received extensive attention and, as a result, a huge amount of literature is available regarding the occurrence and the functional relevance of ARs on immune cells, which have been the subject of several excellent reviews (e.g. Kohm and Sanders 2000, 2001; Elenkov et al. 2000; Kin and Sanders 2006; Nance and Sanders 2007; Flierl et al. 2008). Among ARs,  $\beta_2$ -ARs are usually the most expressed on immune cells and they have been consequently regarded as the main receptors mediating the immune effects of noradrenaline and adrenaline. It was only over the last two decades that evidence began to increase regarding the occurrence of other ARs, in particular the  $\alpha_1$ -AR subtype (reviewed by Kavelaars 2002). Also thanks to novel molecular techniques allowing the sorting of highly purified cell subsets, it is becoming increasingly evident that different immune cell populations express distinct patterns of ARs, which in turn undergo up/downregulation upon cell maturation, activation, etc. In summarizing current knowledge regarding ARs on immune cells, attention will be devoted mainly to studies addressing specific cell types (and not, e.g. peripheral blood mononuclear cell preparations). In addition, also in view of the large amount of available literature, results obtained in human



samples will be preferentially considered. Finally, here it will be only mentioned the issue of sympathoadrenergic control of thymic function, which has been recently reviewed (Leposavić et al. 2008).

## 2.2.1 T and B Lymphocytes

### 2.2.1.1 AR Expression

Although in initial studies using radioligand binding techniques the density of  $\beta$ -ARs was reported as apparently similar on human T and B lymphocytes (Pochet et al. 1979; Bishopric et al. 1980), subsequently it was shown that T cells exhibited a lower number of binding sites than B cells (Bidart et al. 1983; Paietta and Schwarzmeier 1983), with T helper and T suppressor cells showing similar binding capacities (Landmann et al. 1984). Another study however showed the following rank order of  $\beta$ -AR (likely  $\beta_2$ -AR) density: T suppressor > T cytolytic > T helper (Khan et al. 1986). These findings were confirmed by another study showing that B lymphocytes had the greatest number of  $\beta$ -ARs with  $12.1 \pm 1.8$  fmol/ $10^6$  cells, followed by CD8+ T lymphocytes with  $3.4 \pm 0.4$  fmol/ $10^6$  and CD4+ T lymphocytes with  $1.2 \pm 0.1$  fmol/ $10^6$  cells (Karaszewski et al. 1990). In another study, the same authors reported  $2.8 \pm 0.3$  fmol/ $10^6$  cells in CD8+CD28- (suppressor) T cells versus  $1.4 \pm 0.4$  fmol/ $10^6$  cells in CD8+CD28+ (cytotoxic) T cells (Karaszewski et al. 1991).

The density of  $\beta$ -ARs on human lymphocytes is possibly subject to rapid changes. In a longitudinal study in ten healthy subjects, the absolute values of circulating CD4+ and CD8+ T lymphocyte frequency showed little variation,  $\beta$ -AR density variance was greater on both cell subsets (Anstead et al. 1998). Interestingly, it was reported that 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). Another factor affecting  $\beta$ -AR density is the level of cell activation. Cultivation of human peripheral blood T-lymphocytes in the presence of interleukin-2 (IL-2) and phytohemagglutinin (PHA) increases  $\beta_2$ -AR expression (Korichneva and Tkachuk 1990), as well as isoprenaline-induced cAMP production, possibly by a calcium-independent mechanism (Carlson et al. 1994). PHA stimulation has been reported to prevent both sequestration of  $\beta$ -ARs and their dissociation from  $G_s$  proteins in response to isoprenaline stimulation (but not the functional uncoupling from adenylyl cyclase) (Carlson et al. 1994). In human CD4+ and CD8+ T lymphocytes, exposure to IL-1 $\beta$  has no effect on  $\beta_2$ -AR expression, however incubation with IL-2 up-regulated  $\beta_2$ -ARs on CD8+ cells (Wahle et al. 2001).

No evidence is currently available regarding the expression of  $\beta_1$ - or  $\beta_3$ -ARs in human lymphocytes with the only notable exception of the occurrence of  $\beta_1$ -AR mRNA (together with  $\beta_2$ - but not  $\beta_3$ -AR mRNA) in human CD4+CD25+ T regulatory cells (Cosentino et al. 2007), however their membrane expression as well as their possible functional relevance has never been investigated so far. Expression of  $\beta_1$ -ARs in CD4+CD25+ T cells was recently confirmed and it was

tentatively proposed that they may mediate the effects of stress on this specific cell subset (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, but no correlation found with specific functional responses (Borger et al. 1998).

As regards  $\alpha$ -ARs, only a few evidence exists regarding human T and B lymphocytes. Ligand binding studies suggest the occurrence of  $\alpha_2$ -ARs in human CD4+ and CD8+ T lymphocytes, as well as their upregulation after in vivo administration of adrenaline (Jetschmann et al. 1997). On the contrary, no direct evidence exists regarding the expression of  $\alpha_1$ -ARs in T and B lymphocytes in humans. However, it was shown that  $\alpha_1$ -ARs can be induced in peripheral blood mononuclear cells stimulated with the T lymphocyte-preferring mitogen PHA, suggesting that their expression may occur at least on activated T cells (Roupe van der Voort et al. 2000).

### 2.2.1.2 Functional Responses to AR Activation

Stimulation of  $\beta$ -ARs has been reported to down-regulate IL-2 receptors in both mitogen-stimulated lymphocytes and IL-2-dependent T lymphocyte cell lines (Feldman et al. 1987). In agreement with these observations, it was shown that treatment of human subjects with the  $\beta$ -AR antagonist propranolol increased spontaneous and PHA-induced IL-2R expression as well as IL-2 generation in circulating lymphocytes (Malec et al. 1990), although the actual involvement of  $\beta$ -ARs in this effect of propranolol has been subsequently questioned (Mangge et al. 1993). The  $\beta$ -AR isoprenaline inhibits the anti-CD3 mAb-induced proliferation of T cells, without synergistic effects with dexamethasone. Isoprenaline-induced inhibition is however nearly completely overcome by the addition of anti-CD28 mAb to anti-CD3 mAb-stimulated T cells (Elliott et al. 1992). The inhibitory effect of isoprenaline on anti-CD3 mAb-induced proliferative response of T cells affects also their CD4+, CD8+, or CD45RO+ subsets, as well as anti-CD3 mAb-induced IL-2 production, although to a lower extent than PGE2 (Bartik et al. 1993). Such difference may be explained on the basis of differential activation of cAMP-induced PKA I and II isozymes (Bauman et al. 1994). In contrast to freshly isolated T cells however,  $\beta_2$ -AR-inhibition of Th1 (IFN- $\gamma$ ) and Th2 (IL-4, IL-5) cytokine production and induction of CREB phosphorylation is reduced in polarized T helper cells, possibly as the result of a generalized loss of the negative feedback by receptors coupled to the AC/cAMP system (Heijink et al. 2003). In CD8+ human T lymphocytes activation of  $\beta$ -ARs has been shown to decrease the peak current amplitude and to increase the rate of inactivation of the delayed rectifier  $K^+$  current. Since inhibition of the delayed rectifier  $K^+$  current has been found to decrease the proliferative response in T lymphocytes,  $\beta$ -AR-induced modulation of  $K^+$  current may well serve as a feedback control mechanism limiting the extent of cellular proliferation (Soliven and Nelson 1990). Concanavalin A (Con A)-induced production of IFN- $\gamma$ , GM-CSF, and IL-3 (but not IL-4) by human T lymphocytes is inhibited by activation of  $\beta_2$ -ARs (but not of  $\beta_1$ - or  $\beta_3$ -ARs, although at least  $\beta_3$ -AR mRNA was detectable in Con A-activated cells) (Borger et al. 1998).

Although activation of  $\beta$ -ARs on human lymphocytes is usually believed to result in antiinflammatory effects, evidence exists that immunostimulatory effects may occur depending on the time of exposure and degree of cell differentiation and activation. Indeed, expression of  $\beta_2$ -ARs occurs on resting and activated B cells, naive CD4+ T cells, T helper 1 (Th1)-cell clones and newly generated Th1 cells, but not in Th2-cell clones and newly generated Th2 cells (Sanders et al. 1997; Kohm and Sanders 1999). In agreement with such observations, noradrenaline may promote IL-12-mediated differentiation of naive CD4+ T cells into Th1 effector cells, and increase the amount of IFN- $\gamma$  produced by Th1 cells (Swanson et al. 2001), but has no apparent effect on IL-4-mediated differentiation of Th2 cells (Sanders et al. 1997). The effect of noradrenaline seems to depend on the state of cell activation even in B lymphocytes, which produce more IgG1 and IgE when noradrenaline is added either during antigen processing or within the first 12 h of culture with Th2 cells (Kasproicz et al. 2000), while in plasma cells noradrenaline decreases antibody production (Melmon et al. 1974).

### 2.2.2 Natural Killer Cells

Several lines of evidence indicate that Natural Killer (NK) cells express high levels of  $\beta$ -AR. Maisel et al. (1990), studying  $\beta$ -AR expression and cAMP production in lymphocyte subsets sorted by positive selection with specific monoclonal antibodies, found the highest number of receptors ( $1,934 \pm 122$  sites/cell) in CD16+CD56+ NK cells, which after physical exercise increased (to  $2,617 \pm 289$  sites/cell) together with isoprenaline-stimulated cAMP accumulation.

Both noradrenaline and adrenaline decrease NK cell cytotoxicity, pharmacological evidence suggesting the involvement of  $\beta$ -AR (likely  $\beta_2$ -AR) pathways (Whalen and Bankhurst 1990; Takamoto et al. 1991), however adrenaline resulted in stimulation of NK cell cytotoxicity at lower (submicromolar-picomolar) concentrations (Hellstrand et al. 1985). In vitro,  $\beta_2$ -AR activation on NK cells also results in reduction of cell adhesion to endothelial cells (Benschop et al. 1994, 1997). The in vivo relevance of this effect is confirmed by the observation that in human subjects both adrenaline and noradrenaline modulate the migratory capacity of human NK cells via spleen-independent  $\beta_2$ -AR mechanism (Schedlowski et al. 1996; Benschop et al. 1997).

Human NK cells express also  $\alpha$ -ARs. In CD16+ 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  $\beta_2$ - and  $\alpha_1$ -AR numbers on NK cells. Expression of  $\alpha_2$ -ARs as well was decreased by adrenaline infusion on NK cells, but increased in CD4+ and CD8+ T lymphocytes (Jetschmann et al. 1997). No evidence exists so far however regarding the functional relevance of  $\alpha$ -AR pathways in human NK cells.

### 2.2.3 Monocytes/Macrophages

Extensive evidence support the occurrence of  $\beta$ -AR on human monocytes/macrophages:  $\beta_2$ -ARs are usually regarded as mainly antiinflammatory, while recent evidence suggest under certain circumstances the occurrence of  $\beta$ -AR (possibly  $\beta_1$ -AR)-mediated proinflammatory responses (Grisanti et al. 2010). Alpha-ARs can also occur upon appropriate stimulation and their functional role is presently a matter of active investigation.

The expression of  $\beta$ -ARs on human monocytes was initially documented by means of classical binding experiments, which showed that  $\beta$ -AR density on human circulating monocytes was about 2,400 binding sites/cell and increased to 3,220 binding sites/cell after physical exercise (Ratge et al. 1988). Recently however, by means of flow cytometry, it was shown that  $\beta_2$ -AR expression on monocytes was elevated in anticipation of an acute bout of resistance exercise and decreased during the exercise (Fragala et al. 2011). Expression of  $\beta$ -ARs on human macrophages is regulated upon activation in a stimulus-dependent manner, suggesting that changes in receptor number can be regulated with different states of cell maturation and function (Radojcic et al. 1991). Indeed, during the maturation of human monocytes to macrophages in vitro, despite a functional adenylyl cyclase system,  $\beta$ -AR responsiveness is lost (Baker and Fuller 1995). In particular, it was recently shown that as human monocytes adhere to surfaces to begin differentiation into macrophages, they selectively lose their surface  $\beta_2$ -ARs and hence become insensitive to the inhibitory effects of  $\beta_2$ -AR agonists on LPS-induced TNF- $\alpha$  production, and this has been as a possible explanation to the lack of significant anti-inflammatory effect of  $\beta_2$ -AR agonists on alveolar macrophages or in clinical asthma (Ezeamuzie et al. 2011). On the other side,  $\beta_2$ -AR agonists like terbutaline, salmeterol and formoterol have been shown to inhibit to a variable extent the release of inflammatory mediators such as LTB<sub>4</sub>, PGE<sub>2</sub> and IL-1 $\beta$  from human monocytes possibly through  $\beta$ -AR-independent mechanisms (Linden 1992). Prolonged  $\beta_2$ -AR stimulation up-regulates cAMP phosphodiesterase activity in human monocytes (Manning et al. 1996), thus leading to receptor desensitization. In U937 cells, which are commonly used as a model of human monocytes,  $\beta_2$ -ARs are the main subtype of  $\beta$ -ARs expressed and their expression is lower on undifferentiated (monocytes) than in PMA-differentiated U937 (macrophages), and care should be therefore exerted when using these cells to study the physiopharmacology of  $\beta$ -ARs in human monocytes (Izeboud et al. 1999).

Noradrenaline and adrenaline acting on human monocytes through  $\beta$ -ARs (possibly,  $\beta_2$ -ARs) have been usually regarded as anti-inflammatory. Pharmacological evidence suggests that  $\beta$ -ARs activation may inhibit the production of oxygen radicals (Schopf and Lemmel 1983), upregulate TNF receptors and inhibit TNF (Guirao et al. 1997), reduce the phagocytosis of *C. albicans* (Borda et al. 1998), inhibit 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). In particular, selective activation of  $\beta_2$ -ARs may inhibit the production of TNF- $\alpha$  and of IL-6 and increase

the production of IL-10 in PMA-differentiated U937 human macrophages (Izeboud et al. 1999), and 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, suggesting that the stimulation of  $\beta_2$ -ARs might be beneficial in the treatment of sepsis through inhibiting LPS-elicited IL-18 (Mizuno et al. 2005). On the other side, reversal of the inhibitory effects of noradrenaline and adrenaline on human monocytes may result in immunostimulation. In agreement with this hypothesis, recently the  $\beta_2$ -AR antagonist propranolol has been shown to reduce circulating immunosuppressive M2b monocytes in severely burned children, suggesting that the increased susceptibility of severely burned patients to opportunistic pathogens might be controlled by propranolol (Kobayashi et al. 2011).

Evidence exists however that, under certain conditions,  $\beta$ -AR stimulation may lead to proinflammatory responses. Indeed,  $\beta_2$ -AR activation in unstimulated monocytes may increase the production of IL-18, although it had no effect on IL-12, TNF- $\alpha$ , IFN- $\gamma$  and IL-10, possibly due to  $\beta_2$ -AR-induced inhibition of IL-18-elicited upregulation of both CD40 and CD40 ligand (CD40L/CD154) expressions (Takahashi et al. 2004). Moreover, in human monocytes stimulated with either LPS or IL-1, treatment with  $\beta_2$ -AR agonists was shown to increase the production not only of the antiinflammatory cytokine IL-10 but also of the proinflammatory 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-regulated MMP-1 and potentiated LPS-induced expression of MMP-1 in peripheral blood monocytes and monocyte-derived macrophages (Speidl et al. 2004). Activation of  $\beta_2$ -ARs may also result in upregulated IL-4-induced CD23 (low affinity IgE receptor/Fc epsilon RII) expression in human monocytes (Mencia-Huerta et al. 1991), resulting in potentiated IgE/anti-IgE-induced production of IL-6 (Paul-Eugene et al. 1992, 1994), IgE (Paul-Eugene et al. 1993) as well as generation of superoxide anion and of nitric oxide, and of TxB2 (Paul-Eugène et al. 1994). 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).

Although pharmacological evidence suggesting the possible occurrence of functional  $\alpha$ -ARs in human monocytes enhancing the synthesis of complement components (Lappin and Whaley 1982), direct evidence for their existence was provided only recently. In particular, in human monocytes expression of  $\alpha_{1B}$ - and  $\alpha_{1D}$ -AR mRNA could be obtained by culturing human circulating monocytes with dexamethasone or the  $\beta_2$ -AR agonist terbutaline (Roupe van der Voort et al. 1999) or with LPS, resulting in the activation of ERK-2 (Roupe van der Voort et al.

2000b). Alpha-ARs are also expressed in the human THP-1 monocytic cell line, where  $\alpha_{1B}$ - 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).

Fragmentary evidence is available regarding the functional relevance of  $\alpha$ -AR in human monocytes. In a recent study, by means of radioligand binding techniques a homogenous  $\alpha_{1B}$ -AR subtype population was characterized on monocytes, which changed to a heterogeneous receptor subtype expression pattern when differentiated to macrophages. 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). It should be also mentioned that in human whole blood incubated with PHA and LPS, noradrenaline and the  $\alpha_2$ -AR agonist clonidine reduced the production of TNF- $\alpha$ , while the  $\alpha_2$ -AR antagonist yohimbine inhibited the production of IL-1RA (Maes et al. 2000). Pharmacological evidence however is not convincing and no data were provided regarding the actual expression of functional  $\alpha_2$ -ARs on these cells.

### 2.2.4 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 DCs-T cells interactions thus contributing to the shaping of the appropriate adaptive immune response (reviewed by Maestroni (2005, 2006)). Murine DCs express both  $\alpha_1$ - and  $\beta_2$ -ARs, which play opposite roles in the modulation of cell migration, the former being stimulatory while the latter being inhibitory. Exposure of both skin and bone marrow-derived DCs to noradrenaline after stimulation with bacterial toll-like receptor (TLR) agonists results in decreased IL-12 and increased IL-10 production and, as a consequence, impaired T helper-1 (Th1) priming. On the other side, reduced noradrenaline activity in the skin may contribute to contact sensitizers-induced Th1 responses (Maestroni 2004). Noradrenaline has also been shown to activate  $\beta_2$ -AR-mediated cAMP-PKA pathways to enhance DC production of IL-33, resulting in direct Th2 differentiation and possibly contributing to the stress-related progression of Th2-associated disorders (Yanagawa et al. 2011). Interestingly, however, it has been shown that sympathoadrenergic modulation of the skin innate and adaptive immune response occurring after stimulation with TLR-2 but not TLR-4 agonists may promote a Th1 adaptive response possibly relevant to Th1-sustained autoimmune inflammatory skin diseases (Manni and Maestroni 2008). In agreement with these findings, it has been recently reported that  $\beta_2$ -AR agonists like salbutamol bias DCs preexposed to TLR-2 and nucleotide-binding oligomerization domain (NOD) 2 agonists towards increasing the Th17/Th1 cell ratio finally resulting in an IL-17 immune response, which may be relevant to the defense against extracellular bacteria, the pathogenesis of inflammatory diseases as well as the antitumor response (Manni et al. 2011). Recently,

pharmacological evidence was also provided for the occurrence on murine DCs of  $\alpha_2$ -ARs, which may mediate enhancement of antigen capture, possibly contributing to explain immune enhancement following acute stress (Yanagawa et al. 2010).

The extensive knowledge about sympathoadrenergic regulation of murine DCs and its potential relevance to an array of disease conditions is in sharp contrast with the very few information available regarding human DCs. It has been reported that in human dendritic cells stimulated via CD40 activation of  $\beta_2$ -ARs increases intracellular cAMP and inhibits IL-12 production, resulting in inhibition of Th1 and promotion of Th2 differentiation (Panina-Bordignon et al. 1997). More recently, it was shown that in human dendritic cells obtained by differentiating human cord blood CD34+ precursor cells, noradrenaline acting through  $\beta_2$ -ARs and increased cAMP inhibited LPS-stimulated production of IL-23, IL-12 p40, TNF- $\alpha$  and IL-6 without affecting IL-10 (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+ T cells. These findings provide new insight into the immunological consequences of the clinical use of  $\beta_2$ -AR agonists and may suggest new approaches for the treatment of Th1-mediated diseases.

### 2.2.5 Granulocytes

Limited data exist regarding AR expression and function in human granulocytes. Available evidence concern nearly only polymorphonuclear cells (PMN) and  $\beta$ -AR. Expression of  $\beta$ -AR on human 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. 1999b). 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 also debated. Low concentration of the  $\beta$ -AR agonist isoprenaline inhibited the respiratory burst induced by the chemotactic peptide *N*-formyl-methionyl-leucyl-phenylalanine (fMLP) or by calcium ionophores (A23187, ionomycin), as well as leukotriene B4 generation (Nielson 1987). In another study, however, production of IL-8 and expression of the adhesion molecules CD15, CD44, and CD54 was only slightly reduced by adrenaline and only at very high concentrations (1 mM), suggesting that, although functionally coupled to signaling cascades, the functional relevance of  $\beta$ -AR in PMN is limited. It should be however considered that  $\beta$ -AR desensitization has been reported after activation of PMN respiratory burst (Vago et al. 1990). Decreased  $\beta$ -AR responsiveness in PMN has been reported in the elderly (Cotter and O'Malley 1983).

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).

### 2.2.6 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). No data exist regarding the existence and functional relevance of adrenergic mechanisms in human microglia, therefore main evidence obtained in the murine model will be reviewed hereafter.

Direct evidence for the expression of AR on microglial cells has been recently provided by Hertz et al. (2010), who showed, by means of microarray and immunohistochemistry, the occurrence in murine microglia of  $\beta_2$ -AR and possibly of  $\beta_1$ -AR and  $\alpha_{2A}$ -AR.  $\beta$ -AR activation 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 (Tomozaawa et al. 1995) as well as ERK1/2 and P38 MAPK (Wang et al. 2010). Interestingly, however, NA acting on  $\beta$ -AR 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. In this study, IL-1  $\beta$  expression was not affected by NA (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  $\alpha_2$ -AR and the  $\alpha_2$ -AR agonist dexmedetomidine exerted analgesic effects involving the blockade of spinal glial activation (Xu et al. 2010).

### 2.2.7 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  $\beta_2$ -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  $\beta_2$ -AR-pathway might be involved into 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)). It has been recently reported however that  $\beta$ -AR stimulation together with TNF-receptor triggering may also induce synergistic IL-6 expression in astrocytes, an effect which warrants further investigation also in view of the role of uncontrolled expression of IL-6 in the CNS in neurodegeneration and glioma development (Spooren et al. 2011).

Circumstantial evidence also exists regarding the occurrence of  $\alpha_1$ -AR, e.g. in astrocytes from human optic nerves (Mantyh et al. 1995). The human U373 MG astrocytoma cell line, widely used as a model system for the investigation of astrocyte function, express a single class of  $\alpha_1$ -AR, the  $\alpha_{1B}$ -AR subtype, which are coupled to phosphoinositide hydrolysis and calcium mobilization, and which mediate a mitogenic response to  $\alpha_1$ -AR-agonists (Arias-Montaña et al. 1999).

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## 2.3 Endogenous Noradrenaline and Adrenaline in Immune Cells

Traditional criteria to assess the role of a substance as neurotransmitter in the nervous system usually include (see e.g. Purves et al. 2001):

- Presence of the substance within the cell (either synthesized by the cell or taken up from other cells that release it).
- Stimulus-dependent release.
- Mechanisms for removal (i.e. by degradation or reuptake).
- Action on target cells through specific receptors (effects mimicked by exogenous application of the substance in appropriate amounts).

As regards immune cells, evidence for the presence and the functional relevance of ARs has been reviewed in the previous section. Hereafter, data regarding endogenous noradrenaline and adrenaline, their synthesis, storage, release and removal will be discussed and experimental evidence about their possible functional role in immune cells will be summarized.

### 2.3.1 Presence and Synthesis

Noradrenaline and adrenaline (as well as dopamine and their major metabolites) have been identified in several types of immune cells, such as: murine lymphocytes (Josefsson et al. 1996), peritoneal macrophages (Spengler et al. 1994), bone marrow derived mast cells (Freeman et al. 2001), human peripheral blood mononuclear cells (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+CD25+ regulatory T lymphocytes (Cosentino et al. 2007), granulocytes (Cosentino et al. 1999), and hematopoietic cell lines (Cosentino et al. 2000). Table 2.2 summarizes available information obtained in human immune cells.

**Table 2.2** Endogenous noradrenaline and adrenaline in human immune cells

Cells	Treatments	Analytical assay	Noradrenaline <sup>a</sup>	Adrenaline <sup>a</sup>	Ref.
Peripheral blood mononuclear cells		HPLC-ED	0.206 ± 0.030 <sup>b</sup>		Musso et al. (1996)
Peripheral blood mononuclear cells		HPLC-ED	0.129 ± 0.005 <sup>b</sup>		Musso et al. (1997)
Peripheral blood mononuclear cells		Mass spectrometry	170.0817 <sup>c</sup>		Bergquist and Silberring (1998)
Peripheral blood mononuclear cells		HPLC-ED	0.125 ± 0.015	0.856 ± 0.469	Marino et al. (1999)
Peripheral blood mononuclear cells	48 h-culture	HPLC-ED	1.153 ± 1.121	0.450 ± 0.539	Cosentino et al. (2002a)
Peripheral blood mononuclear cells	ACh 60-120 µM, 1 h	HPLC-ED	0.173 ± 0.003 <sup>b</sup>		Musso et al. (1997)
Peripheral blood mononuclear cells	nicotine 250 µM, 1 h	HPLC-ED	0.216 ± 0.026 <sup>b</sup>		Musso et al. (1997)
Peripheral blood mononuclear cells	tyrosine 50 µM, 1 h	HPLC-ED	0.176 ± 0.014 <sup>b</sup>		Musso et al. (1997)
Peripheral blood mononuclear cells	PHA 10 µg/mL, 48 h	HPLC-ED	38.533 ± 9.629	35.717 ± 6.011	Cosentino et al. (2002a)
Freshly isolated lymphocytes		HPLC-ED	0.227 ± 0.039 <sup>b</sup>		Musso et al. (1996)
Total lymphocytes		Flow cytometry		402 ± 70 <sup>d</sup>	Pallinger and Csaba (2008)
CD3+ T lymphocytes		HPLC-ED	1.26 ± 0.69	0.45 ± 0.27	Cosentino et al. (2000)
CD3+ T lymphocytes		Flow cytometry		421 ± 78 <sup>d</sup>	Pallinger and Csaba (2008)
CD3+CD4+ T lymphocytes		Flow cytometry		437 ± 84 <sup>d</sup>	Pallinger and Csaba (2008)
CD3+CD8+ T lymphocytes		Flow cytometry		420 ± 106 <sup>d</sup>	Pallinger and Csaba (2008)
CD4+CD25-effector T lymphocytes		HPLC-ED	1.32 ± 1.18	0.30 ± 0.24	Cosentino et al. (2007)
CD4+CD25+ regulatory T lymphocytes		HPLC-ED	25.61 ± 15.23	25.16 ± 15.86	Cosentino et al. (2007)
CD19+ B lymphocytes		HPLC-ED	1.18 ± 0.57	0.69 ± 0.31	Cosentino et al. (2000)
Granulocytes		HPLC-ED	84.61 ± 1.58	11.2 ± 2.0	Cosentino et al. (1999)
Granulocytes		HPLC-ED	0.21 ± 0.04	0.05 ± 0.01	Cosentino et al. (2000)

(continued)

**Table 2.2** (continued)

Cells	Treatments	Analytical assay	Noradrenaline <sup>a</sup>	Adrenaline <sup>a</sup>	Ref.
Granulocytes		Flow cytometry		not detected	Pallinger and Csaba (2008)
CD14+ monocytes		HPLC-ED	0.82 ± 0.70	0.35 ± 0.25	Cosentino et al. (2000)
CD45+CD14+ monocytes		Flow cytometry		549 ± 80 <sup>d</sup>	Pallinger and Csaba (2008)
Jurkat (T lymphoblastoid)		HPLC-ED	0.67 ± 0.48	0.03 ± 0.00	Cosentino et al. (2000)
NALM-6 (pre-B)		HPLC-ED	1.83 ± 0.72	0.87 ± 0.58	Cosentino et al. (2000)
U937 (promonocytic)		HPLC-ED	0.55 ± 0.13	0.07 ± 0.01	Cosentino et al. (2000)

<sup>a</sup> Means ± SD, expressed as 10<sup>-12</sup> mol/10<sup>6</sup> cells, unless otherwise indicated.

<sup>b</sup> pmol/10<sup>7</sup> cells.

<sup>c</sup> *m/z* values in 4–10 × 10<sup>9</sup> PBMC/L.

<sup>d</sup> Detected with affinity isolated highly antigen-specific antibodies to epinephrine [Ab 35020, Lot 293141].

Intracellular levels of noradrenaline and adrenaline (as well as of dopamine, the direct precursor of noradrenaline) sharply increase in human peripheral blood mononuclear cells after 48–72 h stimulation with phytohemagglutinin (Cosentino et al. 2002a) as well as with anti-CD3/anti-CD28 monoclonal antibodies (Cosentino M., unpublished observations). Similar results were subsequently published in rodent lymphocytes stimulated with concanavalin A, and in the same study by use of immunohistochemistry it was shown that TH-positive cells in rodent lymphoid organs had 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. 2000) and suggests a preferential involvement of intracellular catecholamines-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>++</sup>-dependent mechanisms (Cosentino et al. 2002a).

The existence of a classical pathway (Fig. 2.1) 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, the RNA-polymerase inhibitor actinomycin D and the protein synthesis inhibitor cycloheximide to prevent intracellular enhancement of catecholamine levels (Cosentino

et al. 2002a, b; Reguzzoni et al. 2002). Only fragmentary evidence however exists regarding the expression and activity in immune cells of other key enzymes such as phenylethanolamine *N*-methyltransferase (Andreassi et al. 1998; Ziegler et al. 2002) or dopamine  $\beta$ -hydroxylase (Giubilei et al. 2004).

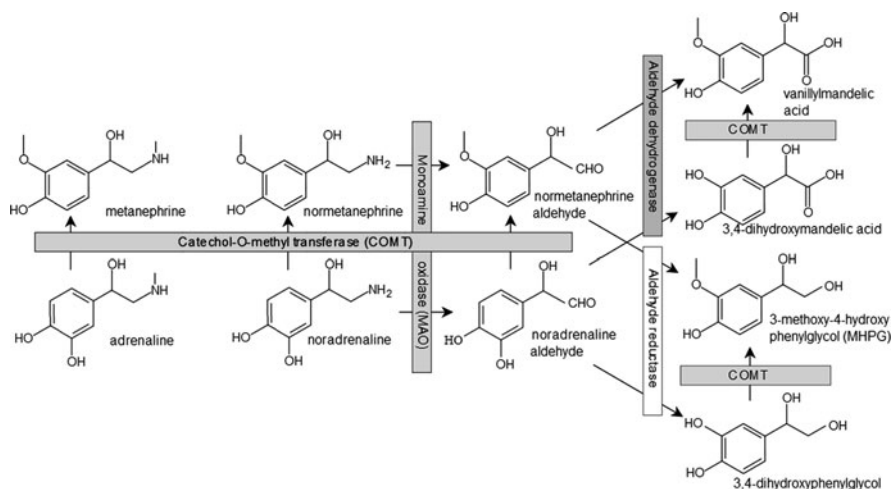
In human peripheral blood mononuclear cells stimulated *in vitro* with phytohemagglutinin, TH mRNA expression and catecholamine production occurs only in T and B lymphocytes and is reduced by dopamine (but not by noradrenaline or adrenaline) through dopaminergic D1-like receptor-dependent mechanisms which include inhibition of TH gene transcription (Ferrari et al. 2004). The proinflammatory cytokine interferon- $\gamma$  exerts similar effects and its action is counteracted by interferon- $\beta$  (Cosentino et al. 2005). TH expression and catecholamine production are on the contrary enhanced by agents which induce catecholamine release (see next section).

### 2.3.2 Storage and Release

Intracellular storage of catecholamines in human lymphocytes occurs in reserpine-sensitive compartments (Marino et al. 1999; Cosentino et al. 2000, 2007), which suggests the involvement of vesicular monoamine transporters (VMAT) similar to those expressed in neural and neuroendocrine cells (Henry et al. 1994), in agreement with preliminary evidence suggesting the occurrence of VMAT-1 and 2 in rat thymus and spleen (Mignini et al. 2009) and possibly also in human peripheral blood lymphocytes (Amenta et al. 2001).

In particular, in human activated lymphocytes release can be effectively induced by biological agents such as interferon- $\beta$  (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. It should be noted that, at least *in vitro*, catecholamine release from activated lymphocytes increases extracellular catecholamines from pico-nanomolar up to submicromolar concentrations (and possibly to even higher values in the vicinity of the cells), which may be well within the effective concentration range to exert immunomodulating effects.

Release of catecholamines is usually associated with induction of TH mRNA expression and increased catecholamine production (Cosentino et al. 2000, 2005), a response which closely resembles the increased activity of catecholamine-synthesizing pathways observed in neurons following depletion with reserpine, and which has been ascribed to increased TH activity (see e.g. Mallet 1996).



**Fig. 2.2** Degradation of adrenaline and noradrenaline (modified from the Wikimedia Commons – <http://commons.wikimedia.org>)

### 2.3.3 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. 2.2).

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 the only indirect evidence for the presence of NET was provided nearly three decades ago, when Audus and Gordon (1982) described in murine lymphocytes a single population of desipramine-binding sites with an apparent dissociation constant ( $K_d$ ) of about 0.4 nM. More convincing evidence however exists in immune cells for the expression and the functional relevance of DAT (DopAmine Transporter) (reviewed in Marazziti et al. 2010). Interestingly, the affinity of noradrenaline for NET and for DAT is about the same (see e.g. the PDSP  $K_i$  database – <http://pdsp.med.unc.edu/pdsp.php>). Evidence exists that incubation of human peripheral blood mononuclear cells with the NET inhibitor desipramine or with the DAT inhibitor GBR 12909 increased the extra-cellular 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. No data however exist about the possible differential expression of catecholamine transporters on different immune cell populations, on the effects of cell activation and/or on their functional role, and it remains to be established 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.

Indirect evidence for the existence of classical enzymatic pathways for the degradation of noradrenaline and adrenaline in immune cells is provided by the identification of all the main metabolites of these catecholamines in phagocytes as well as in lymphocytes in both rodents and humans (Bergquist et al. 1994, Bergquist and Silberring 1998; Spengler et al. 1994; Musso et al. 1996; Marino et al. 1999; Cosentino et al. 1999, 2000, 2002a, 2007; Freeman et al. 2001) (Fig. 2.2). Occurrence in human immune cells of both MAO and COMT is also 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 was 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). Various groups indeed provided experimental evidence indicating that 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). Support to its functional relevance has been provided mainly by use of pargyline, which 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 interleukin-4, and it has been suggested that upregulation of MAO-A expression may contribute in switching naive monocytes into a resolving phenotype (Chaitidis et al. 2004, 2005).

### 2.3.4 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
- Interference with intracellular storage/release/uptake

Modulation of synthesis and release could be obtained through both pharmacological and non-pharmacological approaches (e.g. suppression of expression of key proteins – TH, VMAT, etc. – by means of gene silencing techniques). Available evidence however has been provided so far mainly through pharmacological experiments (Table 2.3). 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 tumor necrosis factor- $\alpha$  production, which – together with the presence of intracellular noradrenaline in these cells – was taken as an evidence of the existence of an adrenergic

**Table 2.3** Functional role of endogenous noradrenaline and adrenaline in immune cells

Experimental model	Treatments	Experimental approach	Functional role	Notes	Reference
In vitro, mouse peritoneal macrophages	LPS	$\alpha$ -AR antagonism with idazoxan, $\beta$ -AR antagonism with propranolol	$\beta$ -AR-mediated decrease and $\alpha_2$ -AR-mediated increase of tumor necrosis factor- $\alpha$ production		Spengler et al. (1994)
In vitro, mouse peritoneal macrophages	LPS	$\alpha$ -AR antagonism with idazoxan, $\beta$ -AR antagonism with propranolol	$\beta$ -AR-mediated decrease and $\alpha_2$ -AR-mediated increase of tumor necrosis factor- $\alpha$ production	Effects increased in animals with streptococcal-cell-wall-induced arthritis	Chou et al. (1998)
In vitro, murine phagocytes	LPS		LPS induced release of catecholamines and induction of catecholamine-generating and degrading enzymes		Flierl et al. (2007)
In vivo, rats with acute lung injury		$\alpha_2$ -AR agonists/antagonists, inhibitors of catecholamine synthesizing/degrading enzymes	$\alpha_2$ -AR-mediated increase of lung inflammation, suppressed by $\alpha_2$ -AR antagonists or inhibitors of catecholamine synthesizing enzymes		Flierl et al. (2007)
In vitro, mouse peritoneal macrophages		adrenaline, noradrenaline	NF $\kappa$ B activation, enhanced release of tumor necrosis factor- $\alpha$ , IL-1 $\beta$ , IL-6 and MIP-2		Flierl et al. (2009)
In vivo, rats with immune complex-induced acute lung injury		$\alpha_2$ -AR antagonism with RX821002	$\alpha_2$ -AR-mediated increase of the severity of acute lung injury	Effect increased in adrenalectomized rats	Flierl et al. (2009)
In vitro, rodent lymphocytes	Con A	TH inhibition with $\alpha$ -methyl- <i>p</i> -tyrosine, MAO inhibition with pargyline, $\alpha$ -AR blockade with phentolamine,	$\beta$ -AR-mediated inhibition of IL-2 production		Qiu et al. (2004, 2005)

(continued)

**Table 2.3** (continued)

Experimental model	Treatments	Experimental approach	Functional role	Notes	Reference
		$\beta$ -AR blockade with propranolol			
In vitro, rodent lymphocytes	Con A	TH inhibition with $\alpha$ -methyl- <i>p</i> -tyrosine, MAO inhibition with pargyline, $\alpha_1/\alpha_2$ - and $\beta_1/\beta_2$ -AR blockade	$\alpha_1$ - and $\beta_2$ -AR-mediated increase of apoptosis	Involvement of cAMP-PKA- and PLC-PKC-linked CREB-Smac/DIABLO pathways	Jiang et al. (2007, 2009)
In vitro, human peripheral blood mononuclear cells	PHA	TH inhibition with $\alpha$ -methyl- <i>p</i> -tyrosine	Catecholamine-mediated increase of apoptosis		Cosentino et al. (2002b)
In vivo, human lymphocytes			Intracellular levels of adrenaline and noradrenaline correlate with basal and isoprenaline-stimulated cAMP		Knudsen et al. (1996)

autocrine loop, which is 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 lipopolysaccharide 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). These results were confirmed in adrenalectomized rodents, which show greatly enhanced catecholamine release from phagocytes as well as enhanced expression of TH and DBH in these cells (Flierl et al. 2009). It is thus suggested that noradrenaline and adrenaline directly activate NF $\kappa$ B at least in rodent phagocytes, causing enhanced release of proinflammatory cytokines such as tumor necrosis factor- $\alpha$ , IL-1 $\beta$  and IL-6, resulting in amplification of the acute inflammatory response via  $\alpha_2$ -ARs (Flierl et al. 2009).

Experimental evidence for the functional relevance of endogenous noradrenaline and adrenaline also exists in rodent lymphocytes. Qiu et al. (2004) 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, suggesting that endogenous catecholamines may exert a tonic inhibition on the production of this cytokine. In further studies (Qiu et al. 2005), the same group showed that rodent lymphocyte proliferation is increased by  $\alpha$ -methyl-*p*-tyrosine but decreased by the monoamine oxydase inhibitor pargyline, which at the same time increased intracellular cAMP, the second messenger acted upon by  $\beta$ -ARs. By use of AR antagonists, evidence indeed was provided that the effects of pargyline required activation of  $\beta$ -ARs, possibly through increased levels of noradrenaline and/or adrenaline.

In human immune cells, the first evidence for a functional role of endogenous noradrenaline and adrenaline was provided by Knudsen et al. (1996), who showed that intracellular levels of both monoamines in circulating lymphocytes from healthy subjects were strongly correlated with both basal and isoprenaline-stimulated cAMP in these cells. In a subgroup of subjects, variability in endogenous lymphocyte concentration of adrenaline also correlated with concomitant changes in number of NK (CD3-CD56+) cells and cAMP. More direct evidence came a few years later from studies in human peripheral blood mononuclear cells, where stimulation with phytohemagglutinin 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. 2002b). Similar findings were subsequently obtained in rodent lymphocytes activated with concanavalin A, where the proportion of apoptotic cells as well as the expression of apoptosis-related genes and proteins, Bax, Fas, Fas-Ligand and caspase-3 were decreased by  $\alpha$ -methyl-*p*-tyrosine but increased by the monoamine oxydase inhibitor pargyline, which on the contrary decreased the expression of the antiapoptotic protein Bcl-2 (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).

In summary, at least circumstantial evidence exists for each of the criteria needed to establish the role of noradrenaline and adrenaline as transmitters in immune cells. Nonetheless, systematic application of such criteria to specific immune cell types and functional conditions is still lacking, and for these reasons noradrenaline and adrenaline should be still referred to as “putative” transmitters in immune cells.

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## 2.4 Noradrenaline, Adrenaline and Immune-Mediated Disease

A huge amount of evidence exists regarding the involvement of sympathoadrenergic neuroimmune mechanisms in several disease conditions. Hereafter, specific attention will be dedicated to *multiple sclerosis*, *rheumatoid arthritis* and

*cancer* with emphasis on human data. Other diseases in which catecholamine modulation of the immune response has been suggested as pathogenetic and/or therapeutic mechanism will be also summarized.

### 2.4.1 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). Classical observations in rats with experimental allergic encephalomyelitis (EAE) support the relevance of sympathoadrenergic mechanisms in MS pathogenesis (Bellinger et al. 1992; Chelmicka-Schorr and Arnason 1999). In particular, EAE is worsened by chemical sympathectomy (Chelmicka-Schorr et al. 1988) and suppressed by  $\beta$ -adrenergic agonists (Wiegmann et al. 1995).

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+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 have been reported to be significantly higher in the first-attack of MS whilst noradrenaline levels were significantly 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* interferons (IFNs) profoundly affect endogenous catecholamines in human lymphocytes: while IFN- $\beta$  increases their production following stimulation with PHA and induces their extracellular release, IFN- $\gamma$  profoundly decreases catecholamines production as well as the mRNA expression of the catecholamines-synthesizing enzyme tyrosine hydroxylase, and coincubation with both IFNs prevents the inhibitory effect of IFN- $\gamma$ ,

as well as the enhancing/releasing effect of IFN- $\beta$  (Cosentino et al. 2005). The relevance of these findings for MS is confirmed by the observation that in lymphocytes from patients treated with IFN- $\beta$  for 12 months the production of catecholamines hugely increased and was less sensitive to IFN- $\gamma$ -induced inhibition. Expression of mRNA for TH and  $\beta_2$ -AR (and also dopaminergic receptors D5) was already enhanced after 1 month and further increased up to 6–12 months of treatment (Zaffaroni et al. 2008). Thus, 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, which could result in reduced T cell proliferation and IFN- $\gamma$  secretion (Giorelli et al. 2004). 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 of 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.

As regards 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). These observations led to the speculation that in MS astrocytes may serve as primary (facultative) antigen-presenting cells due a failure to on one side of  $\beta_2$ -AR-mediated suppression of class II major histocompatibility complex molecules (De Keyser et al. 2003). Astrocyte  $\beta_2$ -AR dysregulation however may contribute to MS pathogenesis and progression through several other mechanisms, including on one side deficient suppression of nitric oxide and proinflammatory cytokine production and glutamate uptake, and on the other side deficient glycogenolysis and production of trophic factors (De Keyser et al. 2004), as well as also contributing to 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 astrocytes, however preliminary results need to be confirmed and extended in larger, randomized studies.

## 2.4.2 Rheumatoid Arthritis

Extensive experimental and clinical evidence support the occurrence of dysregulated immune system and response to the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system in rheumatoid arthritis (RA), and targeting the neuroimmune network is increasingly regarded as an attractive therapeutic strategy (reviewed in: Baerwald et al. (2000), Wahle et al. (2002a), Lorton et al. (2003), Straub et al. (2005)).

Several studies over the last two decades documented modification of AR signaling in immune cells of patients with RA, such as decreased density and affinity of  $\beta_2$ -ARs on PBMC and in particular on CD8+ lymphocytes, showing negative correlation with disease activity (Baerwald et al. 1992b, 1997) 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 upon 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+ T cells are responsible for the impaired adrenergic control of IFN- $\gamma$  production (Wahle et al. 2006).

In patients with RA the density of  $\beta_2$ -ARs is decreased also on peripheral CD19+ B lymphocytes (a finding which occurs also in patients with systemic lupus erythematosus and with systemic sclerosis), and negatively correlates with systemic disease activity. Furthermore, although basal intracellular cAMP levels in these cells are raised, the increase of cAMP upon stimulation of  $\beta_2$ -ARs is low (Wahle et al. 2001). Cell death induced by exposure to  $\beta_2$ -AR agonists is also diminished in RA CD19+ B lymphocytes exhibiting decreased  $\beta_2$ -AR density (Wahle et al. 2002b).

It should be mentioned however that at least one study 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. Indeed, patients with JRA have an altered function of the autonomic nervous system associated with increased central noradrenergic outflow, which is associated with changes in the response of leukocytes via  $\beta_2$ -ARs: leukocytes of patients with active JRA have a lower cAMP response to a  $\beta_2$ -AR agonist, presumably due to increased cAMP-phosphodiesterase activity in these cells (Kuis et al. 1996). In particular, 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. 2000a). In subjects with polyarticular JRA (but not in healthy controls or subjects with the oligoarticular form of the disease),  $\alpha_1$ -ARs expressed on circulating lymphocytes mediate noradrenaline-induced production of the proinflammatory cytokine IL-6 (Heijnen et al. 1996).

Factors contributing to dysregulated sympathoadrenergic tuning of the immune response may include  $\beta_2$ -AR gene variants. Responsivity of  $\beta_2$ -ARs are affected by

polymorphisms at positions 16 and 27, which determine the propensity for agonist-induced downregulation and associated subsensitivity (Green et al. 1993, 1995). According to genetic studies performed in northern Sweden (Xu et al. 2005) and in Germany (Malysheva et al. 2008), carriage of Arg16 and of Gln27 was associated with RA, carriage of Gln27 was associated with activity of the disease and in combination with non-carriage of Arg16 with higher levels of rheumatoid factor, and homozygosity for Arg16 exhibited the greatest risk for RA in combination with HLA-DRB1\*04. Association of Arg16 and of Gln27 was not found in a population of children with JRA (Pont-Kingdon et al. 2009). According to current models of  $\beta_2$ -AR kinetics, homozygous Arg16 would be relatively resistant to downregulation by endogenous catecholamines, while homozygous Gln27 would be relatively sensitive to downregulation (Liggett 2000).

In RA the sympathoadrenergic tuning of the immune response is extensively dysregulated also at the local level, in synovial tissue, where sympathetic innervation is reduced while sensory innervation is increased, and the differential patterns of innervation are dependent on the severity of the inflammation (Miller et al. 2000). Local noradrenaline production is maintained by TH+ cells, mainly synovial macrophages, and its levels correlate with the degree of inflammation and with spontaneous IL-8 secretion, while density of TH+ cells correlates positively with spontaneous secretion of IL-6, IL-8, and MMP-3 (Miller et al. 2002). In RA patients treated with corticosteroids, synovial tissue shows decreased spontaneous cytokine secretion, less T cells, CD163+ macrophages and TH+ cells, reduced inflammation and reduced noradrenaline secretion (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 in the progressing course of the inflammatory disease ( $\beta$ -to- $\alpha$  adrenergic shift) (reviewed by Straub and Härle 2005). Noradrenaline secreted by TH+ cells occurring in synovial tissue during RA would thus represent an antiinflammatory mechanism to counteract local inflammation. Indeed, in RA patients clear evidence has been provided that systemic secretion of cortisol together with local production of noradrenaline are required to lower synovial 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). Further evidence for a critical role of local production of catecholamines by TH+ cells in RA synovium has been recently provided by showing that increased catecholamine release induced after blockade of vesicular monoamine transporter 2 (VMAT2) results in strong reduction of TNF (occurring through cAMP increase but possibly without involvement of classical  $\beta$ -ARs) 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).

Finally, it has been reported that, at least in vitro,  $\alpha_2$ -AR stimulation of type A (macrophage-like) and B (fibroblast-like) synoviocytes produced an increase and a decrease in the respective cell number, probably through Gi-coupled PLC activation and the resulting stimulation of the PKC betaII/MAP kinase (Mishima et al. 2001), providing preliminary evidence for a role of  $\alpha_2$ -ARs in RA.

### 2.4.3 Cancer

Evidence showing a direct connection between sympathoadrenergic function and tumor development has been obtained mainly in animal models, where 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), although it was shown that also chemical denervation may lead to tumor growth, thus suggesting a complex role of the sympathetic nervous system in the regulation of antitumor immunity (Brenner et al. 1992). 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; Ben-Eliyahu et al. 2000a), although nor-adrenaline has also been shown to inhibit the generation of specific antitumor cytotoxic T lymphocytes (Kalinichenko et al. 1999). Interestingly, 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 type-C CpG oligodeoxynucleotides (CpG-C ODN) was shown to improve NK activity and immunocompetence, potentially reducing metastatic dissemination after enhanced sympathetic stress responses (Goldfarb et al. 2009) and in association with pharmacological blockade of  $\beta$ -ARs and COX inhibition it was proposed as a potential approach to limit postoperative immunosuppression and metastatic progression (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.

Activation of  $\beta$ -ARs may also result in direct stimulation of tumor proliferation, e.g. in human colon adenocarcinoma where adrenaline stimulates cell growth via both  $\beta_1$ - and  $\beta_2$ -AR- and COX-2-dependent pathways (Wong et al. 2011), while antagonism at  $\beta$ -ARs may have direct antitumor effects, e.g. in pancreatic cancer cells where  $\beta_2$ -AR blockade synergizes with gemcitabine to induce apoptosis (Shan et al. 2011).

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 randomized 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 is a well characterized feature of pathologic cells from chronic and acute lymphocytic leukemia (Sheppard et al. 1977; Paietta and Schwarzmeier 1983), although at least one study in intact B lymphocytes from patients with chronic lymphocytic leukemia found normal  $\beta$ -AR binding and a single overexpressed population of  $\alpha_2$ -ARs (Goin et al. 1991). Loss of  $\beta$ -AR function and class I major histocompatibility complex antigen surface expression was also reported in the murine S49 lymphoma cell line in association with a higher rate of proliferation (Cremaschi et al. 1994), and  $\beta$ -AR activation induces apoptosis in these cells via G(s) $\alpha$  and PKA, possibly providing a means to control proliferation of immature T cells (Yan et al. 2000). A decreased number of  $\beta$ -ARs involved in cell proliferation was described also on the T cell lymphoma BW5147 (Cremaschi et al. 2000). Impaired AR expression in circulating cells from patients with chronic lymphocytic leukemia 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 chronic lymphocytic leukemia (CLL) cells, the proapoptotic effect of the long acting  $\beta_2$ -AR agonists salmeterol and formoterol in these cells have 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 COHX inhibitors even in patients with hematological malignancies (Inbar et al. 2011).

It should also be mentioned that noradrenaline and adrenaline may act through specific ARs to increase the synthesis of proangiogenic factors, thus promoting tumor growth (while dopamine through dopaminergic receptors may have opposite effects by suppressing the actions of vascular permeability factor/vascular endothelial growth factor-A). These issues have been recently reviewed by Chakroborty et al. (2009).

#### 2.4.4 Other Diseases

The density of  $\beta_2$ -ARs on circulating lymphocytes is decreased in several other chronic inflammatory diseases, including *Crohn's disease* (Krause et al. 1992) and



*systemic lupus erythematosus* (Baerwald et al. 1992a; Wahle et al. 2001). Evidence regarding the role of the sympathetic nervous system in systemic lupus erythematosus has been recently reviewed (del Rey and Besedovsky 2008).

Patients with *myasthenia gravis* (MG) have decreased  $\beta_2$ -AR density on peripheral blood mononuclear cells (Xu et al. 1997) and circulating antibodies and T cells that react with  $\beta_1$ - and  $\beta_2$ -ARs (Yi et al. 1996), which might be implicated in the few patients with myasthenia gravis who have heart disease (Xu et al. 1998).

In *Alzheimer's disease* (AD),  $\beta$ -ARs on circulating lymphocytes were usually studied as peripheral markers of central disruption of adrenergic transmission, as described in AD post-mortem brains. Although initial studies provided no clear evidence of disrupted  $\beta$ -AR responsiveness in lymphocytes of AD subjects (Oppenheim et al. 1984; Gietzen et al. 1989), later it was shown that isoprenaline-induced cAMP increase may be reduced (Garlind et al. 1997) GRK2 expression may be increased (Leosco et al. 2007). Interestingly, using a cDNA microarray representing 3,200 distinct human genes it was shown that in AD lymphocytes the  $\alpha_2C$ -AR gene is among 20 candidate genes whose expression is altered, although its eventual physiopathological and clinical meaning remains a matter of speculation (Kálmán et al. 2005). Recently, in murine microglial cells it was shown that both noradrenaline and isoprenaline promote amyloid  $\beta$  peptide uptake and degradation through activation of  $\beta_2$ -ARs, thus providing a potential link between central noradrenergic neurotransmission and neuroinflammatory mechanisms in AD (Kong et al. 2010).

Although extensive evidence exists regarding the role of neuroimmune mechanisms in *allergy and asthma* (Marshall 2004), sympathoadrenergic modulation of immunity in this field received attention mainly regarding the ability of  $\beta_2$ -AR agonists to exert anti-inflammatory effects (Hanania and Moore 2004). Nonetheless, peripheral blood lymphocytes of patients with asthma have reduced  $\beta$ -AR binding capacity (Hataoka et al. 1993), and in long-term smokers with mild to moderate chronic obstructive pulmonary disease (COPD) smoking cessation is associated with a significant increase in T lymphocyte  $\beta_2$ -AR density (Leader et al. 1994), which is probably not only a good marker of change in pulmonary response to  $\beta_2$ -AR agonists but, first of all, an indicator of reduced chronic low-grade systemic inflammation.

Lymphocyte  $\beta$ -ARs received considerable attention in *cardiac disease*, however usually only as a surrogate tissue for myocardium to assess  $\beta$ -AR function, despite the apparent absence of any direct relationship between lymphocyte and myocardial  $\beta$ -AR density (Dzimiri and Moorji 1996). For instance, it was shown that plasma noradrenaline and adrenaline were increased and lymphocyte  $\beta$ -AR density was reduced in patients with congestive ischemic disease and coronary artery bypass grafting was associated with clinical and hemodynamic improvement as well as with improvement of lymphocyte  $\beta$ -AR density and function (Chello et al. 1995). In another study in patients with chronic severe heart failure it was reported that decreased lymphocyte  $\beta$ -ARs were increased after treatment with angiotensin converting enzyme inhibitors, which also induced significant improvement in cardiac function (Townend et al. 1993). Density of lymphocyte  $\beta$ -ARs was shown to be reduced also in infants and children with heart failure secondary to



congenital heart disease (Wu et al. 1996) and in patients with rheumatic heart valvular disease (Dzimiri et al. 1995). Only in the last decade however increased sympathetic activity and altered immune function occurring in chronic heart failure began to be more carefully considered, for instance showing that in subjects with chronic heart failure reduced  $\beta$ -AR on lymphocytes results in impaired  $\beta$ -adrenergic control of lymphocyte activation, which in turn contributes to the chronic low-intensity inflammation occurring in heart disease (Werner et al. 2001).

Noradrenaline and adrenaline exert extensive effects on innate immunity, as discussed in previous sections. Monocytes/macrophages as well as granulocytes are affected by catecholamines and can themselves produce and utilize these transmitters (reviewed by Flierl et al. 2008), which may have significant relevance for *bacterial infections and sepsis*. The therapeutic effects of  $\alpha_2$ -AR antagonism or pharmacological inhibition of catecholamine synthesis in rodent models of acute lung injury has been discussed previously (Flierl et al. 2007, 2009). Recently, it has been shown that the  $\beta$ -AR antagonist propranolol may control the susceptibility of severely burned patients to opportunistic pathogens by reducing the occurrence of immunosuppressive M2 monocytes (Kobayashi et al. 2011).

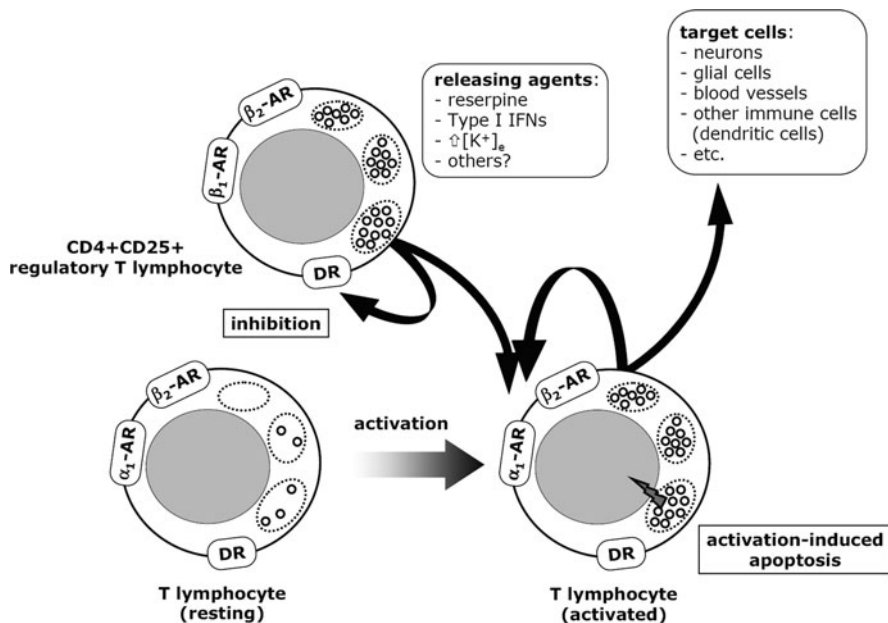
Evidence exists that highly stressful events may promote *viral infections* (e.g. herpes simplex virus type-1 and varicella zoster virus) through activation of the sympathetic nervous system. For instance, catecholamines directly stimulate the human cytomegalovirus immediate-early (IE) enhancer/promoter in monocytic cells via beta-2 adrenergic receptors, possibly leading to the development of an active human cytomegalovirus infection in latently infected patients (Prösch et al. 2000). Noradrenaline has also been shown to accelerate human immunodeficiency virus (HIV) replication in quiescently infected PBMC via  $\beta$ -AR and PKA activation (Cole et al. 1998). In the central nervous system, HIV coat protein gp120 may interfere with the  $\beta$ -AR-mediated regulation of astrocytes and microglia and may alter astroglial “reactivity” thus promoting neuroinflammation and impairing defense against viral and opportunistic infections (Levi et al. 1993).

Decreased  $\beta$ -ARs have been consistently reported in subjects with *depression* (reviewed by Werstiuk et al. 1990), and electroconvulsive therapy has been reported to increase lymphocyte  $\beta$ -AR responsivity (Mann et al. 1990). Decreased lymphocyte  $\beta$ -ARs may occur also in *panic disorder* (Brown et al. 1988), and even in normal subjects with *increased tension and anxiety* traits (Yu et al. 1999). These findings however need to be evaluated in the context of dysregulated immunity occurring in depression (reviewed by Blume et al. 2011).

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## 2.5 Concluding Remarks

Sympathoadrenergic mechanisms represent the main channel of communication between the nervous system and the immune system, and the origins of neuroimmunology itself can be traced back to the understanding of the role of noradrenaline and adrenaline in the modulation of the immune response. It may therefore sound paradoxical that so much remains to elucidate before AR-mediated



**Fig. 2.3** Speculative scheme depicting the cellular network sustained by endogenous catecholamines in human lymphocytes. CD4+CD25+ regulatory T lymphocytes constitutively express TH, the key enzyme in the synthesis of catecholamines, dopaminergic receptors, and  $\alpha$ - and  $\beta$ -ARs, and contain high amounts of catecholamines stored in reserpine-sensitive compartments. Upon release, endogenous catecholamines may subserve autocrine/paracrine modulatory loops, leading to e.g. impaired suppressive activity of CD4+CD25+ regulatory T lymphocytes toward mitogen-induced T lymphocyte proliferation (Cosentino et al. 2007). In addition to the chromaffin granule depletant reserpine, candidate agents that may induce the release of catecholamines from lymphocytes include type I IFNs (Cosentino et al. 2005), tetrabenazine, as well as even high  $[K^+]_e$  (Cosentino et al. 2003). The picture also shows that, in the absence of stimulation, effector T lymphocytes express dopaminergic receptors and  $\alpha$ - and  $\beta$ -ARs and contain trace amounts of catecholamines. Upon stimulation, intracellular catecholamines increase by several 10-fold, and expression and function of both dopaminergic receptors and ARs may also undergo significant changes. Under these conditions, endogenous catecholamines either may directly affect cell survival and apoptosis from within the cell (lightning bolt) (Cosentino et al. 2002a), or they can be released (arrows) to act upon lymphocytes themselves and/or upon neighboring cells. The picture does not include the potential role of catecholamines that are normally present in the extracellular space or that can be released from sympathoadrenergic terminals innervating lymphoid organs and tissues, nor does it include catecholamines, which lymphocytes can encounter when they enter the brain in physiological (or pathological) situations

pathways can be fully exploited as pharmacotherapeutic targets. Indeed, according to experimental and clinical evidence, several key points awaiting clarification are critical for the therapeutic efficacy (or failure) of agents acting on catecholaminergic mechanisms:

- Adrenergic and dopaminergic receptors exist in multiple subtypes 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;

- Receptor dysregulations occurring in disease states is not only specific for the receptor type but even for the cell subset(s).
- Receptors may be acted upon not only by exogenous but also by endogenous catecholamines directly produced by immune cells (Fig. 2.3).
- Dynamic changes occur to receptor expression and responsiveness (and to endogenous catecholamine production) during treatment with immunomodulatory drugs (e.g. the case of IFN- $\beta$  in MS).

Exploitation of AR-operated mechanisms in human immune cells as targets for therapeutic interventions can be approached by several pharmacological strategies, not limited to direct ligation of membrane receptors by agonists/antagonists. The catecholamine systems can be indeed modulated at several levels:

- Intracellular uptake and storage (e.g. using selective inhibitors of NET or VMAT).
- Receptor activation/blockade by selective agonists (e.g.  $\beta$ -AR agonists used in asthma) or antagonists ( $\alpha$ -AR antagonists, e.g. antihypertensives;  $\beta$ -AR antagonists, e.g. beta-blockers).
- Inhibition of catecholamine synthesis (e.g. by using the anti-hypertensive agent alpha-methyl-p-tyrosine, a TH selective inhibitor).
- Enhancement of catecholamine synthesis (e.g. by using the anti-Parkinson drug L-DOPA).
- Inhibition of catecholamine metabolism (e.g. by use of MAO or COMT inhibitors).

Reserpine is currently used as an anti-hypertensive agent, although its use is limited by a burden of adverse effects. Other therapeutic agents however have been shown at least *in vitro* to interfere with the storage of catecholamines in lymphocytes (Fig. 2.3).

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.

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