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INVESTIGATION OF ADRENERGIC MODULATION ON SHOCK INDUCED BY PLATELET ACTIVATING FACTOR

C. Iaccarino[1*] and R. Galzio[2]

[1] Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy;
[2] Neurosurgery Unit, Department of Surgical Sciences, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

[*]*Correspondence to*:
Dr. Corrado Iaccarino,
Department of Biomedical, Metabolic and Neural Sciences,
University of Modena and Reggio Emilia,
41125 Modena, Italy.
e-mail: Iaccarino.corrado@gmail.com

ABSTRACT

Platelet activating factor (PAF) is a lipid mediator which is released by the immune system during inflammatory processes and causes an anaphylactoid reaction when it is administered in rodents. Two models which have been widely used to investigate the systemic pathophysiology of PAF are PAF-induced hypotension in rats and PAF-induced death in mice. Utilizing these models, studies have suggested that the sympathetic nervous system plays a key role in modulating the detrimental effects of PAF. In this study, we sought to systematically evaluate the effects of adrenergic blockade and pharmacological augmentation of adrenergic reflexes on PAF-induced hypotension and death in rodents. Intravenous PAF administration in rats caused profound systemic arterial hypotension affecting the heart which was associated with bradycardia, suggesting an inability of the rats to compensate for the decreased arterial pressure. The beta blocker propranolol also significantly potentiated the mortality of intravenous administration of PAF in mice. In contrast to the beta-adrenergic system, alpha-adrenergic mechanisms appear less integral in the adaptive response to the PAF challenge. In rats, phentolamine, an alpha-adrenergic blocker, prolonged the hypotension provoked by PAF, but heart rate remained responsive. This effect suggest that cardiac reflexes were intact, and phentolamine had no effect on PAF-induced lethality in mice. Naloxone and thyrotropin releasing hormone (TRH) are two drugs which augment sympathetic responses, and these were also tested against PAF-induced death in mice. Both drugs were protective against PAF lethality, providing further evidence of the adaptive role of the sympathetic system against systemic PAF. Therefore, these studies support the concept that beta-adrenergic mechansims are an essential component for compensatory responses to systemic anaphylactoid responses involving PAF, and suggest a potentially lethal effect of beta blockers during systemic immune or inflammatory reactions involving PAF. This demonstrates that the beta-adrenergic system is a necessary component for the adaptive response to systemic PAF.

KEYWORDS: *PAF, anaphylactic shock, thyrotropin releasing hormone, propranolol, naloxone, phentolamine*

INTRODUCTION

Platelet activating factor (PAF) (1-0-alkyl 2-acetyl sn glyceryl phosphoryl choline) is released by leukocytes, platelets, vascular endothelium, and other tissue and is a potent mediator of immune and inflammatory reactions (1). Its major systemic effects include promotion of vascular permeability, bronchoconstriction, hypotension, and above all, platelet aggregation. *In vivo* studies have demonstrated a role for PAF in diverse physiological and pathological states, including IgE-induced systemic anaphylaxis (2), endotoxin shock (3,4), IgG-induced shock (5), and transplant rejection (6).

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Different models exist for studying the systemic action of PAF, and one which is simple and useful is PAF-induced mortality in mice (7-10). In this model, the intravenous injection of PAF causes dose-dependent hypotension, hemoconcentration, and death. The lethality of i.v. PAF in mice is thought to be due to the combination of the effects shock and bronchoconstriction, but not thrombosis. This is because platelets of rodents are not directly responsive to PAF (11), and so, PAF toxicity in mice has been proposed as a model for lethal anaphylactic shock. The mortality in this model can be prevented by pretreatment with steroidal anti-inflammatory drugs such as cortisone, inotropic drugs, PAF antagonists, or specific antibodies against PAF, and is exacerbated by beta-adrenergic blocking drugs (specifically beta-2 antagonists) (12-14).

The effects of adrenergic manipulation in this model are very interesting, since the sympathetic nervous system plays a central role in the response to circulatory collapse in shock. Since PAF is an important mediator of anaphylactic and septic shock, it activates the sympathetic nervous system, and adrenergic blockade should prove deleterious in PAF-induced shock. In fact, the i.v. infusion of PAF in rats results in elevated plasma catecholamine levels (15), and beta blockers, in addition to enhancing the lethality of PAF in mice, also slow the recovery of blood pressure to normal levels after the PAF challenge. In contrast to the harmful effects of beta blockade, thyrotropin releasing hormone (TRH), which stimulates sympathetic outflow and catecholamine release, has been shown to reverse PAF-induced hypotension in guinea pigs (16).

These observations implicate the sympathetic nervous system as a mechanism for modulating the systemic effects of PAF in rodents. The PAF- adrenergic interaction should be further studied, focusing on the role of alpha-adrenergic mechanisms, to determine whether, and to what extent, enhanced sympathetic outflow can improve survival and hemodynamics in rodents challenged with PAF. The main goals of this study were to systematically evaluate the effects of alpha- and beta-adrenergic blockers, and to compare the effects of these blockers with drugs which stimulate or enhance sympathetic outflow in PAF-induced death in mice. In addition to TRH, naloxone was also tested, as it enhances sympathetic outflow and thus also improves hemodynamic recovery in some shock models.

MATERIALS AND METHODS

PAF-induced hypotension in rats

Male Wistar rats, weighing approximately 225 g, were purchased from Charles River Laboratories and were randomly assigned to control and experimental groups. Rats were anesthetized with sodium pentobarbital (60 mg/kg i.p.) and placed on a heating pad with a rectal temperature probe to maintain body temperature above 37.5°C. The right carotid artery and jugular vein were cannulated for recording arterial blood pressure and for injecting drugs, respectively. Propranolol, phentolamine (2.5 mg/kg each), or the 0.9% NaCl vehicle was injected, followed by the injection of PAF (2 μg/kg) or its vehicle (0.9% NaCl) after three minutes. The dose of PAF was selected as one which produces profound but reversible hypotension. Both the adrenergic blockers and PAF were dissolved at concentrations which resulted in injection volumes of 1 ml/kg body weight. Each of the four PAF-challenged groups (propranolol or phentolamine pretreatment groups and the two respective vehicle-pretreated control groups) included 10 rats, whereas the drug-only control groups consisted of 7 animals.

Blood pressure was monitored continuously for the following 30 min by a P23 ID pressure transducer and transducer amplifier and recorder. Heart rate (HR) was measured each minute. For each adrenergic blocker (propranolol or phentolamine) and its two associated control groups (vehicle pretreated, PAF challenged group and drug pretreated, vehicle challenged group), mean arterial pressure (MAP) and HR were compared between the three groups by one-way analysis of variance (ANOVA). When the ANOVA indicated statistically significant between-group differences, it was followed by specific comparison of the adrenergic blocker pretreated, PAF-challenged group to each of the two control groups by the Bonferroni method. $P<0.05$ was considered to be statistically significant.

PAF toxicity in mice

Male CD-1 mice, weighing approximately 25 g, were obtained from Charles River Laboratories and assigned randomly to the groups below. Mice were anesthetized with sodium amytal (100 mg/kg ip). Propranolol (2.5 mg/kg, Sigma Chemical Co.), phentolamine (2.5 mg/kg, Ciba Pharmaceutical Co.) or the combination of both drugs (2.5 mg/kg each) was then administered into the jugular vein. Drugs were dissolved in 0.9% NaCl at a concentration of 0.5 mg/ml, resulting in an injection volume of 5 μl/g body weight. For each of these treatment groups, a control group of mice received an injection of the 0.9% NaCl vehicle. Initially, each experimental and control group consisted of 15 mice, but the propranolol group and its control were expanded to 40 mice to confirm initial positive findings. Five minutes after drug or vehicle pretreatment, an approximate LD_{50} of PAF (15 μg/kg, iv) was administered. Mice were then observed

until either death or full recovery of the righting reflex, which occurred within 4 hours in all cases. PAF (Calbiochem™) was prepared in 0.9% NaCl solution at a concentration resulting in an injection volume of 5 μl/g body weight to achieve the desired dose. Mortality was compared between drug and vehicle treated groups by the Chi square test.

Additional groups of 15 mice were pretreated with TRH (2 mg/kg, i.v.), naloxone (2 mg/kg, i.v.), or the NaCl vehicle 2 min before the PAF challenge. TRH and naloxone were tested against the approximate PAF LD_{80} (40 μg/kg) and TRH was also tested using the lower dose of PAF (15 μg/kg). Again, all drugs and the vehicle were dissolved in 0.9% NaCl and were administered at injection volumes of 5 μl/g body weight. The Chi square test was used to compare the mortality between the drug pretreatment and control groups.

RESULTS

PAF-induced hypotension in rats

The injection of 2.0 μg/kg i.v. PAF resulted in severe, rapidly developing hypotension, with only partial recovery of MAP within 30 min. However, HR was unaffected by PAF in vehicle-pretreated rats. The combination of propranolol and PAF produced a peak hypotensive response similar to PAF alone (vehicle/PAF group), but MAP was significantly depressed in the propranolol/PAF rats relative to the vehicle/PAF control group during the recovery period at several time points. HR was markedly different in these two groups, with significantly lower HR in the propranolol-pretreatment group for the duration of the study. Notably, propranolol alone produced a similar effect on HR and caused mild hypotension as well.

Like propranolol, phentolamine treatment alone significantly reduced blood pressure, and phentolamine in combination with PAF resulted in lower MAP during the recovery period compared to vehicle-pretreated rats. The alpha-adrenergic blocking drug by itself also resulted in a prolonged reduction in HR. Immediately following the PAF challenge, MAP was significantly lower in the phentolamine/PAF group compared to the vehicle/PAF rats ($P<0.05$); this comparison was also significant at later time points. Although HR was diminished by phentolamine for the duration of the study in the vehicle-challenged group, it was significantly reduced in the phentolamine/PAF rats (relative to the vehicle/PAF group) only immediately prior to PAF injection and in the first 2 min after the challenge. HR then recovered rapidly to control levels. The two phentolamine-treated groups also had different MAP levels before the challenge with PAF or vehicle ($P<0.05$).

PAF toxicity in mice

Propranolol pretreatment significantly exacerbated the acute toxicity of i.v. PAF in mice. Injection of the approximate LD_{50} of PAF (based on previous studies) in the propranolol-treated group resulted in a significantly greater mortality rate than the same challenge in the control group ($P<0.01$) (Fig. 1). On the other hand, phentolamine pretreatment had no significant effect on PAF toxicity (Fig. 1). The combination of propranolol and phentolamine produced effects similar to propranolol alone, with a higher mortality rate than the control group ($P<0.01$) (Fig. 1).

TRH exerted a protective effect against both the approximate PAF LD_{80} ($P<0.01$) and LD_{50} ($P<0.05$) (Fig. 2). Similarly, pretreatment with naloxone significantly reduced the lethality of the high dose PAF challenge ($P<0.05$) (Fig. 2).

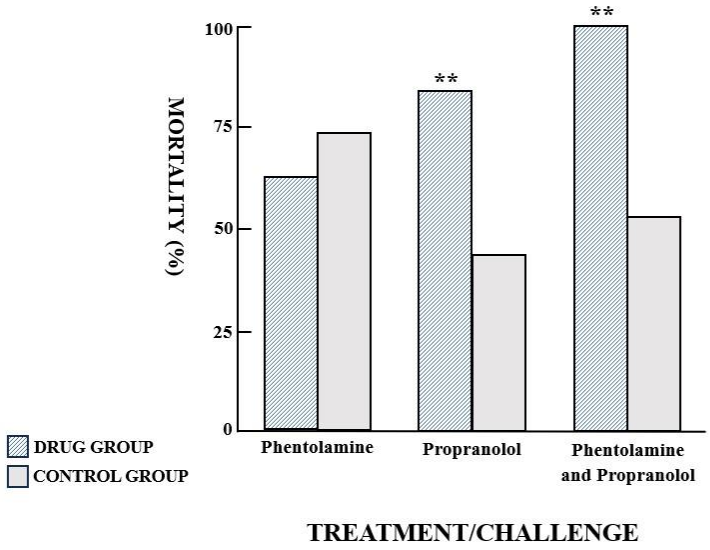

Fig. 1. *Mortality in groups of mice challenged with an approximate LD_{50} of platelet activating factor (PAF) (15μg/kg, i.v.). Mice were pretreated i.v. with either the alpha-adrenergic antagonist phentolamine (2.5 mg/kg), the beta-adrenergic antagonist propranolol (2.5mg/kg) or a combination of both drugs (2.5 mg/kg each) prior to PAF administration. Control mice received a 0.9% NaCl injection before the PAF challenge. **P<0.01, compared to the appropriate control group.*

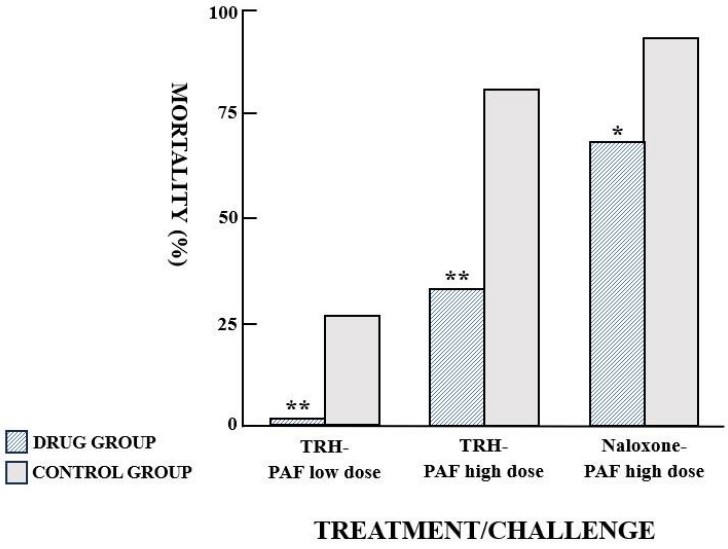

Fig. 2. *Mortality in groups of mice challenged with platelet activating factor (PAF) (low dose, 15 μg/kg, i.v., or high dose, 40 μg/kg, i.v.). Mice were pretreated i.v. with thyrotropin releasing hormone (TRH) (2 mg/kg, i.v.) or naloxone (2 mg/kg, i.v.) prior to PAF administration. Control mice received a 0.9% NaCl injection before the PAF challenge. *P<0.05, **P<0.01, compared to the appropriate control group.*

DISCUSSION

A harmful interaction has been suggested between adrenergic blocking drugs and PAF in shock. PAF administration elevates plasma levels of catecholamines in the rat, probably due to a sympathetic reflex provoked by hypotension (15). Intravenous or intracerebroventricular injection of TRH activates the sympathetic nervous system through a central nervous system (CNS) mechanism and reverses PAF-induced hypotension in guinea pigs (16). Beta-adrenergic blockers potentiate PAF toxicity in mouse models, an effect which is probably mediated by beta-2 receptors based on differential effects of selective beta blockers (17). It has been speculated that the bronchopulmonary effects of the beta blockers increased PAF mortality.

The results of the experiments presented here shed light on the interaction between adrenergic mechanisms and PAF in shock states and support the important role that the sympathetic nervous system plays in counteracting the effects of PAF in anaphylactic reactions. These studies clearly demonstrate that in one model (PAF toxicity in mice), the two drugs which increase sympathetic outflow through different mechanisms (TRH and naloxone) and the beta-adrenergic blocker propranolol have opposite effects on PAF lethality. Enhancement of sympathetic reflexes is apparently protective against lethal shock, whereas blockade of the beta-adrenergic component of the sympathetic system is harmful.

The present studies also suggest the lack of significant involvement of alpha-adrenergic processes in modulating acute responses to PAF. Unlike propranolol, phentolamine did not increase the lethality of PAF in mice. Because of this result, and previous studies which showed that the adrenergic system and PAF included beta blockers and adrenal demedullation but not alpha blockers, the effects of both phentolamine and propranolol on PAF-induced alterations in MAP and HR in rats were examined in the current experiments. These hemodynamic studies also confirm the importance of beta, rather than alpha, adrenergic mechanisms in modulating the acute effects of PAF and suggest that the cardiovascular and bronchopulmonary system are involved in the potentiation of PAF toxicity by beta blockers.

In line with previous studies, propranolol in combination with PAF provoked a more prolonged hypotension than PAF alone in the anesthetized preparation used here. Propranolol itself produced persistent bradycardia and a moderate fall in MAP; this effect might contribute to the delay in recovery from PAF-induced hypotension in the propranolol/PAF group. The combination of PAF and propranolol resulted in an initial fall in MAP to the same level as PAF without propranolol, but the prolonged hypotensive phase was accompanied by bradycardia when propranolol was present. These results differ from those observed in the conscious rat, in which PAF promoted tachycardia which was blocked by propranolol. In the anesthetized rat, there is most likely significant adrenergic tone, prior to the administration of any drug. It is likely that bradycardia in the presence of hypotension reflects an inability of the propranolol-treated rats to respond to the PAF-induced fall in MAP, which is related largely to peripheral vasodilation by increasing cardiac output (18). On this basis, the actions of propranolol in the mouse model could be due to cardiovascular effects of the beta blocker, in addition to the bronchopulmonary action (17). the protective actions of positive inotropic drugs against PAF support the idea that cardiovascular dysfunction is involved in the lethal actions of PAF in mice.

Phentolamine, like propranolol, produced bradycardia and hypotension independent of PAF administration. No particular significance is attached to the marginally significant difference in MAP in the two phentolamine-treated groups before PAF or vehicle challenge. The difference might have been related to the slightly different basal MAP levels in the two groups. Phentolamine-pretreated rats had depressed MAP immediately after the challenge with PAF and during the recovery phase, compared to saline-pretreated PAF-challenged animals. The prolonged hypotension probably reflects the vasodilatory actions of both phentolamine and PAF, and the inhibition of compensatory (alpha-adrenergic) vasoconstriction. The bradycardia associated with phentolamine treatment was quickly reversed following the PAF challenge, but was persistent in the phentolamine-treated, saline-challenged group. This suggests that although PAF-induced hypotension is prolonged under alpha-adrenergic blockade, the cardiac compensatory, beta-adrenergic mechanisms are maintained and result in increased HR and, possibly, enhanced cardiac output.

CONCLUSIONS

This study lends support to the idea that beta-adrenergic mechanisms are an adaptive and crucial component of the response to the anaphylactoid effects of PAF. However, alpha-adrenergic mechanisms seem to be less significant in the acute response to PAF-induced effects. Finally, because beta-adrenergic function is important in the recovery from PAF, the combination of propranolol and PAF results in a potentially lethal interaction, while agents which increase adrenergic systems protect against PAF. PAF-induced mortality and hypotension in rodents could help to explain the sympathetic responses in pathological states of immunity.

Statement of ethics

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

The authors declare that they have no conflict of interest.

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TRIGEMINAL NEURALGIA: NEUROPATHIC PAIN ORIGINATING IN THE CNS

P. Di Emidio* and D. Cardinelli

Oral and Maxillo-Facial Unit, ASL Teramo - G. Mazzini Hospital, Teramo, Italy.

Correspondence to:
Dr Paolo Di Emidio,
Oral and Maxillo-Facial Unit,
ASL Teramo - G. Mazzini Hospital,
Teramo, Italy.
e-mail: paolodiemidio@gmail.com

ABSTRACT

Trigeminal neuralgia (TN) is a condition characterized by recurrent severe paroxysmal pain and neurovascular dysfunction. The pain can occur sporadically or can be triggered by mild mechanical insults, and is described as being similar to that of an eletric shock. The pain is often restricted to one side of the face, and the duration ranges from seconds to minutes. TN is caused by the loss of the myelin sheath that surrounds Schwann cells of the trigeminal nerve. This demyelization exposes the nerve, rendering it vulnerable, and causes the axon to become sensitive and hyperexcitable. Therapeutic treatments for TN include the use of sodium channel blockers such as carbamazepine and oxcarbazepine, and when this is not effective, surgical intervention is suggested, such as microvascular decompression and gamma knife radiosurgery, with the main goal being to alleviate the severe pain in the patient and thus improve quality of life.

KEYWORDS: *trigeminal neuralgia, pain, neuropathy, nerve, treatment, surgery*

INTRODUCTION

Trigeminal neuralgia (TN) is a disorder characterized by recurrent severe paroxysmal pain that is restricted to the trigeminal area and presents neurovascular dysfunction (1). TN can be classified into mild idiopathic TN, classic TN with morphological changes of the trigeminal root near the pons, and secondary TN due to other diseases (2). The disorder often occurs on one side of the face and affects one or more parts of the trigeminal nerve (3). Neuropathic pain is a unilateral disorder that can occur sporadically or can also be caused by mild mechanical insults. The duration of the pain ranges from just a few seconds to up to two minutes (4). Various daily activities such as drinking, eating, chewing, speaking, combing the hair, yawning, etc. can trigger this neuralgic pain (5).

TN generally arises between the ages of 40 and 60, with an incidence of approximately 16 individuals per 100,000. It affects mostly women and is characterized by intermittent pain that is described as similar to electric shocks (6). In approximately 12-18% of patients, secondary TN can be caused by benign tumors or multiple sclerosis (7). The disease can appear sporadically in children and could be due to genetic alterations that contribute to the pathological state. Moreover, TN causes very severe facial pain, which can present in different forms (8). The patient feels pain in the second maxillary or third mandibular area of the face, with the right side being affected with greater incidence. The disease usually affects only one side of the face and is rarely bilateral (9). When it does occur bilaterally, it provokes great concern because there could be other underlying causes, such as tumors. Furthermore, patients suffering from this painful disease can experience difficulty in sleeping and can develop anxiety and depression (10).

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DISCUSSION

In TN, the trigeminal nerve leaks the myelin sheath surrounding its Schwann cells due to vascular problems (11). Neurophysiological and histological studies show that the loss of the myelin sheath makes the nerve vulnerable, and the axon becomes hypersensitive and hyperexcitable (12) (Fig.1). The fibers that demyelize are the non-nociceptive and more sensitive type II sensory Aβ fibers (13). Hyperexcitability may cause high-frequency writhing in the patient that may be unrelated to neuropathic pain (14). Facial pain can be continuous and different from paroxysmal pain. The demyelization of the nerve root causes damage to the nociceptive system by inhibiting it, which is an effect that can also occur after surgical treatment (15).

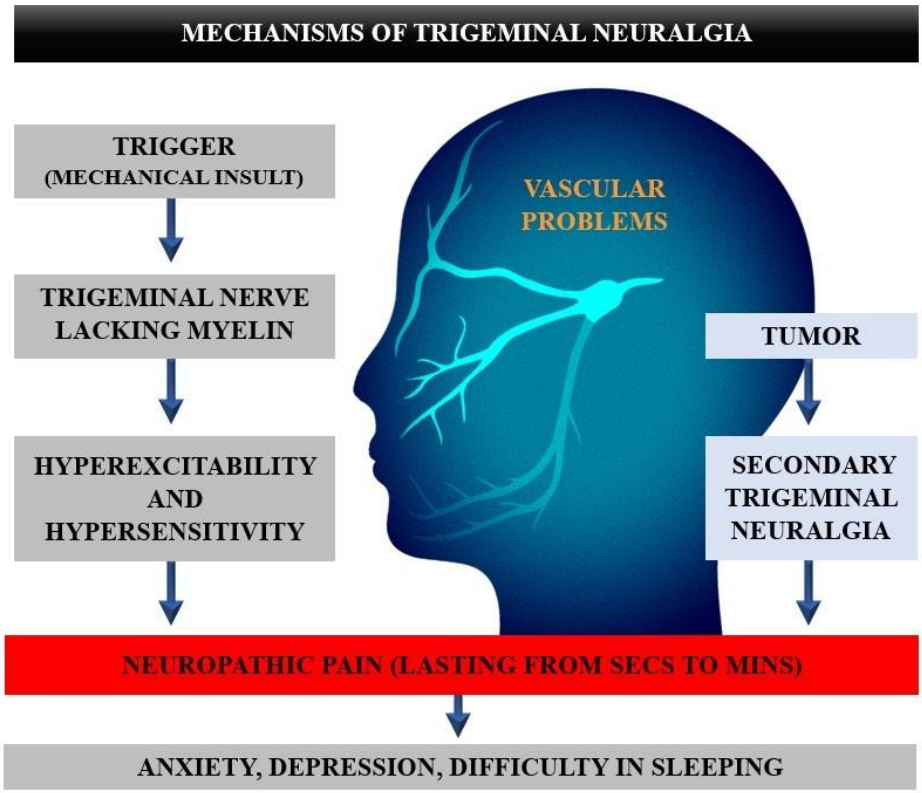

Fig. 1. *A trigger, which is often a mechanical insult, activates the trigeminal nerve that lacks myelin and is hyperexcitable and hypersensitive, resulting in neuropathic pain that can lead to anxiety, depression, and sleep problems. A tumor can cause secondary trigeminal neuralgia, which provokes neuropathic pain.*

Diagnosis and Treatment

The diagnosis of TN is made based on the medical history of the patient that is conducted by neurologists and/or maxillofacial experts in the field (16) (Table I). The treatment of acute pain must be specifically and promptly addressed by doctors, as suggested by the International Headache Society (IHS) and the International Association for the Study of Pain (IASP) (17).

Table I. *Diagnostic criteria for trigeminal neuralgia.*

• Local facial pain on the trigeminal nerve	• Age of onset less than 40 years
• Sudden pain	• Difficulty controlling pain
• Periodicity of onset of pain	• Poor response to carbamazepine
• Pain remission	• Family history of the disease
• Reduction of pain attacks after pharmacological treatment	• Episodes of pain that is similar to electric shock

Therapeutic treatment often includes drugs and may also include surgical interventions such as radio surgery, microvascular decompression, and deep neuromodulator stimulation of the brain and motor cortex (18). Drug therapy is considered the first line in treatment but is not always effective and can cause unwanted side effects. The most widely used pharmaceutical is carbamazepine, a blocker of voltage-gated and frequency-dependent sodium channels which is an anticonvulsant and analgesic drug used to control seizures and bipolar disorder (3). Although the use of sodium channel blockers such as carbamazepine and oxcarbazepine are effective, carbamazepine is often more tolerable. However, further studies are needed to understand the real mechanisms of these two drugs.

Therapeutic drugs can generate side effects such as dizziness, ataxia, diplopia, and increased levels of aminotransferase (also called transaminase), ALT, GPT, or SGPT, which is a fundamental enzyme for our body, especially in the brain and liver (19). Normally, the presence of this enzyme is minimal, but in the case of trigeminal neuropathy, the enzyme, which represents a negative marker for the organism, is released into the body in considerable quantities and ends up directly in the blood (20).

Furthermore, drugs that inhibit serotonin receptors or target the calcitonin gene are often helpful (21). Therefore, monoclonal antibodies against calcitonin gene-related peptide (CGRP) have shown an effective therapeutic effect against headaches (22).

Surgical procedures

When drugs have no effect on chronic trigeminal neuralgia in patients, our group at the Maxillofacial Surgical Unit of the "G. Mazzini" Civil Hospital in Teramo, Italy, suggests the surgical route. Surgery has been shown to be effective in reducing the severity and frequency of neuralgia attacks and allows the patient to avoid excessive doses of therapeutic drugs (23). The study of TN in recent years has seen notable updates in surgical methods, magnetic resonance imaging (MRI), classification, and clinical diagnosis (24). Diagnostic difficulties are often present since many patients suffering from this pathology present both proximal attacks and continuous localized pain. But these difficulties are now overcome with new MRI methods that are capable of distinguishing a small neurovascular contact and real vascular compromise (25).

The most widely used and effective surgical interventions are microvascular decompression and gamma knife radiosurgery, with the help of MRI. Surgery may involve the peripheral block of the branches of the trigeminal nerve (neurectomy) which anesthetizes the neuralgic part of the face. However, this procedure is rarely used as it is too painful (26). Other surgical methods involve damaging the trigeminal ganglion using radiofrequency thermocoagulation, treatment with glycerol, or through mechanical compression (27). Alternatively, a lesion of the trigeminal root can be performed with a gamma knife, without damaging the pons. This is a more updated procedure that eliminates pain and has been found to be successful in various studies (28).

However, according to data in the literature, it seems that the most effective and long-lasting surgical method is microvascular decompression of the trigeminal nerve root, although the mechanisms for this still remain unclear (29). In TN, vascular compression of the trigeminal nerve root seems to be the main cause of pain, but sclerotic plaques can also be responsible for the disease. In most cases, these surgical treatments relieve pain significantly and create important relief for the patient.

CONCLUSIONS

TN causes neuropathic pain (usually unilateral) that can be induced by low-intensity mechanical insults, and which may last for seconds to minutes. The cause of this pain is due to the loss of the myelin sheath of Schwann cells, which makes the nerve vulnerable (Aβ fibers) and causes the axon to become sensitive and hyperexcitable. Drug therapy usually involves the use of carbamazepine, a sodium channel blocker that is also used for seizures, bipolar disorder, and epilepsy. When pharmacological therapy does not work, a surgical course is suggested, such as microvascular decompression, percutaneous ganglion lesions and gamma knife radiosurgery. With TN, the main goal is to alleviate the severe pain and improve the patient's quality of life.

Conflict of interest

The authors declare that they have no conflict of interest.

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NEUROIMMUNOLOGY AND LYMPHOCYTE HOMING AND ADHESION

I. Frydas[1*], A. Caraffa[2] and S. Martinotti[3]

[1] Department of Parasitology, Aristotle University, 54124 Thessaloniki, Greece;
[2] School of Pharmacy, University of Camerino, Camerino, Italy;
[3] Department of Medical and Oral Sciences and Biotechnology, University "G. D'Annunzio", Chieti, Italy.

Correspondence to:
Ilias Frydas, PhD,
Department of Parasitology,
Aristotle University,
54124 Thessaloniki, Greece.
e-mail: stavfd1991@gmail.com

ABSTRACT

Physical and mental health are strongly connected, with one affecting the other. Neuroimmunology investigates the physiological relevance, the pathological significance, and the cytological and biochemical mechanisms of the communication between the nervous and immune systems. The migration of lymphocytes to and from lymphoid organs is essential to the physiological regulation of the immune response, and the efficiency of cellular immune processes depends largely upon the distribution of and interaction between lymphocytes. This process is dependent upon specific homing and adhesion membrane receptors. In this paper, we report that neuroendocrine elements modulate lymphocyte homing and adhesion.

KEYWORDS: *white blood cell, neuroimmunology, lymphocyte adhesion molecule, lymphocyte homing receptor, immune response*

INTRODUCTION

Neuroimmunology, a field of psychoneuroimmunology, seeks to define and characterize the physiological relevance, pathological significance, and cytological and biochemical mechanisms of the communication between the nervous and immune systems, which interact together (1). Neuroendocrine mediators include cholinergic and catecholaminergic neurotransmitters, as well as others such as opioids and growth factors, and steroids and other hormones (2). These factors modulate immune responses, and immune mediators such as cytokines, colony stimulating factors, and other immune products, modulate neuroendocrine processes. Immune cells and neurons share receptors, gene products, and signal transduction mechanisms (3). Evidence suggests that neuroendocrine elements modulate lymphocyte homing and adhesion, which is discussed below.

Lymphocyte Homing and Adhesion

The efficiency of cellular immune processes depends largely upon the distribution of and interaction between lymphocytes since the migration of lymphocytes to and from lymphoid organs is central to the physiological regulation of the immune response (4). Lymphocyte homing is lymphoid organ-specific, lymphocyte population-specific, and lymphocyte state of maturation and state of activation-specific. Lymphocyte homing is dependent upon specific ligand/receptor interactions (5). Lymphocytes express "homing" membrane receptors, which mediate cellular and tissue

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immunity. Cells of high-endothelial venules (HEVs) express tissue-specific "vascular addressins", the endothelial ligands for homing receptors (6). Homing receptors include the leukocyte adhesion molecule-1 (LAM-1) family, represented by Leu8/TQ1 (human homologue of the murine homing receptor, Mel-14), and the homing-cellular adhesion molecule (H-CAM) family, including the CD44 cluster (7).

Cellular immune responses, including homing, are modulated by cell-to-cell interaction which is directed in part by adhesion receptors. Adhesion molecules comprise two important members of the integrin family: the leukocyte function-associated antigens (LFAs) and the very late antigens (VLAs) (8). LFA-1 consists of two membrane clusters (CD11a and CD18) and is found primarily on lymphocytes. Related membrane clusters (LFA-2: CD11b/CD18 and LFA3: CD11c/CD18) are expressed in higher density on macrophages (9). VLA-4 also consists of two membrane clusters (CDw49d and CDw29) and is expressed primarily on lymphocytes (10). The expression of homing receptors and adhesion molecules is finely regulated by cytokines and other factors, including neuroendocrine products (11-13).

The tissue-specific nature of interactions between lymphocytes and HEVs mainly depends on which homing and adhesion molecule is expressed (14). The anti-Leu8 antibody effectively prevents binding to peripheral lymph node-derived HEVs, and anti-CD44 and anti-CD49d antibodies specifically block binding to mucosal-derived HEVs (15). Differential expression of homing and adhesion molecules is also evident in virgin and memory CD4 cells and directs their specific patterns of migration (16). Virgin CD4 cells are characterized by both the cluster of differentiation CD4 and by the high molecular weight isoform of the common leukocyte antigen (p220, CD45RA) (CD4+ CD45RA+), and express relatively few homing receptors (17). In contrast, memory CD4 cells, which lose CD45RA upon exposure to an antigen during the post-thymic process of maturation to memory cells (18), express homing receptors in higher density (19).

Experimental Models in Lymphocyte Homing and Adhesion

There is a cyclic pattern of variations in cellular immunity that results from the interactions of the immune and nervous systems (20,21). Steroids show marked diurnal fluxes and have several immunoregulatory functions, including lymphocyte (preferentially CD4 cells) homing and redistribution (22). In fact, in healthy donors, diurnal changes in the number of circulating lymphocyte populations are in a consistent negative phase relationship with cortisol circadian variations (23,24).

Certain neuroendocrine changes that occur in reaction to stressful stimuli disrupt diurnal fluxes in cellular immunity (25). For example, research has shown that the anxiety from the experience of a major earthquake results in significant changes in the number and percentage of circulating lymphocytes involved in natural killer (NK) cytotoxic events (NK-acting; CD16 + or CD56 +) in healthy adults, which could perhaps be consequential to an activation of the endogenous opioid system (26). Stimulation of the neuroendocrine system associated with strenuous exercise also leads to a rise in circulating CD56 + cells and in NK activity immediately after cessation of exercise (27). These values decrease to below pre-basal levels at 120 minutes after exercise, and normalize by 20 hours, regardless of sex or level of physical training (28). Studies have shown that physical stress results in an immediate (i.e., within minutes of cessation of exercise) and significant rise in circulating CD16+ and CD56+ cells, and an elevation in NK activity (29). These outcomes are in part prevented by prior intravenous administration of the opioid receptor antagonist naloxone, thus implicating the endogenous opioid system (30). Taken together, these findings suggest that opioids are important in the specific modulation of lymphocyte homing and distribution (31).

It is still unknown whether these outcomes can be primarily attributed to vasodilation and increased tissue permeability or to modulation of lymphocyte homing and adhesion receptors. Ongoing studies are testing the role of opioids and other neuroendocrine products in the regulation of expression of homing and adhesion molecules and their ligands (32). Some studies show that established human lymphoid lines express constitutive levels of CD18, the beta-chain of LFA-1 (33). CD18 expression is unimodally "bright" in some lines, but bi-modally "dim" and "bright" in other lines. Mitogenic stimulation shifts CD18 expression from "bright" to "dim" in all tested cell lines, without altering the relative number of cells positive for this marker. Activation with atropine shifts CD18 into the "dim" region; activation with steroids fails to change CD18 expression compared to unstimulated cells; and activation with proopiomelanocortin gene products (e.g., beta-endorphin, ACTH) has mixed effects on CD18 expression (34). The Kolmogorov-Smirnov statistic indicates that these shifts in fluorescence intensity are significant. However, further research should be continued to confirm these results.

Clinical Research Models in Lymphocyte Homing and Adhesion

The relationship between hormones and cellular immunity has been effectively studied in groups of patients characterized by alterations in neuroendocrine or immune regulation. For instance, administration of dexamethasone results in a significant decrease in the number and percentage of circulating virgin, but not memory CD4 cells in normal

subjects. The number and percentage of virgin CD4 cells are not altered in patients with anorexia nervosa, who have dysregulated cortisol levels (e.g., elevated plasma cortisol), following dexamethasone administration (35).

Studies have shown that the administration of dexamethasone fails to reduce the number of glucocorticoid receptors on peripheral blood mononuclear cells and the lymphoproliferative response of these cells to phytohemagglutinin in dexamethasone-resistant (i.e., cortisol non-suppressors) patients with major depression (36). More than half of the patients suffering from depression have dysregulated steroid hormone secretion, with elevated levels of plasma cortisol and cortisol non-suppression by dexamethasone (37). This may also occur in aged patients who manifest alterations in both neuroendocrine and immune regulation (38). Clinical studies are investigating the neuroimmune regulation of lymphocyte homing and adhesion in aged subjects and patients with Alzheimer's disease (39).

Certain groups of patients with autoimmune diseases show both neuroendocrine and immune dysfunction (40). Animal models have been successfully utilized to clarify these mechanisms. For example, the non-obese diabetic mouse is a spontaneous autoimmune animal model for human type I (insulin-dependent) diabetes mellitus and provides a unique opportunity to study the immune process leading to beta-cell destruction (41). This model is very useful because it offers the possibility to conduct well-controlled studies with precise immune and neuroendocrine endpoints and is particularly relevant to studies of lymphocyte distribution and homing because the progressive infiltration of pancreatic islets by lymphocytes is characteristic of the inflammatory process that leads to clinical diabetes. Adoptive transfer studies have shown that the homing of T cytotoxic/suppressor lymphocytes (CD8+) to the pancreas is mediated in part by CD4 cells, however more research is needed to clarify the role of adhesion and homing receptors (42). Thus, lymphocyte-lymphocyte interactions are essential events in the development of diabetes, and elucidation of the mechanisms of the adhesion and homing receptors involved in these processes will lead to greater understanding of this disease, and to the development of treatment interventions.

Infection with human immunodeficiency virus (HIV) is associated with spontaneous LFA-1-dependent fusion of infected lymphoid and myeloid cells (i.e., syncytium formation) (43). HIV infection can also lead to severe neuroendocrine disease. Levels of cortisol are often elevated in some HIV+ patients, while others have circulating cortisol levels lower than the normal range (44). This could be an outcome of HIV-induced adrenopathy resulting from cytomegalovirus opportunistic infection. Twenty four-hour circulating levels of two adrenocortical androgen steroids, dehydroepiandrosterone and its sulfate derivative, are significantly lower in HIV + patients compared to control subjects. The circadian fluxes in these three steroids are flattened in HIV disease, as well as diurnal patterns of circulating CD4 cells (45).

Taken together, these findings, obtained from varied models of clinical research, support the hypothesis that the interaction between the neuroendocrine and immune systems is physiologically relevant and pathologically significant, particularly in the context of lymphocyte adhesion and distribution.

CONCLUSIONS

There is a strong connection between physical and mental health. The field of psychoneuroimmunology seeks to define and characterize the interactions between the environment, the brain, the hormonal system, and resistance to disease. Intense research has been focused on the interaction between neurons and immune cells.

The interaction between the endocrinal system and immune cells is present in diverse situations. For example, in healthy subjects, fluctuations in plasma levels of cortisol are in a negative phase relationship to those of immune cells. When cortisol levels are higher (mid-morning), the number of immune cells is lower. Studies suggest that this interrelationship does not occur in HIV+ patients. These relationships may also be disrupted in certain groups of psychiatric patients, in the elderly, or in normal subjects following strenuous exercise or psycho-emotional stress. However, in humans, lymphocyte subsets in the blood do not necessarily mirror lymphocyte distribution in other immune compartments. Therefore, further research should be continued in this field to improve the understanding of lymphocyte homing in neuroimmunology.

Conflict of interest

The authors declare that they have no conflict of interest.

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BIOLOGICAL EFFECTS OF SUBSTANCE P IN THE BRAIN

I. Robuffo*

CNR Section of Chieti, 66100 Chieti, Italy.

Correspondence to:
Iole Robuffo, MD,
CNR Section of Chieti,
66100 Chieti, Italy.
e-mail: iole.robuffo@cnr.it

ABSTRACT

Substance P (SP) is a non-cholinergic neuropeptide produced at different levels in different cell types, including mast cells (MCs) and neurons. SP is involved in the regulation of many central nervous system (CNS) disorders such as anxiety, stress, mood disorders, and neurogenesis, and functions such as synapse growth, dendritic formation, respiration, neurotoxicity, nociception and pain. This neuropeptide produces inflammation after binding to its natural killer (NK) cell receptor. MCs and neurons possess the NK1 receptor and are activated by SP to produce inflammatory molecules such as cytokines and chemokines. In this article, we report that SP not only induces the generation of pro-inflammatory proteins, but also acts synergistically with cytokines such as IL-33 to enhance the inflammatory process.

KEYWORDS: *substance P, brain, CNS, immunology, inflammation*

INTRODUCTION

Substance P (SP) was discovered in 1931 by V. Euler and Gaddum who found that extracts from brain and intestinal tissues had hypotensive and spasmogenic activity. Subsequently, a protein was extracted from these tissues which was called SP. Further studies highlighted that SP is a neuropeptide member of the tachykinin (TAC) family that is present in mammals and distinguished in three subgroups: TAC1, 3, and 4. SP is a non-cholinergic neurotransmitter that is present at different concentrations in different areas of the central nervous system (CNS) (1). For example, SP is found at higher concentrations in the dorsal spinal roots, while it is lower in the ventral roots (2). Levels of SP are elevated in the grey matter, midbrain, postrema area, nuclei, and medullary fibers (3). However, SP concentrations in various brain areas could be species-specific and therefore vary in the various experimental animals used (4).

SP is involved in the regulation of anxiety, stress, mood disorders, neurogenesis, the growth of synapses, dendritic formation, respiration, neurotoxicity, and nociception and pain (5). When SP is injected into the third ventricle in experimental animals, it stimulates respiration and causes a slight increase in blood pressure (6).

DISCUSSION

Substance P (SP) in inflammation

SP is a protein made up of 11 amino acids that is produced by several cell types, including neurons and immune cells (7). SP acts by binding to its G protein-coupled neurokinin receptors (NKR), which include NK1R, NK2R, and NK3R (8). From these receptors, NK1R appears to have greater affinity for SP. SP binds the NK1R receptor in immune cells,

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causing an immune response, including the reaction towards microbes (9). In addition, SP has been observed to mediate tissue homeostasis and wound healing (9).

SP can mediate neurogenic inflammation and can be released after stimulation of the sensory nerves (10,11). This neuropeptide is biologically active in endothelial cells and smooth muscle cells and increases vascular permeability with the consequent leakage of plasma and the formation of edema (12,13). SP also activates intracellular adhesion molecules (ICAMs) as well as vascular cell adhesion molecules (VCAMs) in vascular epithelial cells (14,15). Mast cells (MCs) treated *in vitro* with SP generate more VEGF than untreated samples (16,17). The action of SP on the vessels causes an increase in vascularization with inflammatory cells crossing the tissues (18,19). SP works by binding to its NK1 receptor and mediates itching, which can be inhibited by antagonist drugs that block NK1 (20,21) (Fig.1).

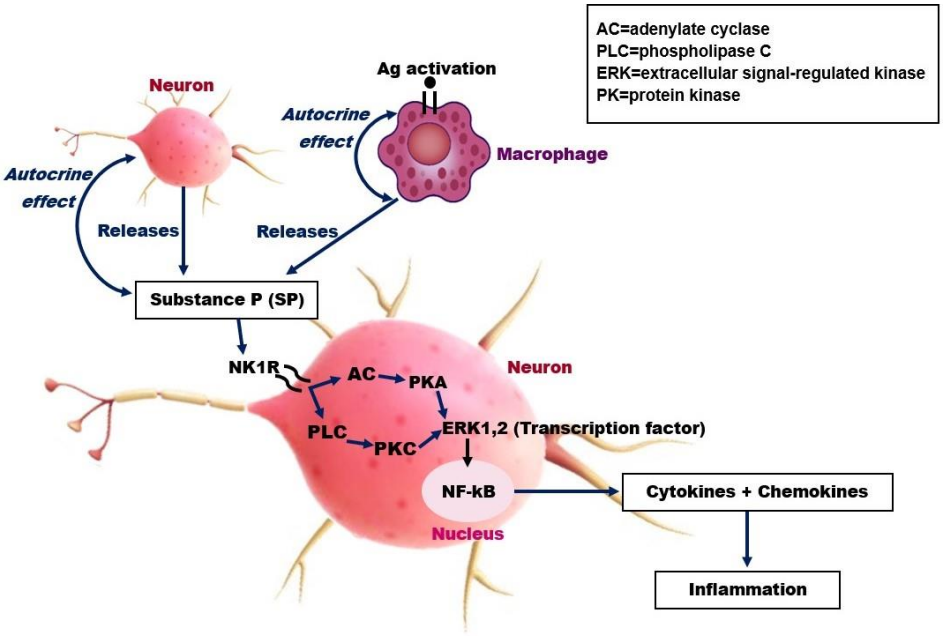

Fig. 1. *A schematic reproduction depicting Substance P (SP) secretion by neurons and macrophages.*

Substance P and mast cells (MCs)

MCs are immune cells derived from bone marrow that migrate and mature in tissues throughout the human body, which mediate innate and adaptive immunity (22,23). In addition to expressing the FceRI receptor, MCs show other ligands on their surface, including those of neuropeptides such as SP (24,25).

It has been reported that IL-33 significantly increases the ability of SP to stimulate MCs to secrete VEGF, tumor necrosis factor (TNF), and IL-1β, selectively without tryptase granule release (26,27) In their interesting article, Theoharides et al. provide much information on SP-mediated inflammation in relation to IL-33 (26).

In an *in vitro* study, the treatment of a line of MCs (LAD2) with SP plus the cytokine IL-33 achieved a synergistic effect on the stimulation of the potent pro-inflammatory cytokine IL-1β, compared to the administration of cells treated with IL-33 alone (28). These results demonstrate that SP is not only a potent pro-inflammatory molecule, but that it is also able to synergistically enhance other inflammatory cytokines such as IL-33 (29,30). In addition, the authors reported that SP alone has a stimulatory effect on IL-1β production in MCs only at high concentrations (1μM), while at lower concentrations (0.01–0.1 μM) there was no effect. These effects were also confirmed by IL-1β gene expression which demonstrated an active participation of SP in inflammatory effects induced by IL-1β. However, these reactions did not affect the inflammasome protein (NLRP3 or ASC) levels. Blocking the NK1 receptor on MCs suppressed the secretion of IL-1β. In this study, it was evident that SP and its receptor NK1 were involved in the induction of IL-1β. The authors concluded that in combination with IL-33, SP synergistically induces IL-1β secretion from MCs.

CONCLUSIONS

In conclusion, SP that is produced by different cells, including neurons and MCs, induces cytokines and chemokines that mediate many neurological disorders. In addition, by binding its receptor NK1, SP can act synergistically with certain cytokines, such as IL-33, and induce inflammation.

Conflict of interest
The author declares that they have no conflict of interest.

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THE ROLE OF SEROTONIN IN IMMUNITY AND INFLAMMATION

F. Gaudelli[1*] and C. Annicchiarico[2]

[1] School of Dentistry, University of Foggia, Foggia, Italy;
[2] Independent researcher, Bari, Italy.

Correspondence to:
Federico Gaudelli,
School of Dentistry,
University of Foggia,
71100 Foggia, Italy.
e-mail: fed-erico_gaudelli.563780@unifg.it

ABSTRACT

Serotonin (5-HT) is a neurotransmitter that regulates different functions of the human body. 5-HT has immunomodulatory effects and plays an important role in the brain, regulating body temperature, mood, emotions, sexuality, sleep, appetite, and cognitive functions, amongst other functions. In the immune system, this neurotransmitter is produced by monocytes/macrophages, lymphocytes, and mast cells (MCs), and interacts with circulating immune cells in peripheral tissues. 5-HT production can be enhanced by increases of cytokines such as IL-1β, IL-33, and IL-13, and can have both inhibitory and stimulatory effects on innate immune cells. At physiological levels, 5-HT can stimulate the immune system, which can be helpful for the body, but at elevated concentrations, it can activate inflammation and be harmful.

KEYWORDS: *serotonin, 5-HT, neurotransmitter, immunity, inflammation, CNS*

INTRODUCTION

Neurotransmitters are proteins that transmit information across synapses between neurons. They are contained in the synaptic vesicles of neurons that fuse to the neuronal membrane after a stimulus and release neurotransmitters into the synaptic cleft. These neuropeptides bind to their specific receptors and/or ion channels located on the postsynaptic neuron membrane and cause a biological response. Neurotransmitters can be derived from amino acids such as aspartic acid, glutamic acid, glycine, and γ-aminobutyric acid (GABA) (Table I).

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Table I. *Some of the most well-known neurotransmitters.*

Monoamine (from phenylalanine and tyrosine):	dopamine, norepinephrine, epinephrine
From tryptophan:	serotonin (5-HT), melatonin, histidine, histamine
Peptides and neuropeptides:	neurotensin (NT), galanin, bombesin, gastrin-releasing peptide (GRP), neuromedin B
neurohypophysis:	vasopressin, oxytocin, neurophysin (type I and II), neuropeptide Y, pancreatic polypeptide, peptide YY
Tachykinins:	neurokinin A, neurokinin B, neuropeptide A, gamma neuropeptide, substance P
Other neurotransmitters:	acetylcholine, glucagon, vasoactive intestinal peptide (VIP), somatostatin, endorphin, enkephalin

Serotonin or 5-hydroxy tryptamine (5-HT) (molecular formula: C10H12N2O) was discovered in 1935, when it was isolated in Pavia by Vittorio Erspamer (1) (Fig.1). 5-HT is a neurotransmitter that plays an important role in the brain. 5-HT is synthesized from tryptophan, an amino acid produced in high quantities by the neurons of the central nervous system (CNS) and in the enterochromaffin cells of the gastrointestinal system (2). Levels of 5-HT are more concentrated in different areas of the brain; For example, the hypothalamus contains more 5-HT than the neopallium and cerebellum, where the quantity is lower. 5-HT levels depend on the amount of dietary tryptophan that enters the CNS (3).

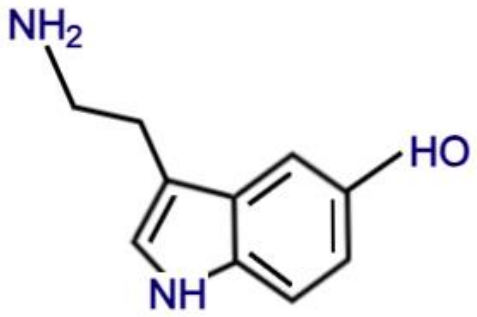

Fig. 1. *The chemical structure of serotonin (5-HT).*

The precursor amino acid of 5-HT is tryptophan, which is converted to 5-hydroxytryptophan (5-HTP) from hydroxylated tryptophan. Subsequently, the 5-HTP is decarboxylated by the enzyme decarboxylase to form 5-HT (4) (Fig.2). 5-HT is stored in neurons as a neurotransmitter and cooperates with hormones including substance P and somatostatin. The degradation of 5-HT is carried out by the monoamine oxidase (MAO) pathway which produces 5-hydroxyindole acetic acid (5-HIAA), and by the sulfotransferase enzyme that leads to the generation of tryptamine-O-sulphate with a reduction of 5-HT.

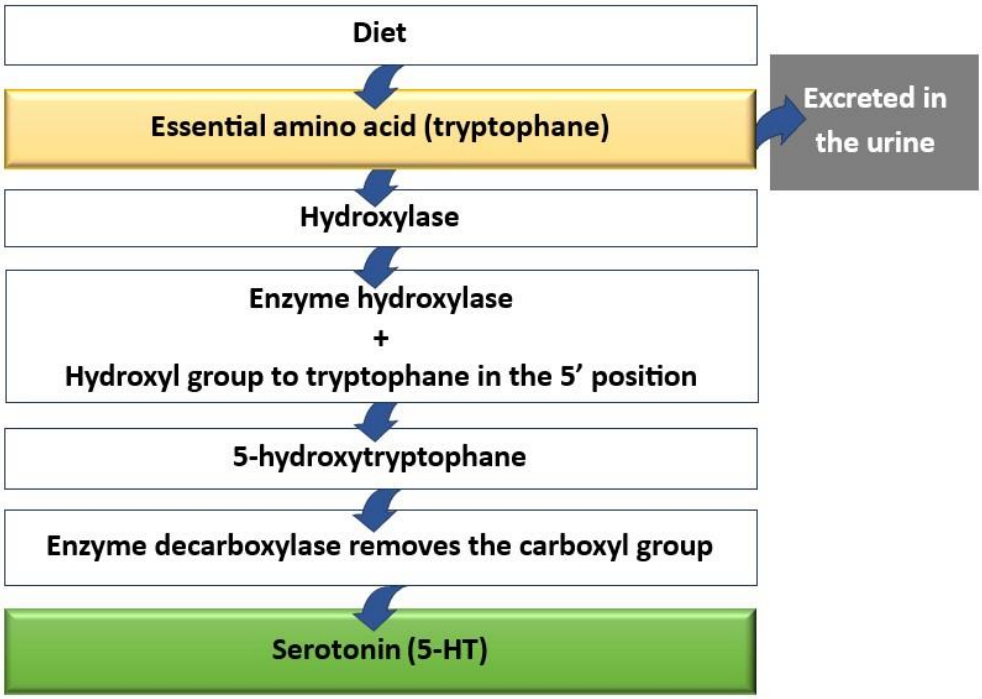

Fig. 2. *The biochemical cascade for serotonin (5-HT) synthesis, starting from tryptophan.*

5-HT is dispersed differently throughout the body, with some organs having a higher concentration. The walls of the small intestines and stomach possess enterochromaffin cells with high amounts of 5-HT, which regulates intestinal motility and secretion (5). Platelets are another source of 5-HT, which is released into the bloodstream, acts on the dilation of vessels, and helps regulate homeostasis and heal wounds (6). 5-HT is produced by nine brain nuclei In the CNS that extend to the spinal cord, and it performs various functions such as regulation of body temperature, mood, emotions, sexuality, cognitive functions, sleep, creativity, and appetite (7,8) (Table II). In mice, 5-HT causes pain if injected subcutaneously (9). Additionally, 5-HT plays an important role in the immune system where it is involved in interactions with T cells, mast cells (MCs), macrophages, dendritic cells, and platelets (10).

Table II. *Some functions of the human body that are regulated by serotonin.*

• Mood and emotions	• Sexual health	• Nausea
• Sleep	• Bone health	• Cognitive functions
• Digestion and appetite	• Wound healing	• Body temperature

The role of serotonin (5-HT) in immunity and inflammation

5-HT has immunomodulatory effects and interacts with circulating immune cells in peripheral tissues (11). It seems that cells such as monocytes/macrophages, lymphocytes, MCs, platelets, vascular smooth muscle cells, and adipocytes are all sources of 5-HT in the human body (12). However, 5-HT is mostly stored in and released by platelets after activation (13).

5-HT that is synthesized in the brain and peripheral tissues causes various effects and represents a classic neurotransmitter with both autocrine and paracrine action. 5-HT is implicated in peristaltic motility and gastric disorders, and in intestinal secretion (14). 5-HT is involved in the immune response and is released by endothelial cells and then subsequently stored in platelet granules, which are a source of 5-HT for the cells of the immune system. 5-HT participates in innate and adaptive immunity after being secreted by macrophages, MCs, and T lymphocytes (15).

In humans, there are 7 types of 5-HTR receptors, which are numbered from 1 to 7 (5-HTR1-5-HTR7) and are involved in different functions. For example, the 5-HTR1 and 5-HTR5 receptors downregulate the synthesis of cyclic adenosine monophosphate (cAMP) (16), and 5-HTR4, 6, and 7 activate adenylate cyclase and promote cAMP activity (17). The activation of 5-HTR2 stimulates inositol triphosphate and diacylglycerol and increases Ca^{2+} fluxes in the cell cytoplasm,

and 5-HTR3 causes the influx of Ca^{2+} and Na^{+} with the exit of K^{+}, causing a depolarization of the cell membrane (18). In turn, 5-HTR1 includes 5 subtypes ranging from A to F (but not including C), 5-HTR2 has 3 subtypes (A, B, and C), while 5-HTR3, 4, 5, 6, and 7 have no subtypes.

5-HT that is produced by endothelial cells can exert an effect on circulating naïve lymphocytes, influencing the immune system (10). An increase in the cytokines IL-1β, IL-33, and IL-13 has been reported to enhance 5-HT production from endothelial cells (19)

In animal experiments, it was noted that injecting 5-HT into the cerebral ventricles sharply elevated body temperature (probably by mediating IL-1 activation), while catecholamines lowered it, actions that are mediated by the hypothalamus (20). 5-HT can have both stimulatory and inhibitory effects on innate immune cells, such as macrophages, depending on the dose administered. With low concentrations of interferon gamma (IFN-γ) stimulation, 5-HT can increase phagocytosis, while with high concentrations of IFN-γ, 5-HT inhibits phagocytosis (21). In *in vitro* studies, macrophages treated with 5-HT binding the 5-HTR1A receptor secrete more pro-inflammatory cytokines than untreated macrophages (19), an effect that involves the upregulation of nuclear factor kappa B (NF-kB) activation. In addition, 5-HT stimulates the production of tumor necrosis factor (TNF) and upregulates the expression of M2 polarization through the activation of 5-HTR2B and 5-HTR7 (22).

By activating the 5-HTD1 receptors, 5-HT contracts blood vessels, including those in the brain which, when dilated, cause migraines (23). In addition, by binding to 5-HT3 receptors, 5-HT stimulates nociceptive sensory nerve endings and plays a key role in the excitation and inhibition of neurons and in the regulation of CNS functions (24). 5-HT elevates cortisol and prolactin levels, inhibiting gonadotropin-releasing factor and inhibiting ejaculation (25). In fact, low levels of 5-HT cause premature ejaculation (26). 5-HT dysfunction has been associated with neuropsychiatric disorders including bulimia and anorexia (27), anxiety (28), schizophrenia (29), and obsessive-compulsive disorder (30), although the mechanisms by which 5-HT causes these diseases is not yet clear, and it could be that targeting 5-HT may represent new therapeutic strategies (Table III).

Table III. *Neurological effects associated with low serotonin (5-HT) levels.*

• Anxiety	• Obsessive-compulsive disorder
• Sleep problems	• Schizophrenia
• Depression	• Suicidal behavior
• Panic disorders	• Phobias
• Bulimia	• Post-traumatic stress disorder

Sometimes 5-HT deficiency can provoke depression; in fact, it is called the “happiness hormone”. The effects of 5-HT on depression were found to be conflicting in different studies (31). When administered through the diet, tryptophan, the essential amino acid precursor of serotonin, was seen to alleviate behaviors associated with depression and anxiety in mice (32). It was seen that the reduction of tryptophan introduced through the diet was not able to induce depression, although animal studies may not reflect those on man.

Tryptophan is an essential aromatic amino acid and its metabolism is mediated by intestinal bacterial degradation that occurs through two pathways: 5-HT bioamine and kynurenine (19). Tryptophan metabolites are involved in the immune response and in brain functioning. Studies have reported that pharmacologically inhibiting tryptophan hydroxylase can cause depression in around 30% of cases. (33,34).

The binding of 5-HT on the 5-HTR1A and 5-HTR2A receptors of natural killer (NK) cells has a stimulatory effect with increased cytotoxicity and IFN-γ secretion (35). 5-HT also has an anti-apoptosis action and an action against oxidative damage to NK cells. Furthermore, in depression patients treated with 5-HT inhibitors, increased cytotoxicity and proliferation of NK cells has been noted (36). All these effects strictly depend on the concentration of 5-HT used, which can give opposite results.

CONCLUSIONS

Therefore, in conclusion, the concentration of 5-HT seems to affect the actions of the immune system, even if the data in the literature appears to be conflicting. At physiological concentrations, 5-HT can stimulate the immune system, while at high concentrations, it can activate inflammation and be harmful to health.

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

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Letter to the Editor

SIMILARITIES IN THE PATHOGENESIS OF NEURODEGENERATIVE DISEASES AND THE DIFFICULTY WITH DIAGNOSIS

E. Toniato*

Department of Innovative Technologies in Medicine and Dentistry, G. D'Annunzio University, Chieti, Italy.

**Correspondence to*:
Prof. Elena Toniato,
Department of Innovative Technologies in Medicine and Dentistry,
G. D'Annunzio University,
Chieti, Italy.
e-mail: elena.toniato@unich.it

KEYWORDS: *neurodegenerative disease, pathogenesis, diagnosis, protein, Alzheimer's disease*

INTRODUCTION

It is possible that diseases involving neuronal pathology share a similar pathogenesis, including inflammation and the aggregation of abnormal proteins. Molecular advances have shown that malformed proteins, such as amyloid beta (Aβ), cause damage to the brain by creating toxicity and inflammation (1,2). The deposition and aggregation of abnormal proteins in the brain is involved in some neurodegenerative diseases, including Alzheimer's Disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Today the pathogenesis of these diseases is a little clearer, but it is not yet fully explained and there seems to be much more to discover. The diagnosis of neurodegenerative disease is often difficult to make, as diseases often share many similarities, and it can sometimes only be made after the patient's death. The various pharmacological therapies available are limited and are often determined on the basis of the symptoms that the patient presents. However, the more we learn about these diseases, the more therapeutic tools can be constructed.

DISCUSSION

Neurodegenerative disorders are diseases that present central nervous system (CNS) dysfunction with the loss of neurons. The most common of these diseases are AD and PD, and the pathogenesis is mediated by protein dysfunction in both disorders. AD and PD present a similar pathogenic mechanism which concerns the alteration of proteins, their deposition, and their folding (3).

In AD, the protein dysfunction involves the misfolding of Aβ and the Tau protein, which leads to the formation of destructive Aβ plaques in the brain. In PD, there is misfolding of the protein alpha-synuclein (α-syn), which aggregates to form neuronal inclusions called Lewy bodies. This pathogenic mechanism is also present in Huntington's disease (HD), where the huntingtin protein is misfolded and aggregated. This shows that many neurological disorders may present similar characteristics and therefore require common therapy.

Often, the symptoms and therapy of the different brain disorders overlap, making the diagnosis difficult, even if considerable progress has been made today with biomarkers. Neurodegenerative diseases can be classified based on clinical symptoms, anatomical region, biochemical modification of neuronal or glial proteins, and abnormalities of extracellular proteins. Clinical signs may include cognitive decline or alterations in CNS functions and/or dementia. The

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involved tissues may concern the limbic system, neocortical areas, hippocampus, and cortex. In addition, there are protein abnormalities and the loss of neurons, processes that can be highlighted with immunohistochemistry, which can help in the diagnosis.

The diagnosis should take the accumulation of both intracellular and extracellular proteins into consideration. Different proteins can be involved in neurodegeneration, which can be seen in the brains of elderly people presenting alterations in brain structures. The distribution of abnormal proteins in the brain and their characterization can be of great help in the classification of these diseases.

Misfolded proteins generate the formation of Aβ oligomers in the CNS and therefore, amyloidosis (Fig.1). Aβ oligomers were found in *in vitro* experiments using cell cultures from mouse models mimicking AD and brain tissue samples from post-mortem AD patients, demonstrating that these peptides are key components of amyloidosis and illness (4). It is hypothesized that in addition to amyloidosis, other abnormal protein molecules may also participate in brain disorders. Furthermore, as there are different types of Aβ formations, these can interact with each other, damaging neurons and causing disease.

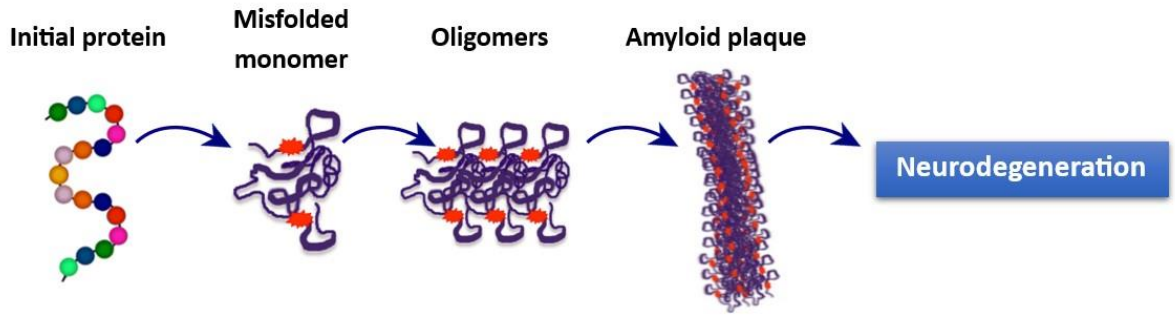

Fig. 1. *Misfolded proteins are generated by an initial protein that forms a monomer. Monomers join to create oligomers which aggregate and form amyloid (Aβ) plaques, which damages neurons and leads to neurodegeneration.*

Aggregated plaques of Aβ protofibrils cause neurotoxicity with neuronal damage and play an important role in the pathogenesis of neurodegenerative diseases such as AD. The accumulation of Aβ in the brain precedes the disease, which can manifest even after several years. The in-depth study of Aβ facilitates therapeutic research for these neurodegenerative diseases as there is much needed for resolving this dilemma that affects a substantial amount of people around the world.

CONCLUSIONS

Recently it has been observed that the inhibition of Aβ with proteases may be the right path for therapeutic research. For example, different studies utilizing the transport protein transthyretin (TTR), which binds and alters the augmentation of Aβ clustering, have shown that it inhibits the Aβ toxicity both *in vitro* and *in vivo* (5-7). However, more studies are needed to clarify many obscure points presented by these neurodegenerative diseases.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

IL-1 AND TNF SECRETION BY MICROGLIA AND DOWN-REGULATION SIGNALS

F. Mastrangelo*

Department of Clinical and Experimental Medicine, University of Foggia, Italy.

**Correspondence to*:
Filiberto Mastrangelo,
Department of Clinical and Experimental Medicine,
University of Foggia Medical School,
71122, Foggia, Italy.

e-mail: filiberto.mastrangelo@unifg.it

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INTRODUCTION

Microglia are macrophage-type innate immune cells resident in the brain that perform various functions such as maintaining neuronal health, repairing neuronal damage caused by injuries, and brain regulation and development. In addition, microglia eliminate infectious agents, dead cells, and harmful antigens. The excessive activation of these cells causes a high production of cytokines mediating inflammation which can even lead to the death of the individual. Here, we discuss the current understanding of the potential signaling mechanisms and the secretion of cytokines by microglia.

DISCUSSION

Microglia are macrophage-like cells that reside in the central nervous system (CNS) and when activated with appropriate antigens, or by pathological states such as necrotic and apoptotic cells, they produce pro-inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and chemokines. These cytokines are produced in defense of the organism, but when they are activated, they produce highly inflammatory products with effects that are deleterious for neurons and for the life of the individual. Excessive production of cytokines and chemokines by microglia activation can lead to neurological diseases including Alzheimer's disease and Parkinson's disease, amongst others.

IL-1 and TNF are polypeptide cytokine soluble products released by activated monocytes/macrophages with a broad range of biological activities, most importantly of which is that they have potent regulatory effects on the immune system (1). These two monokines are generated by a variety of cell types but are predominantly secreted by monocyte-macrophage cells and other cells, which play an important role in different phases of the immune response to both foreign and certain self-antigens. However, many aspects of the production and actions of IL-1 and TNF remain largely unknown (2,3). It has been reported by many authors that the roles of microglia and other antigen-activated macrophage cells in monokine production and T-cell activation are very critical for orchestrating the immune response by the host (4). Antigens are known to stimulate macrophages (and microglia in the brain) to generate IL-1 and TNF, two important initial signals for activating quiescent T cells to become antigen-specific T cells. Indeed, T cells recognize antigens displayed on the surface of macrophages in association with major histocompatibility complex II (MHCII). Naïve T cells respond to IL-1 and TNF to become activated T cells capable of expressing the IL-2 receptor, producing soluble IL-2, and secreting other cytokines such as IL-4, IL-6, and gamma interferon (IFN-γ) (5).

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In recent years, there has been substantial progress in the understanding of cytokine production and regulation pathways by macrophages, even though the exact mechanisms are still an enigma. However, results reported in the immunological literature tell us that IL-4, a growth and regulatory factor for activated B cells and T cells, and IL-6, downregulate the production of IL-1 and TNF by human monocytes (6,7).

Moreover, immunosuppressive products of cyclooxygenase, such as inflammatory prostaglandin E2 and thromboxane A2 cellular aggregation, are produced by macrophages after stimulation with antigen and/or some cytokines such as IL-1 and TNF. It has been hypothesized that some cyclooxygenase products are also negative feedback signals for the downregulation of IL-1 and TNF production by macrophages. For example, IL-4 produced by T helper cells appears to downregulate and inhibit the generation of fever *in vivo* induced by IL-1 and TNF (8). The means by which IL-4 and IL-6 downregulate the generation of IL-1 and TNF may involve the regulation of other protein syntheses, such as IL-10, IL-1 receptor antagonist (IL-1Ra), IL-37, IL-38, and the soluble TNF receptor, molecules that are all released during immune activation.

In addition, it is possible that IL-4 and IL-6 may mediate their downregulatory effects on IL-1 and TNF production at the level of DNA transcriptional control. For example, IL-4 and IL-6 can influence cytokines and the cytokine receptor gene that assist immunoregulatory molecules, such as specific enhancers and promoters of DNA binding proteins at AP-1 and NF-κB sites. Interestingly, many side effects observed in cytokine immunotherapy appear to be mediated by IL-1 and TNF, in part through the production of arachidonic acid metabolites that can cause fever, cell aggregation, release of cytoplasmic granules, hypotension, capillary leak, edema, and other side effects (9).

Therefore, the inhibitory effects of IL-4, IL-6, IL-10, and other cytokines on the production and activity of IL-1 and TNF could play an extremely important role in controlling the delicate immunoregulatory balance in the brain during the immunological response and inflammation.

CONCLUSIONS

Here we report that the IL-1 family members secreted by microglia can have dual effects as pro or anti-inflammatory cytokines. Taken together, recent findings suggest that microglial activation with the release of pro-inflammatory cytokines deserves interest as the target of treatment for neurodegenerative disorders.

Conflict of interest

The author declares that they have no conflict of interest.

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