

Role of nonsynaptic communication in regulating the immune response

Zsolt Selmeczy^{a,*}, E. Sylvester Vizi^a, Balázs Csóka^c, Pál Pacher^b, György Haskó^{a,c}

^aDepartment of Pharmacology, Institute of Experimental Medicine, Hungarian Academy of Sciences, P.O.B. 67, H-1450 Budapest, Hungary

^bSection on Oxidative Stress Tissue Injury, Laboratory of Physiological Studies, National Institutes of Health/NIAAA, 5625 Fishers Lane, Bethesda, MD 20892-9413, USA

^cDepartment of Surgery, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103, USA

Received 27 March 2007; received in revised form 7 June 2007; accepted 8 June 2007

Available online 17 June 2007

Abstract

The discovery of nonsynaptic communication in the 1960s and 1970s was an important milestone in investigating the function of the nervous system, and it revolutionized our view about information transmission between neurons. In addition, nonsynaptic communication has a practical importance not only within the nervous system, but in the communication between the peripheral nervous system and other organ systems. Nonsynaptic communication takes place in different immune organs, which are innervated by sympathetic nerve terminals. In addition, the function of microglia, one of the immunocompetent cell types of the brain, can also be affected by neurotransmitters released from axon varicosities. The various functions of immune cells are modulated by released neurotransmitters without any direct synaptic contact between nerve endings and targeted immune cells requiring only functional neurotransmitter receptors on immune cells. Here, we briefly overview the role of the various receptor subtypes mediating nonsynaptic modulation of the function of immunocompetent cells both in the periphery and in the central nervous system.

© 2007 Elsevier Ltd. All rights reserved.

Keywords: Nonsynaptic communication; Immune cells; Microglia; Adenosine receptors; Adrenergic receptors

1. Introduction

The communication between different cell types of the body is important in maintaining the functioning of the organism, and it is especially important in the nervous system, where billions of cells specialized for information transmission can be found. In the 19th century, Ramon y Cajal, His, Sherrington and others developed the Neuron Theory, specifying a nervous system composed of discrete nerve cells communicating through their synaptic contacts. Information can be transmitted by direct contact between two cells, as in gap junctions, but in mammals' nervous system there is mainly an indirect connection between nerve endings and their targets. Here, the information is transmitted from one neuron to the other one chemically (Dale, 1935; Elliot, 1904; Loewi, 1921). The idea of how information is transmitted chemically from cell to cell was based on the observation that the transmitter acetylcholine

(ACh) is stored in vesicles and released into the synaptic cleft in quanta on the arrival of action potential at the neuromuscular junction (reviewed in Vizi, 2000). The actions of transmitters (GABA, ACh, glutamate, and glycine), which mediate synaptic transmission characterized by ligand-gated ion channels with low affinity for the transmitters, are restricted to the synaptic region. The termination of their actions requires uptake (in case of GABA, glutamate and glycine) or enzymatic degradation (in case of ACh) of transmitters (Vizi et al., 2004). However, it was not at all clear what the mechanism of transmission is in autonomic neuroeffector systems, which are not organized in units, but the innervation is quite diffuse.

In the 1980s it was shown that in many cases there are mismatches between the release sites and localization of receptors sensitive to the chemical signals suggesting the existence of functional interactions between neurons without any synaptic contact (Herkenham, 1987). To explain this controversial phenomenon, the theory of nonsynaptic interaction was formed by Vizi which states that neurotransmitters and/or neuromodulators are released from a varicosity or axon terminal that is devoid of synaptic specialization, and

* Corresponding author at: Institute of Experimental Medicine, Szigyony utca 43, H-1083 Budapest, Hungary. Tel.: +36 1 210 9975; fax: +36 1 210 9423.

E-mail address: selmeczy@koki.hu (Z. Selmeczy).

they diffuse some distance to have their effects at target cells via high-affinity receptors (Vizi, 1984). This nonsynaptic interaction between neurons would be a form of communication that is transitional between discrete classic neurotransmission and the relatively nonspecific neuroendocrine secretion.

This hypothesis was supported by neuroanatomical studies revealing that in those monoaminergic systems in which cell bodies are located in small subcortical nuclei and the rich axon arborisation innervates large brain regions, the majority of monoaminergic varicosities fail to make synaptic contacts in the brain (Descarries and Mechawar, 2000). Thus, monoamines like dopamine, adrenaline (Adr), noradrenaline (NA) and serotonin could be released not only into the synaptic cleft but also directly into the extrasynaptic space. Further studies demonstrated that, in addition to monoaminergic systems, the normal cholinergic innervation of adult rat parietal cortex and hippocampus is predominantly also nonsynaptic (more than 85% of varicosities) (Umbriaco et al., 1994, 1995).

In addition to neuroanatomical studies, functional evidence of nonsynaptic transmission was also provided. It has been shown in the gut (Knoll and Vizi, 1970; Paton and Vizi, 1969; Vizi, 1968, 1974, 1980a; Vizi and Knoll, 1971, 1976) and in the brain (Vizi, 1972, 1974) that in response to the activation of noradrenergic neurons, there is an alpha adrenergic receptor (α -AR)-mediated inhibition of ACh release from neighboring cholinergic terminals. NA depletion by reserpine and guanethidine (Paton and Vizi, 1969; Vizi, 1968) and by 6-hydroxydopamine treatment (Knoll and Vizi, 1970) increased ACh release at rest, as well as in response to nerve activity, suggesting a local permanent control by noradrenergic nerves of cholinergic function (Vizi, 1974). Morphological studies (Silva et al., 1971) showed a lack of synaptic contacts between these partners, confirming the existence of functional nonsynaptic interactions between neurons (Vizi, 1980b, 1984).

Nonsynaptic communication has a practical importance not only within the nervous system but in the communication between peripheral nervous system and other organ systems. Here, we briefly overview the role of nonsynaptic communication between the nervous- and the immune systems, with special focus on the effects of NA, and consequently the activation of adrenergic receptors as well as adenosine and adenosine receptors, in governing immune cell activation.

2. The role of adrenergic receptors in the modulation of immune processes in the periphery

One interesting aspect of nonsynaptic communication is the connection between the sympathetic nervous system and the immune response (Table 1), and Vizi et al. (1995) played an important role in revealing this interaction. They showed the presence of both tyrosine hydroxylase (TH) and dopa- β -hydroxylase (DBH)-immunostained nerve fibers in the thymic capsule, subcapsular region, and connective tissue septa. The vast majority of these nerves was found to be localized around the vasculature, but some TH- and DBH-stained fibers branched into the cortical parenchyma. At the ultrastructural level, noradrenergic varicosities are seen in proximity to thymocytes, mast

cells, fibroblasts, and eosinophils (Novotny et al., 1990; Vizi et al., 1995). Similarly, the presence of noradrenergic fibers was demonstrated in the spleen (Felten et al., 1985; Felten and Olschowka, 1987; Klein et al., 1982; Williams and Felten, 1981), in lymph nodes and tonsils (Felten et al., 1984; Fink and Weihe, 1988; Novotny and Kliche, 1986), in the bone marrow (Felten et al., 1988), and in mucosa-associated lymphoid tissues (Bellinger et al., 1992; Bienenstock et al., 1989; Carpenter et al., 1998; Cooke, 1986; Felten et al., 1985; Weihe et al., 1991).

Adr and NA, after released from axon varicosities, mediate their effects on target cells via stimulation of two principal receptors: alpha (α) and beta (β) adrenergic receptors (ARs). These receptors are subdivided into α_1 , α_2 , β_1 , β_2 and β_3 subtypes. Virtually all lymphoid cells express β -ARs, with exception of T helper T(h)2 cells, and the numbers of β -ARs differ between different types of lymphoid cells (Elenkov et al., 2000). Expression of β_2 -ARs was demonstrated on the surface of Th1 cells, thymocytes, thymic epithelial cells, neutrophils, basophils, eosinophils, B cells, and monocytes (Kurz et al., 1997; Maisel et al., 1989; Plaut, 1987; Sanders et al., 1997; Yukawa et al., 1990), but not on Th2 cells (Sanders et al., 1997). The presence of α_2 -ARs on peripheral blood mononuclear cells (PBMC) that contain mainly lymphocytes and monocytes, is controversial. No α_1 - and α_2 -ARs could be identified on platelet-depleted mononuclear cells (Casale and Kaliner, 1984), in contrast to preliminary reports showing the presence of α_2 -ARs on PBMCs. However, some functional studies implicate both α_1 - and α_2 -ARs in modulation of some immune parameters. Thus, alternatively, α -ARs probably are not expressed under normal conditions on lymphocytes and monocytes; however, they may be expressed in certain lymphoid compartments, such as alveolar and peritoneal macrophages, or hematopoietic cells, or under certain pathologic conditions (Elenkov et al., 2000).

In vivo, both increasing sympathetic outflow and augmenting the release of catecholamines by selective α_2 -AR antagonists, as well as applying exogenous catecholamines or blocking noradrenaline transporters genetically or chemically results in inhibition of lipopolysaccharide (LPS)-induced tumour necrosis factor-alpha (TNF- α) (Elenkov et al., 1995; Selmečzy et al., 2003; Szelenyi et al., 2000a,b; Szelenyi and Selmečzy, 2002), interleukin (IL)-6 (Hasko et al., 1995), macrophage inflammatory protein (MIP)-1 α (Hasko et al., 1998c), and IL-12 production (Elenkov et al., 1995; Hasko et al., 1998d). In studying the modulation of cellular and humoral immunity by catecholamines, nonselective β - and selective β_2 -AR agonists were shown to inhibit the production of IL-12, TNF- α , MIP-1 α and nitric oxide (NO) by monocytes and dendritic cells in both in vitro and in vivo conditions (Hasko et al., 1998a,c; Panina-Bordignon et al., 1997). Furthermore, it was demonstrated that β_2 -AR agonists inhibited the development of Th1-type cells, and the production of TNF- α by LPS-treated monocytes, microglial cells, and astrocytes (Hetier et al., 1991; Nakamura et al., 1998; Severn et al., 1992; van der Poll et al., 1994), while promoting Th2 cell differentiation (Panina-Bordignon et al., 1997). Meanwhile, the production of IL-10, which is one of the most potent anti-inflammatory cytokines induced by LPS in human monocytes or mouse peritoneal macrophages, is potentiated by

Table 1
Milestones in revealing the role of nonsynaptic communication in regulating immune response

Event	References
Developing Neuron Theory	Ramon y Cajal, His, Sherington, 19th century
Description of chemical transmission	Elliot (1904), Dale (1935), and Loewi (1921)
First functional evidence of nonsynaptic transmission	Vizi (1968)
Demonstration of the presence of noradrenergic fibers in immune organs	Vizi et al. (1995), Felten et al. (1985), Novotny et al. (1990), Weihe et al. (1991) and others
Forming of hypothesis of nonsynaptic transmission	Vizi (1984)
Demonstration of expression of β -ARs on the surface of Th1 cells but not on Th2	Kurz et al. (1997), Maisel et al. (1989), Plaut (1987), Sanders et al. (1997), Yukawa et al. (1990), and others
Revealing the effect of NA on the cytokine- and chemokine production, and the development of different types of Th cells	Elenkov et al. (1995), Hasko et al. (1995, 1998a,b,c,d), van der Poll et al. (1994), and others
Revealing effects of Adr and NA on microglia immune functions	Whittemore et al. (1993), Mori et al. (2002), Farber et al. (2005), Dello Russo et al. (2004)
Demonstration of expression of adenosine receptors on lymphoid cells	Reviewed by Cronstein (1994)
Demonstration of presence of adrenergic receptors on microglia	Chang and Liu (2000), Colton and Chernyshev (1996), Fujita et al. (1998), Thery et al. (1994)
Neuroanatomical evidence of nonsynaptic transmission	Umbriaco et al. (1994, 1995), Descarries and Mechawar (2000), and others
Revealing the effects of adenosine on immune functions	Hasko et al. (1996, 1998a,b,c,d, 2000a,b), Cronstein (1994), Di Virgilio et al. (1996), and others
Demonstration of the presence of adenosine receptors on microglia	Gebicke-Haerter et al. (1996), Si et al. (1996), Hammarberg et al. (2003), Wittendorp et al. (2004), and others
Demonstration of the presence of α - and β -AR mRNA in microglia	Mori et al. (2002)

NA, Adr, and β_2 -AR agonists, an effect that is β_2 -AR-mediated and cAMP-PKA-dependent (Elenkov et al., 1996; Siegmund et al., 1998; Suberville et al., 1996; van der Poll et al., 1996).

The clinical relevance of these findings was recently highlighted in studies demonstrating that the presence of brain injury in trauma patients is an independent risk factor for infectious complications, due to a CNS-mediated shutdown of the immune defense (Rodriguez et al., 1991; Hsieh et al., 1992). In addition, Prass et al. (2003) showed that experimental cerebral ischemia induces a long-lasting depression of cell-mediated immunity during spontaneous bacteremia and pneumonia, and the occurrence of these life-threatening phenomena could be only prevented by blocking the sympathetic nervous system, but not the hypothalamic–pituitary–adrenal axis, suggesting that catecholamine-mediated lymphocyte dysfunction may be a key factor in the impaired antibacterial immune response after stroke.

3. The role of adenosine in the peripheral immunomodulation

Adenosine is a purine nucleoside that can be released directly from cells (Mitchell et al., 1993) into the extracellular space, or decomposed from ATP, which is co-released and acts as a co-transmitter with NA in the nervous system (Sperlagh and Vizi, 1996). In the immune system, purine nucleosides and nucleotides provide energy for protein synthesis, proteolysis, RNA synthesis, Na^+K^+ ATPase and Ca^{2+} ATPase (Buttgereit et al., 1991), and they can also act as extracellular messengers during an immune response. Different subtypes of both ATP (P2) and adenosine (P1) receptors are expressed on lymphoid cells (Collo et al., 1997; Cronstein, 1994) which regulate diverse immune functions, such as phagocytosis, cytotoxicity, cytokine, chemokine and NO production (Cronstein, 1994; Di

Virgilio et al., 1996; Hasko et al., 1996, 1998b, 2000a,b; Nemeth et al., 2005; Sperlagh et al., 1998; Szabo et al., 1998). These receptors may, therefore, contribute to the modulation of different immunopathological states such as polymicrobial sepsis, trauma/hemorrhagic shock, or colitis (Hasko et al., 2006a,b; Mabley et al., 2003; Nemeth et al., 2006; Csoka et al., 2007).

4. Effect of adrenergic receptor activation on microglial function

Microglia are resident brain mononuclear phagocytes, and have functions similar to those of other tissue macrophages, including phagocytosis, antigen presentation, and production of cytokines, chemokines, eicosanoids, complement components, matrix metalloproteinases, oxidative radicals, and NO (Aloisi et al., 2001). They play a critical role as resident immunocompetent and phagocytic cells in the CNS (Kreutzberg, 1996; Perry and Gordon, 1988), and serve as scavenger cells in the event of infection, inflammation, trauma, ischemia, and neurodegeneration (Gonzalez-Scarano and Baltuch, 1999; McGeer and McGeer, 1995; Thomas, 1992). Despite sharing a common monocytic progenitor with macrophages present in other tissues or associated with the CNS, the ramified microglia found in the normal adult CNS display a downregulated (or perhaps less differentiated) phenotype characterized by lack of endocytic and phagocytic activity, low expression of the leukocyte common antigen (CD45), and low to undetectable levels of membrane ligands and receptors that are essential for mediating or inducing typical macrophage functions (Kreutzberg, 1996; Sedgwick and Hickey, 1997). During various pathological processes including degenerative neurological diseases, neurotoxic neuronal death, and ischemia-induced neuronal death, microglia actively proliferate, change their

ramified shape into an amoeboid one, and begin to phagocytose degenerating cells (Kreutzberg, 1996). These cells are called activated microglia. Activated microglia express more macrophage properties than resting microglia, and they can secrete neurotoxic substances as well as potentially neuroprotective factors (Fujita et al., 1998; Young et al., 1999). Thus, microglia may play a key role in the repair response to neurodegenerative diseases, but they also may confound repair systems under certain circumstances, leading to improper degradation of functional systems, or deposition of unmanageable debris (Whittemore et al., 1993). Microglia express receptors for classical neurotransmitters, such as glutamate (Noda et al., 2000) and GABA (Kuhn et al., 2004), and the presence of adrenergic receptors was also demonstrated (Chang and Liu, 2000; Colton and Chernyshev, 1996; Fujita et al., 1998; They et al., 1994). This suggests that there may be a signaling loop between microglia and neurons. Microglial processes have been reported to be associated with synapses anatomically (Pow et al., 1989), and microglia may also respond to “volume neurotransmission” (Thomas, 1992), in which transmitters may exist and act extrasynaptically.

Adr and NA are both potent regulators of microglial function. It was demonstrated that NA induces an increase in intracellular calcium concentration in microglia (Whittemore et al., 1993). NA can also inhibit IFN- γ -induced microglial expression of Fc receptor and major histocompatibility complex class II (MHC II) antigens (Loughlin et al., 1993). NA has been shown to suppress LPS-induced TNF- α (Mori et al., 2002), IL-6 (Farber et al., 2005), and IL-1 β (Dello Russo et al., 2004) production. NA upregulates the expression of mRNA of 3-phosphoglycerate dehydrogenase (Mori et al., 2002), an enzyme that catalyzes the first step of the synthesis of L-serine and glycine from 3-phosphoglycerate (Greenberg and Ichihara, 1957; Ichihara and Greenberg, 1955), thus decreasing the demand of microglial cells for both amino acids, and enabling neurons to utilize more L-serine and glycine released from astrocytes (Mori et al., 2002). The proliferation of microglia is suppressed by Adr in a concentration-dependent manner (Fujita et al., 1998), while both Adr and NA has an inhibitory effect on microglial NO production (Chang and Liu, 2000), but Adr is more potent than NA.

The expression of α_{1A} -, α_{2A} -, β_1 -, and β_2 -AR mRNAs was demonstrated in cultured rat microglial cells, while the expression of α_{1B} -, α_{1D} -, and β_3 -AR mRNA was not detectable (Mori et al., 2002). Microglia respond to the nonselective β -AR agonist isoproterenol, selective β_1 -AR agonist dobutamine, and selective β_2 -AR agonist terbutaline with an increase in intracellular cAMP, and this increase can be completely blocked by the nonselective $\beta_{1,2}$ -AR antagonist propranolol, the selective β_1 -AR antagonist acebutolol, and the selective β_2 -AR antagonist butoxamine, respectively (Tanaka et al., 2002). Activation of β -AR by isoproterenol increases the LPS-induced release of prostaglandin (PG) E₂, PGD₂, and thromboxane A₂ (Minghetti and Levi, 1995), while it suppresses proliferation (Zhang et al., 2002), LPS-induced TNF- α (Hetier et al., 1991; Levi et al., 1993), NO (Chang and Liu, 2000), and PMA-stimulated superoxide anion (Colton and Chernyshev, 1996)

production of microglial cells. Isoproterenol itself has no effects on these events, but it induces the accumulation of IL-1 α and IL-1 β mRNA, without enhancing the production of bioactive IL-1. Moreover, isoproterenol inhibits LPS-induced IL-1 production (Hetier et al., 1991). The $\beta_{1,2}$ -AR antagonist propranolol prevents the direct effect of isoproterenol on the expression of IL-1 β mRNA as well as on LPS-evoked prostanoïd and NO production, and PMA-induced superoxide anion production (Chang and Liu, 2000; Colton and Chernyshev, 1996; Minghetti and Levi, 1995; Tomozawa et al., 1995). Furthermore, propranolol was shown to reverse the cAMP-elevating effect of NA (Tanaka et al., 2002), and the inhibition of LPS-induced NO accumulation by NA (Dello Russo et al., 2004). These observations strongly suggest that β -ARs have a critical role in the regulation of microglia functions.

To identify whether the β_1 -, or β_2 -AR mediates adrenergic signals, experiments were performed utilizing subtype selective agonist and antagonists. It was shown that the β_2 -AR selective agonist terbutaline significantly suppresses microglial proliferation, while the β_1 -AR selective agonist dobutamine increases the number of proliferating cell nuclear antigen-positive microglial cells (Fujita et al., 1998). Furthermore, the β_2 -AR antagonist butoxamine and nonselective antagonist oxprenolol but not the β_1 -AR antagonist acebutolol abolishes the inhibitory effect of Adr and isoproterenol on microglial proliferation (Fujita et al., 1998). The β_2 -AR selective agonist salbutamol and procaterol, and nonselective β -AR agonist isoproterenol decreases LPS-induced IL-12 release, whereas the release of MIP-1 α and IL-6 is not affected, and TNF- α is only slightly inhibited at the same dose (Prinz et al., 2001). The β_2 -AR selective antagonist ICI-118,551 completely prevents the inhibitory effect of NA on NO accumulation (Dello Russo et al., 2004), while another β_2 -AR selective antagonist, ICI-1158 has been shown to prevent the inhibitory effect of NA on LPS-dependent IL-1 β release (Madrigal et al., 2005). It is interesting to note that although NA has a higher affinity for the β_1 -AR than β_2 -AR, and both receptors stimulate adenylyl cyclase (Bylund et al., 1994), the expression level of β_1 -AR is lower than that of β_2 -AR in microglial cells. Therefore, the action of NA through β_2 -AR on microglial cells appears to be more important than that through β_1 -AR (Mori et al., 2002).

Although the presence of α_{1A} - and α_{2A} -AR mRNA was demonstrated on microglia, the role of α -ARs in the regulation of microglial function has been less intensively studied. The treatment of microglial cells with the α_1 -AR agonist phenylephrine leads to a dose-dependent decrease of LPS-induced NO production, but the IC₅₀ of phenylephrine is higher than that of isoproterenol (Chang and Liu, 2000). Phenylephrine suppresses the expression of LPS-induced IL-6 mRNA and to a lesser extent TNF- α mRNA as well as the release of TNF- α , while the α_2 -AR agonist clonidine does not affect the expression of both mRNAs or the release of both cytokines. Clonidine, however, upregulates the expression of the mRNA that encodes catechol-*O*-methyl-transferase, an important enzyme for the catabolism of NA, and the expression of the mRNA encoding Bcl-xL, an anti-apoptotic factor (Mori et al., 2002). The α_{2A} -AR specific agonist BRL 44408 maleate and

α_{2B} -AR specific agonist imiloxan hydrochloride inhibit the effect of NA on LPS-induced NO release, and application of the α -AR agonist metaraminol induces outward currents and/or reduced inward currents in microglia (Farber et al., 2005). It should be noted that, compared with the β_1 - and β_2 -AR, α_1 - and α_2 -ARs couple to different signaling pathways: α_1 -AR activation induces an increase in inositol phosphate (IP)-turnover and the subsequent rise in intracellular Ca^{2+} concentration (Bylund et al., 1994). Nevertheless, there may be crosstalk between the cAMP-dependent and IP-turnover-dependent signaling systems in microglial cells, which is supported by the observation that there were no differences between the effects of three selective adrenergic agonists, phenylephrine (α_1 -AR), dobutamine (β_1 -AR) and terbutaline (β_2 -AR) on the expression of mRNA encoding TNF- α and the release of TNF- α (Mori et al., 2002). On the other hand, the α_2 -AR inhibits adenylyl cyclase (Bylund et al., 1994), and it appears to act on microglial cells by a mechanism that is different from that used by the other adrenergic receptors.

5. Effect of adenosine receptor activation on microglial function

Functional and pharmacological data have shown that adenosine receptors are expressed on microglia cells; however, results vary concerning the expression of the different adenosine receptor subtypes (Boucein et al., 2003; Hammarberg et al., 2003; Hasko et al., 2005). Simultaneous stimulation of A_1 and A_2 receptors results in the proliferation of naive microglial cells (Gebicke-Haerter et al., 1996), but PMA-stimulated microglial proliferation can be reduced following treatment with an A_1 receptor agonist (Si et al., 1996). Meanwhile, adenosine can also evoke the apoptosis of microglia, which effect is mediated by an atypical adenosine receptor (Ogata and Schubert, 1996). A_{2A} receptors have a role in cAMP-mediated regulation of nerve growth factor (Heese et al., 1997), cyclooxygenase (Fiebich et al., 1996) and K^+ channel (Kust et al., 1999) expression, and in microglial proliferation (Gebicke-Haerter et al., 1996). The A_{2B} receptor, on the other hand, has only been detected by RT-PCR (Hammarberg et al., 2003; Wittendorp et al., 2004), and there are no published reports of the presence of functional A_{2B} receptors on microglia. The presence of functional A_3 receptors was demonstrated in immortalized murine microglial cell lines and primary microglia isolated from mice (Hammarberg et al., 2003). The activation of A_3 receptors inhibits LPS-induced TNF- α production by microglia (Lee et al., 2006), and it completely abolishes the ischemia-induced microglial infiltration after injury, whereas receptor stimulation prior to the injury strongly augments microglial presence in the injured region compared to untreated control (Von Lubitz et al., 2001).

6. Concluding remarks

The discovery of nonsynaptic communication was a revolutionary moment that changed our thinking about the function of the nervous system. At that moment, the

physiological importance of this phenomenon was not clearly understood but today accumulating evidence indicates that this crosstalk is an important constituent of higher brain function. In addition to its contribution to communication between neurons, nonsynaptic communication has an important role in transmitting information between the nervous system and other organ systems. One typical example of this is the relationship between the nervous and the immune systems. Evidence accumulated in the last decades indicating that, peripherally, both NA released from the nonsynaptic nerve terminals in lymphoid organs and blood vessels and Adr released from adrenal medulla are involved in fine-tuning an immune response (Elenkov et al., 2000). Similarly, accumulating data document the modulatory effects of adenosine on immune processes on the periphery (Hasko et al., 2006a). These findings provide us with more knowledge in understanding better the complexity of peripheral immune responses, which may contribute to the development of more effective posttraumatic therapies.

Alternatively, where would nonsynaptic interactions between neurons and immunocompetent cells be more important than in the brain, where microglia, the immunocompetent cells of the brain, can contribute to the development of neurological disorders like Parkinson's disease, Alzheimer's disease, multiple sclerosis, and stroke? In addition, recent studies showed that neurotoxic amphetamine derivatives such as 3,4-methylenedioxymethamphetamine (commonly referred to as Ecstasy), which is a popular recreational drug, also provoke microglial activation, which leads to the release of pro-inflammatory mediators and other injury response factors that ultimately compromise neuronal and oligodendroglial viability (Orio et al., 2004; Thomas et al., 2004; Zhang et al., 2006). These observations indicate that the modulatory roles of both adrenergic and purinergic receptors in regulating microglial functions may be utilized in developing new therapeutic strategies in the treatment of classical pathological conditions as well as neurological damage in people suffering from drug abuse.

Acknowledgements

This study was supported by the Hungarian Research Fund (OTKA T 46520, T 49537, T 46896), the Hungarian National R&D Programme (NKFP 1A/036/2004) and National Institutes of Health Grant R01 GM66189.

References

- Aloisi, F., Ambrosini, E., Columba-Cabezas, S., Magliozzi, R., Serafini, B., 2001. Intracerebral regulation of immune responses. *Ann. Med.* 33, 510–515.
- Bellinger, D.L., Lorton, D., Felten, S.Y., Felten, D.L., 1992. Innervation of lymphoid organs and implications in development, aging, and autoimmunity. *Int. J. Immunopharmacol.* 14, 329–344.
- Bienenstock, J., Croitoru, K., Ernst, P.B., Stanis, A.M., 1989. Nerves and neuropeptides in the regulation of mucosal immunity. *Adv. Exp. Med. Biol.* 257, 19–26.
- Boucein, C., Zacharias, R., Farber, K., Pavlovic, S., Hanisch, U.K., Kettenmann, H., 2003. Purinergic receptors on microglial cells: functional expres-

- sion in acute brain slices and modulation of microglial activation in vitro. *Eur. J. Neurosci.* 17, 2267–2276.
- Buttgereit, F., Muller, M., Rapoport, S.M., 1991. Quantification of ATP-producing and consuming processes in quiescent pig spleen lymphocytes. *Biochem. Int.* 24, 59–67.
- Bylund, D.B., Eikenberg, D.C., Hieble, J.P., Langer, S.Z., Lefkowitz, R.J., Minneman, K.P., Molinoff, P.B., Ruffolo Jr., R.R., Trendelenburg, U., 1994. International Union of Pharmacology nomenclature of adrenoceptors. *Pharmacol. Rev.* 46, 121–136.
- Carpenter, G.H., Garrett, J.R., Hartley, R.H., Proctor, G.B., 1998. The influence of nerves on the secretion of immunoglobulin A into submandibular saliva in rats. *J. Physiol.* 512 (Pt 2), 567–573.
- Casale, T.B., Kaliner, M., 1984. Demonstration that circulating human blood cells have no detectable alpha 1-adrenergic receptors by radioligand binding analysis. *J. Allergy Clin. Immunol.* 74, 812–818.
- Chang, J.Y., Liu, L.Z., 2000. Catecholamines inhibit microglial nitric oxide production. *Brain Res. Bull.* 52, 525–530.
- Collo, G., Neidhart, S., Kawashima, E., Kosco-Vilbois, M., North, R.A., Buell, G., 1997. Tissue distribution of the P2X7 receptor. *Neuropharmacology* 36, 1277–1283.
- Colton, C.A., Chernyshev, O.N., 1996. Inhibition of microglial superoxide anion production by isoproterenol and dexamethasone. *Neurochem. Int.* 29, 43–53.
- Cooke, H.J., 1986. Neurobiology of the intestinal mucosa. *Gastroenterology* 90, 1057–1081.
- Cronstein, B.N., 1994. Adenosine, an endogenous anti-inflammatory agent. *J. Appl. Physiol.* 76, 5–13.
- Csoka, B., Nemeth, Z.H., Virag, L., Gergely, P., Leibovich, S.J., Pacher, P., Sun, C.X., Blackburn, M.R., Vizi, E.S., Deitch, E.A., Hasko, G., 2007. A2A adenosine receptors and C/EBP[β] are crucially required for IL-10 production by macrophages exposed to *E. coli*. *Blood* 110, 2685–2695.
- Dale, H., 1935. Pharmacology and nerve endings. *Proc. R. Soc. Med. Ther. Sect.* 28, 319–332.
- Dello Russo, C., Boullerne, A.I., Gavriljuk, V., Feinstein, D.L., 2004. Inhibition of microglial inflammatory responses by norepinephrine: effects on nitric oxide and interleukin-1 β production. *J. Neuroinflamm.* 1, 9.
- Descaries, L., Mechawar, N., 2000. Ultrastructural evidence for diffuse transmission by monoamine and acetylcholine neurons of the central nervous system. *Prog. Brain Res.* 125, 27–47.
- Di Virgilio, F.P., Ferrari, D., Chiozzi, P., Falzoni, S., Sanz, J.M., dal Susino, M., Mutini, C., Hanau, S., Baricordi, O.R., 1996. Purinoceptor function in the immune system. *Drug Dev. Res.* 39, 319–329.
- Elenkov, I.J., Hasko, G., Kovacs, K.J., Vizi, E.S., 1995. Modulation of lipopolysaccharide-induced tumor necrosis factor- α production by selective alpha- and beta-adrenergic drugs in mice. *J. Neuroimmunol.* 61, 123–131.
- Elenkov, I.J., Papanicolaou, D.A., Wilder, R.L., Chrousos, G.P., 1996. Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. *Proc. Assoc. Am. Phys.* 108, 374–381.
- Elenkov, I.J., Wilder, R.L., Chrousos, G.P., Vizi, E.S., 2000. The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. *Pharmacol. Rev.* 52, 595–638.
- Elliot, T.R., 1904. On the action of adrenaline. *J. Physiol. (Lond.)* 31, 21.
- Farber, K., Pannasch, U., Kettenmann, H., 2005. Dopamine and noradrenaline control distinct functions in rodent microglial cells. *Mol. Cell. Neurosci.* 29, 128–138.
- Felten, D.L., Felten, S.Y., Carlson, S.L., Olschowka, J.A., Livnat, S., 1985. Noradrenergic and peptidergic innervation of lymphoid tissue. *J. Immunol.* 135, 755s–765s.
- Felten, D.L., Livnat, S., Felten, S.Y., Carlson, S.L., Bellinger, D.L., Yeh, P., 1984. Sympathetic innervation of lymph nodes in mice. *Brain Res. Bull.* 13, 693–699.
- Felten, S.Y., Felten, D.L., Bellinger, D.L., Carlson, S.L., Ackerman, K.D., Madden, K.S., Olschowka, J.A., Livnat, S., 1988. Noradrenergic sympathetic innervation of lymphoid organs. *Prog. Allergy* 43, 14–36.
- Felten, S.Y., Olschowka, J., 1987. Noradrenergic sympathetic innervation of the spleen. II. Tyrosine hydroxylase (TH)-positive nerve terminals form synaptic contacts on lymphocytes in the splenic white pulp. *J. Neurosci. Res.* 18, 37–48.
- Fiebich, B.L., Biber, K., Lieb, K., van Calker, D., Berger, M., Bauer, J., Gebicke-Haerter, P.J., 1996. Cyclooxygenase-2 expression in rat microglia is induced by adenosine A2a-receptors. *Glia* 18, 152–160.
- Fink, T., Weihe, E., 1988. Multiple neuropeptides in nerves supplying mammalian lymph nodes: messenger candidates for sensory and autonomic neuroimmunomodulation? *Neurosci. Lett.* 90, 39–44.
- Fujita, H., Tanaka, J., Maeda, N., Sakanaka, M., 1998. Adrenergic agonists suppress the proliferation of microglia through beta 2-adrenergic receptor. *Neurosci. Lett.* 242, 37–40.
- Gebicke-Haerter, P.J., Christoffel, F., Timmer, J., Northoff, H., Berger, M., Van Calker, D., 1996. Both adenosine A1- and A2-receptors are required to stimulate microglial proliferation. *Neurochem. Int.* 29, 37–42.
- Gonzalez-Scarano, F., Baltuch, G., 1999. Microglia as mediators of inflammatory and degenerative diseases. *Ann. Rev. Neurosci.* 22, 219–240.
- Greenberg, D.M., Ichihara, A., 1957. Further studies on the pathway of serine formation from carbohydrate. *J. Biol. Chem.* 224, 331–340.
- Hammarberg, C., Schulte, G., Fredholm, B.B., 2003. Evidence for functional adenosine A3 receptors in microglia cells. *J. Neurochem.* 86, 1051–1054.
- Hasko, G., Elenkov, I.J., Kvetan, V., Vizi, E.S., 1995. Differential effect of selective block of alpha 2-adrenoceptors on plasma levels of tumour necrosis factor- α , interleukin-6 and corticosterone induced by bacterial lipopolysaccharide in mice. *J. Endocrinol.* 144, 457–462.
- Hasko, G., Szabo, C., Nemeth, Z.H., Kvetan, V., Pastores, S.M., Vizi, E.S., 1996. Adenosine receptor agonists differentially regulate IL-10, TNF- α , and nitric oxide production in RAW 264.7 macrophages and in endotoxemic mice. *J. Immunol.* 157, 4634–4640.
- Hasko, G., Nemeth, Z.H., Szabo, C., Zsilla, G., Salzman, A.L., Vizi, E.S., 1998a. Isoproterenol inhibits IL-10, TNF- α , and nitric oxide production in RAW 264.7 macrophages. *Brain Res. Bull.* 45, 183–187.
- Hasko, G., Nemeth, Z.H., Vizi, E.S., Salzman, A.L., Szabo, C., 1998b. An agonist of adenosine A3 receptors decreases interleukin-12 and interferon- γ production and prevents lethality in endotoxemic mice. *Eur. J. Pharmacol.* 358, 261–268.
- Hasko, G., Shanley, T.P., Egnaczyk, G., Nemeth, Z.H., Salzman, A.L., Vizi, E.S., Szabo, C., 1998c. Exogenous and endogenous catecholamines inhibit the production of macrophage inflammatory protein (MIP) 1 α via a beta adrenoceptor mediated mechanism. *Br. J. Pharmacol.* 125, 1297–1303.
- Hasko, G., Szabo, C., Nemeth, Z.H., Salzman, A.L., Vizi, E.S., 1998d. Stimulation of beta-adrenoceptors inhibits endotoxin-induced IL-12 production in normal and IL-10 deficient mice. *J. Neuroimmunol.* 88, 57–61.
- Hasko, G., Kuhel, D.G., Chen, J.F., Schwarzschild, M.A., Deitch, E.A., Mabley, J.G., Marton, A., Szabo, C., 2000a. Adenosine inhibits IL-12 and TNF- α production via adenosine A2a receptor-dependent and independent mechanisms. *FASEB J.* 14, 2065–2074.
- Hasko, G., Kuhel, D.G., Salzman, A.L., Szabo, C., 2000b. ATP suppression of interleukin-12 and tumour necrosis factor- α release from macrophages. *Br. J. Pharmacol.* 129, 909–914.
- Hasko, G., Pacher, P., Vizi, E.S., Illes, P., 2005. Adenosine receptor signaling in the brain immune system. *Trends Pharmacol. Sci.* 26, 511–516.
- Hasko, G., Cronstein, B.N., Szabo, C., 2006a. Adenosine Receptors: Therapeutic Aspects for Inflammatory and Immune Diseases. Taylor & Francis Group, Boca Raton.
- Hasko, G., Xu, D.Z., Lu, Q., Nemeth, Z.H., Jabush, J., Berezina, T.L., Zaets, S.B., Csoka, B., Deitch, E.A., 2006b. Adenosine A2A receptor activation reduces lung injury in trauma/hemorrhagic shock. *Crit. Care Med.* 34, 1119–1125.
- Heese, K., Fiebich, B.L., Bauer, J., Otten, U., 1997. Nerve growth factor (NGF) expression in rat microglia is induced by adenosine A2a-receptors. *Neurosci. Lett.* 231, 83–86.
- Herkenham, M., 1987. Mismatches between neurotransmitter and receptor localizations in brain: observations and implications. *Neuroscience* 23, 1–38.
- Hetier, E., Ayala, J., Bousseau, A., Prochiantz, A., 1991. Modulation of interleukin-1 and tumor necrosis factor expression by beta-adrenergic agonists in mouse ameboid microglial cells. *Exp. Brain Res.* 86, 407–413.

- Hsieh, A.H., Bishop, M.J., Kubilis, P.S., Newell, D.W., Pierson, D.J., 1992. Pneumonia following closed head injury. *Am. Rev. Respir. Dis.* 146, 290–294.
- Ichihara, A., Greenberg, D.M., 1955. Pathway of serine formation from carbohydrate in rat liver. *Proc. Natl. Acad. Sci. U.S.A.* 41, 605–609.
- Klein, R.L., Wilson, S.P., Dzielak, D.J., Yang, W.H., Viveros, O.H., 1982. Opioid peptides and noradrenaline co-exist in large dense-cored vesicles from sympathetic nerve. *Neuroscience* 7, 2255–2261.
- Knoll, J., Vizi, E.S., 1970. Presynaptic inhibition of acetylcholine release by endogenous and exogenous noradrenaline at high rate of stimulation. *Br. J. Pharmacol.* 40, 554P–555P.
- Kreutzberg, G.W., 1996. Microglia: a sensor for pathological events in the CNS. *Trends Neurosci.* 19, 312–318.
- Kuhn, S.A., van Landeghem, F.K., Zacharias, R., Farber, K., Rappert, A., Pavlovic, S., Hoffmann, A., Nolte, C., Kettenmann, H., 2004. Microglia express GABA(B) receptors to modulate interleukin release. *Mol. Cell. Neurosci.* 25, 312–322.
- Kurz, B., Feindt, J., von Gaudecker, B., Kranz, A., Loppnow, H., Mentlein, R., 1997. Beta-adrenoceptor-mediated effects in rat cultured thymic epithelial cells. *Br. J. Pharmacol.* 120, 1401–1408.
- Kust, B.M., Biber, K., van Calker, D., Gebicke-Haerter, P.J., 1999. Regulation of K⁺ channel mRNA expression by stimulation of adenosine A_{2A}-receptors in cultured rat microglia. *Glia* 25, 120–130.
- Lee, J.Y., Jhun, B.S., Oh, Y.T., Lee, J.H., Choe, W., Baik, H.H., Ha, J., Yoon, K.S., Kim, S.S., Kang, I., 2006. Activation of adenosine A₃ receptor suppresses lipopolysaccharide-induced TNF- α production through inhibition of PI 3-kinase/Akt and NF- κ B activation in murine BV2 microglial cells. *Neurosci. Lett.* 396, 1–6.
- Levi, G., Patrizio, M., Bernardo, A., Petrucci, T.C., Agresti, C., 1993. Human immunodeficiency virus coat protein gp120 inhibits the beta-adrenergic regulation of astroglial and microglial functions. *Proc. Natl. Acad. Sci. U.S.A.* 90, 1541–1545.
- Loewi, O., 1921. Über humorale Übertragbarkeit der Herznerve Wirkung. *Pflügers Arch. Gesamte Physiol.* 189, 239–242.
- Loughlin, A.J., Woodroffe, M.N., Czuzner, M.L., 1993. Modulation of interferon-gamma-induced major histocompatibility complex class II and Fc receptor expression on isolated microglia by transforming growth factor-beta 1, interleukin-4, noradrenaline and glucocorticoids. *Immunology* 79, 125–130.
- Mabley, J., Soriano, F., Pacher, P., Hasko, G., Marton, A., Wallace, R., Salzman, A., Szabo, C., 2003. The adenosine A₃ receptor agonist, N⁶-(3-iodobenzyl)-adenosine-5'-N-methyluronamide, is protective in two murine models of colitis. *Eur. J. Pharmacol.* 466, 323–329.
- Madrigal, J.L., Feinstein, D.L., Dello Russo, C., 2005. Norepinephrine protects cortical neurons against microglial-induced cell death. *J. Neurosci. Res.* 81, 390–396.
- Maisel, A.S., Fowler, P., Rearden, A., Motulsky, H.J., Michel, M.C., 1989. A new method for isolation of human lymphocyte subsets reveals differential regulation of beta-adrenergic receptors by terbutaline treatment. *Clin. Pharmacol. Ther.* 46, 429–439.
- McGeer, P.L., McGeer, E.G., 1995. The inflammatory response system of brain: implications for therapy of Alzheimer and other neurodegenerative diseases. *Brain Res.* 21, 195–218.
- Minghetti, L., Levi, G., 1995. Induction of prostanoid biosynthesis by bacterial lipopolysaccharide and isoproterenol in rat microglial cultures. *J. Neurochem.* 65, 2690–2698.
- Mitchell, J.B., Lupica, C.R., Dunwiddie, T.V., 1993. Activity-dependent release of endogenous adenosine modulates synaptic responses in the rat hippocampus. *J. Neurosci.* 13, 3439–3447.
- Mori, K., Ozaki, E., Zhang, B., Yang, L., Yokoyama, A., Takeda, I., Maeda, N., Sakanaka, M., Tanaka, J., 2002. Effects of norepinephrine on rat cultured microglial cells that express alpha₁, alpha₂, beta₁ and beta₂ adrenergic receptors. *Neuropharmacology* 43, 1026–1034.
- Nakamura, A., Johns, E.J., Imaizumi, A., Abe, T., Kohsaka, T., 1998. Regulation of tumour necrosis factor and interleukin-6 gene transcription by beta₂-adrenoceptor in the rat astrocytes. *J. Neuroimmunol.* 88, 144–153.
- Nemeth, Z.H., Csoka, B., Wilmanski, J., Xu, D., Lu, Q., Ledent, C., Deitch, E.A., Pacher, P., Spolarics, Z., Hasko, G., 2006. Adenosine A_{2A} receptor inactivation increases survival in polymicrobial sepsis. *J. Immunol.* 176, 5616–5626.
- Nemeth, Z.H., Lutz, C.S., Csoka, B., Deitch, E.A., Leibovich, S.J., Gause, W.C., Tone, M., Pacher, P., Vizi, E.S., Hasko, G., 2005. Adenosine augments IL-10 production by macrophages through an A_{2B} receptor-mediated posttranscriptional mechanism. *J. Immunol.* 175, 8260–8270.
- Noda, M., Nakanishi, H., Nabekura, J., Akaike, N., 2000. AMPA-kainate subtypes of glutamate receptor in rat cerebral microglia. *J. Neurosci.* 20, 251–258.
- Novotny, G.E., Kliche, K.O., 1986. Innervation of lymph nodes: a combined silver impregnation and electron-microscopic study. *Acta Anat.* 127, 243–248.
- Novotny, G.E., Sommerfeld, H., Zirbes, T., 1990. Thymic innervation in the rat: a light and electron microscopical study. *J. Comp. Neurol.* 302, 552–561.
- Ogata, T., Schubert, P., 1996. Programmed cell death in rat microglia is controlled by extracellular adenosine. *Neurosci. Lett.* 218, 91–94.
- Orio, L., O'Shea, E., Sanchez, V., Pradillo, J.M., Escobedo, I., Camarero, J., Moro, M.A., Green, A.R., Cola, M.I., 2004. 3,4-Methylenedioxymethamphetamine increases interleukin-1b levels and activates microglia in rat brain: studies on the relationship with acute hyperthermia and 5-HT depletion. *J. Neurochem.* 89, 1445–1453.
- Panina-Bordignon, P., Mazzeo, D., Lucia, P.D., D'Ambrosio, D., Lang, R., Fabbri, L., Self, C., Sinigaglia, F., 1997. Beta₂-agonists prevent Th1 development by selective inhibition of interleukin 12. *J. Clin. Invest.* 100, 1513–1519.
- Paton, W.D., Vizi, E.S., 1969. The inhibitory action of noradrenaline and adrenaline on acetylcholine output by guinea-pig ileum longitudinal muscle strip. *Br. J. Pharmacol.* 35, 10–28.
- Perry, V.H., Gordon, S., 1988. Macrophages and microglia in the nervous system. *Trends Neurosci.* 11, 273–277.
- Plaut, M., 1987. Lymphocyte hormone receptors. *Ann. Rev. Immunol.* 5, 621–669.
- Pow, D.V., Perry, V.H., Morris, J.F., Gordon, S., 1989. Microglia in the neurohypophysis associate with and endocytose terminal portions of neurosecretory neurons. *Neuroscience* 33, 567–578.
- Prass, K., Meisel, C., Höflich, C., Braun, J., Halle, E., Wolf, T., Ruscher, K., Victorov, I.V., Priller, J., Dirnagl, U., Volk, H.D., Meisel, A., 2003. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. *J. Exp. Med.* 198, 725–736.
- Prinz, M., Hausler, K.G., Kettenmann, H., Hanisch, U., 2001. Beta-adrenergic receptor stimulation selectively inhibits IL-12p40 release in microglia. *Brain Res.* 899, 264–270.
- Rodriguez, J.L., Gibbons, K.J., Bitzer, L.G., Dechert, R.E., Steinberg, S.M., Flint, L.M., 1991. Pneumonia: incidence, risk factors, and outcome in injured patients. *J. Trauma* 31, 907–912.
- Sanders, V.M., Baker, R.A., Ramer-Quinn, D.S., Kasprovicz, D.J., Fuchs, B.A., Street, N.E., 1997. Differential expression of the beta₂-adrenergic receptor by Th1 and Th2 clones: implications for cytokine production and B cell help. *J. Immunol.* 158, 4200–4210.
- Sedgwick, J., Hickey, W.F., 1997. *Antigen Presentation in the Nervous System*. Oxford University Press, New York, pp. 364–418.
- Selmeczy, Z., Szelenyi, J., Vizi, E.S., 2003. Intact noradrenaline transporter is needed for the sympathetic fine-tuning of cytokine balance. *Eur. J. Pharmacol.* 469, 175–181.
- Severn, A., Rapson, N.T., Hunter, C.A., Liew, F.Y., 1992. Regulation of tumor necrosis factor production by adrenaline and beta-adrenergic agonists. *J. Immunol.* 148, 3441–3445.
- Si, Q.S., Nakamura, Y., Schubert, P., Rudolph, K., Kataoka, K., 1996. Adenosine and propentofylline inhibit the proliferation of cultured microglial cells. *Exp. Neurol.* 137, 345–349.
- Siegmund, B., Eigler, A., Hartmann, G., Hacker, U., Endres, S., 1998. Adrenaline enhances LPS-induced IL-10 synthesis: evidence for protein kinase A-mediated pathway. *Int. J. Immunopharmacol.* 20, 57–69.
- Silva, D.G., Ross, G., Osborne, L.W., 1971. Adrenergic innervation of the ileum of the cat. *Am. J. Physiol.* 220, 347–352.
- Sperlagh, B., Hasko, G., Nemeth, Z., Vizi, E.S., 1998. ATP released by LPS increases nitric oxide production in raw 264.7 macrophage cell line via P2Z/P2X7 receptors. *Neurochem. Int.* 33, 209–215.

- Sperlagh, B., Vizi, E.S., 1996. Neuronal synthesis, storage and release of ATP. *Semin. Neurosci.* 8, 175–186.
- Suberville, S., Bellocq, A., Fouqueray, B., Philippe, C., Lantz, O., Perez, J., Baud, L., 1996. Regulation of interleukin-10 production by beta-adrenergic agonists. *Eur. J. Immunol.* 26, 2601–2605.
- Szabo, C., Scott, G.S., Virag, L., Egnaczyk, G., Salzman, A.L., Shanley, T.P., Hasko, G., 1998. Suppression of macrophage inflammatory protein (MIP)-1alpha production and collagen-induced arthritis by adenosine receptor agonists. *Br. J. Pharmacol.* 125, 379–387.
- Szelenyi, J., Kiss, J.P., Puskas, E., Szelenyi, M., Vizi, E.S., 2000a. Contribution of differently localized alpha 2- and beta-adrenoceptors in the modulation of TNF-alpha and IL-10 production in endotoxemic mice. *Ann. NY Acad. Sci.* 917, 145–153.
- Szelenyi, J., Kiss, J.P., Vizi, E.S., 2000b. Differential involvement of sympathetic nervous system and immune system in the modulation of TNF-alpha production by alpha2- and beta-adrenoceptors in mice. *J. Neuroimmunol.* 103, 34–40.
- Szelenyi, J., Selmeczy, Z., 2002. Immunomodulatory effect of antidepressants. *Curr. Opin. Pharmacol.* 2, 428–432.
- Tanaka, K.F., Kashima, H., Suzuki, H., Ono, K., Sawada, M., 2002. Existence of functional beta1- and beta2-adrenergic receptors on microglia. *J. Neurosci. Res.* 70, 232–237.
- Thery, C., Dobbertin, A., Mallat, M., 1994. Downregulation of in vitro neurotoxicity of brain macrophages by prostaglandin E₂ and a beta-adrenergic agonist. *Glia* 11, 383–386.
- Thomas, D.M., Dowgierta, J., Geddes, T.J., Francescutti-Verbeem, D., Liu, X., Kuhna, D.M., 2004. Microglial activation is a pharmacologically specific marker for the neurotoxic amphetamines. *Neurosci. Lett.* 367, 349–354.
- Thomas, W.E., 1992. Brain macrophages: evaluation of microglia and their functions. *Brain Res.* 17, 61–74.
- Tomozawa, Y., Yabuuchi, K., Inoue, T., Satoh, M., 1995. Participation of cAMP and cAMP-dependent protein kinase in beta-adrenoceptor-mediated interleukin-1 beta mRNA induction in cultured microglia. *Neurosci. Res.* 22, 399–409.
- Umbriaco, D., Garcia, S., Beaulieu, C., Descarries, L., 1995. Relational features of acetylcholine, noradrenaline, serotonin and GABA axon terminals in the stratum radiatum of adult rat hippocampus (CA1). *Hippocampus* 5, 605–620.
- Umbriaco, D., Watkins, K.C., Descarries, L., Cozzari, C., Hartman, B.K., 1994. Ultrastructural and morphometric features of the acetylcholine innervation in adult rat parietal cortex: an electron microscopic study in serial sections. *J. Comp. Neurol.* 348, 351–373.
- van der Poll, T., Coyle, S.M., Barbosa, K., Braxton, C.C., Lowry, S.F., 1996. Epinephrine inhibits tumor necrosis factor-alpha and potentiates interleukin 10 production during human endotoxemia. *J. Clin. Invest.* 97, 713–719.
- van der Poll, T., Jansen, J., Ender, E., Sauerwein, H.P., van Deventer, S.J., 1994. Noradrenaline inhibits lipopolysaccharide-induced tumor necrosis factor and interleukin 6 production in human whole blood. *Infect. Immun.* 62, 2046–2050.
- Vizi, E.S., 1968. The inhibitory action of noradrenaline and adrenaline on release of acetylcholine from guinea-pig ileum longitudinal strips. *Naunyn Schmiedebergs Arch. Exp. Pathol. Pharmacol.* 259, 199–200.
- Vizi, E.S., 1972. Stimulation, by inhibition of (Na⁺-K⁺-Mg²⁺)-activated ATPase, of acetylcholine release in cortical slices from rat brain. *J. Physiol.* 226, 95–117.
- Vizi, E.S., 1974. Proceedings: Interaction Between Adrenergic and Cholinergic Systems: Presynaptic Inhibitory Effect of Noradrenaline on Acetylcholine Release. *J. Neural. Transm. Suppl.* 11, 61–78.
- Vizi, E.S., 1980a. Modulation of cortical release of acetylcholine by noradrenaline released from nerves arising from the rat locus coeruleus. *Neuroscience* 5, 2139–2144.
- Vizi, E.S., 1980b. Non-synaptic modulation of transmitter release—pharmacological implication. *Trends Pharmacol. Sci.* 1, 172–175.
- Vizi, E.S., 1984. Nonsynaptic Interactions Between Neurons: Modulation of Neurochemical Transmission. John Wiley and Sons, Chichester.
- Vizi, E.S., 2000. Role of high-affinity receptors and membrane transporters in nonsynaptic communication and drug action in the central nervous system. *Pharmacol. Rev.* 52, 63–89.
- Vizi, E.S., Kiss, J.P., Lendvai, B., 2004. Nonsynaptic communication in the central nervous system. *Neurochem. Int.* 45, 443–451.
- Vizi, E.S., Knoll, J., 1971. The effects of sympathetic nerve stimulation and guanethidine on parasympathetic neuroeffector transmission; the inhibition of acetylcholine release. *J. Pharm. Pharmacol.* 23, 918–925.
- Vizi, E.S., Knoll, J., 1976. The inhibitory effect of adenosine and related nucleotides on the release of acetylcholine. *Neuroscience* 1, 391–398.
- Vizi, E.S., Orso, E., Osipenko, O.N., Hasko, G., Elenkov, I.J., 1995. Neurochemical, electrophysiological and immunocytochemical evidence for a noradrenergic link between the sympathetic nervous system and thymocytes. *Neuroscience* 68, 1263–1276.
- Von Lubitz, D.K., Simpson, K.L., Lin, R.C., 2001. Right thing at a wrong time? Adenosine A3 receptors and cerebroprotection in stroke. *Ann. NY Acad. Sci.* 939, 85–96.
- Weihe, E., Nohr, D., Michel, S., Muller, S., Zentel, H.J., Fink, T., Krekel, J., 1991. Molecular anatomy of the neuro-immune connection. *Int. J. Neurosci.* 59, 1–23.
- Whittemore, E.R., Korotzer, A.R., Etebari, A., Cotman, C.W., 1993. Carbachol increases intracellular free calcium in cultured rat microglia. *Brain Res.* 621, 59–64.
- Williams, J.M., Felten, D.L., 1981. Sympathetic innervation of murine thymus and spleen: a comparative histofluorescence study. *Anat. Rec.* 199, 531–542.
- Wittendorp, M.C., Boddeke, H.W., Biber, K., 2004. Adenosine A3 receptor-induced CCL2 synthesis in cultured mouse astrocytes. *Glia* 46, 410–418.
- Young, K.A., Hirst, W.D., Solito, E., Wilkin, G.P., 1999. De novo expression of lipocortin-1 in reactive microglia and astrocytes in kainic acid lesioned rat cerebellum. *Glia* 26, 333–343.
- Yukawa, T., Ukena, D., Kroegel, C., Chanez, P., Dent, G., Chung, K.F., Barnes, P.J., 1990. Beta 2-adrenergic receptors on eosinophils. *Am. Rev. Respir. Dis.* 141, 1446–1452.
- Zhang, B., Yang, L., Konishi, Y., Maeda, N., Sakanaka, M., Tanaka, J., 2002. Suppressive effects of phosphodiesterase type IV inhibitors on rat cultured microglial cells: comparison with other types of cAMP-elevating agents. *Neuropharmacology* 42, 262–269.
- Zhang, L., Shirayama, Y., Shimizu, E., Iyo, M., Hashimoto, K., 2006. Protective effects of minocycline on 3,4-methylenedioxymethamphetamine-induced neurotoxicity in serotonergic and dopaminergic neurons of mouse brain. *Eur. J. Pharmacol.* 544, 1–9.