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Neuroprotection: The Way of Anti-Inflammatory Agents

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Abstract

Neurons are basic structural and functional units of the nervous system with major function being that of integration and interpretation of neuronal input or information. The lifespan of a nerve cell generally last throughout the individual lifetime. However, some physiologic or pathologic processes may affect the neuron causing premature death of this cell or tissue. This premature neurological death caused by pathologic circumstances is what we call neurotoxicity. The biochemical mechanisms put forward to explain neurotoxicity are not fully known. Nonetheless, whatever the mechanism involved, the outcome usually results in apoptosis, pyropoptosis, or necrosis. Examples of these mechanisms include excitotoxicity, oxidative stress, glial cell destruction, vascular interruptions, and inflammation. The idea about possibly protecting neurons against insults using pharmacologic means leads to the birth of the neuroprotection concept. This new concept has emerged based on ongoing research, suggesting it is possible through physical and pharmacological means to prevent or avoid neurotoxicity by the abovementioned mechanisms but with the exception of vascular interruption mechanisms. We will present in this chapter a synoptic view of the inflammatory mechanisms implicated in neurotoxicity and bring out the possible implications in neuroprotection.

Keywords: neuroprotection, neurotoxicity, inflammation, inflammasome, NLRP3, metabolic syndrome

1. Introduction

Neurons represent the main component of the nervous system, and they are indispensable for integration and transcription of nerve impulses [1]. The central nervous system (CNS) is made up of about 100 billion neurons and approximately 10–50 times more glial cells [1]. Unlike glial cells, which maintain the ability to undergo cell division even after adult age, neurons are no more capable of mitosis at the adult age. Nevertheless, they are supposed to live all the life of an individual [1]. Unluckily, there are some pathologic and physiologic circumstances during which we observe a premature neuronal death [2]. These include stroke, head trauma, neurodegenerative disease, psychiatric disease, multiple sclerosis, aging, etc. This premature neurological death caused by pathologic circumstances is what we call neurotoxicity. The biochemical mechanisms of neurotoxicity are not all described yet. Nevertheless, no matter the mechanism, the result will be either apoptosis, pyroptosis, or necrosis [3]. Reviewing the literature, we found several biochemical pathways described as being implicated in the process of neurotoxicity. These include excitotoxicity, oxidative stress, glial cell destruction, vascularization

interruption, and inflammation [3]. Being confronted with neurotoxicity, an idea emerged about possibly protecting neurons against insults using pharmacologic means. This was the birth of the neuroprotection concept.

The neuroprotectionα concept regroups all pharmacologic and/or physical resources capable of preventing or avoiding neurotoxicity by affecting one or more biochemical mechanisms of neurotoxicity [4, 5]. This definition excludes all therapeutics that lead to an improvement of the vascularization of the brain [4, 5]. The neuroprotection targets could therefore be avoidance of excitotoxicity, glial cell protection, oxidative stress reduction, and/or inhibition of inflammation. On the theoretical, logic and experimental fields, neuroprotection is evident; however, it remains a concept difficult to prove on the clinical field. Indeed, although many animal experimental researches on neuroprotection have been conclusive, this could not be confirmed in clinical trials. This could be explained by the difficulty to establish clinical criteria for the evaluation of neuroprotection in clinical researches. Despite this methodologic difficulty which tends to discredit the neuroprotection concept in clinical field, we propose to make an analysis of neuroprotection on the prism of inflammation. We will present a synoptic view of the inflammatory mechanisms implicated in neurotoxicity and bring out the possible implications in neuroprotection.

2. Inflammatory reaction and particularities in the central nervous system

Inflammation is the first step in the defense mechanism of the organism by which the actions of different components of the nonspecific immunity are put together in order to fight against an exogenous or endogenous aggression [6]. By definition, inflammation is a local process which takes place in the connective tissue of the organ affected. Nevertheless, according to the amplitude and duration of the local inflammation, it can be secondarily generalized through production of a systemic response such as the synthesis of acute-phase reactants or the endocrine effect of cytokines [6, 7].

2.1 Inflammation response mechanism

The first step of an inflammation reaction is the adhesion of leukocytes on the endothelial membrane. This step takes place essentially in the postcapillary venule. Activated endothelial cells are required for this step as they need to express adhesion molecules on their surfaces. These molecules serve as receptor for their complementary adhesive molecules present on the surface membrane of circulating leukocytes. Leukocyte adhesion to the vascular endothelium occurs in two phases which implicate both adhesion molecules. The first phase is the leukocytes rolling on the vascular endothelium. It involves the E-selectin (CD62E) and the P-selectin (CD62P) expressed on the vascular endothelium transiently interacting the P-selectin glycoprotein ligand-1 (PSGL-1), E-selectin ligand-1 (ESL-1), and L-selectin (CD62L) which are ligands expressed on leukocytes' surface. The second phase is the leukocyte-endothelium firm adhesion. It is realized by the interaction between the vascular endothelium adhesion molecules named vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) and leukocyte integrins known as VLA-4 and LFA-1 (**Figure 1**). The leukocyte adhesion is preceded by a certain number of steps which aid the adhesion phase. These steps are endothelial activation, induced by interleukin-1β (IL-1β) and tumor necrotic factor α (TNFα); the activated endothelium secretes some agents such as
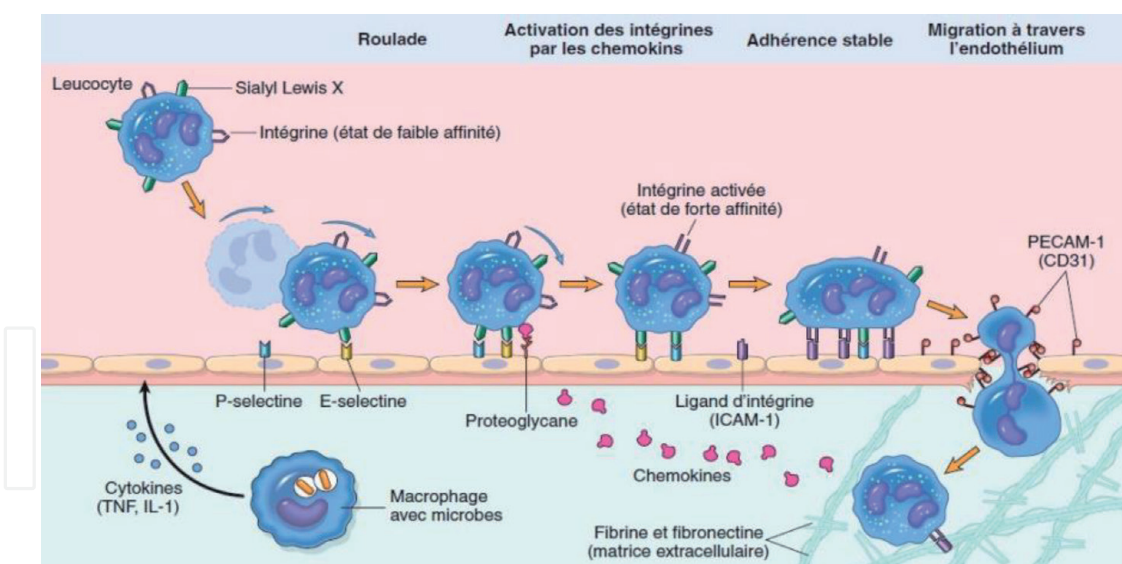
Figure 1.
Mechanism of inflammation reaction.

platelet-activating factor (PAF), prostaglandin E2 (PGE2), and azote monoxide (NO) which lead to a vasodilatation with reduction of blood flow aiding leukocyte rolling. Interleukin-1β and TNFα are also responsible for the adhesion molecules expressed on the endothelial surface and the liberation of chemotactic agents.

The second step of inflammation is diapedesis; it follows the leukocyte adhesion and refers to the passage of leukocytes from blood circulation to the connective tissue where the inflammation process has begun. This leukocyte migration is done across the intercellular endothelial junctions and is affected by chemotactic peptide concentration gradient at the inflammatory focal point. At the inflammatory focal point, leukocytes become activated and start to secrete oxygen-reactive substances, pro-inflammatory cytokines, and lipid inflammatory mediators. They also excrete the contents of their granules. All these actions lead to a systemic inflammatory response by endocrine effects of pro-inflammatory cytokines and also cessation of the cause of the inflammation. However, in certain cases the amplification of the inflammation by pro-inflammatory cytokines is responsible of destruction of the tissue where it takes place [7]. The endocrine effects of pro-inflammatory cytokines are multiple; the principal effects are observed on the liver and the brain [8]. In the liver, they induce the synthesis of acute-phase proteins; on the brain, they result in fever, asthenia, anorexia, and somnolence (**Figure 2**).

2.2 Inflammatory cytokines

The term cytokine regroups the low-molecular-weight glycoproteins implicated in cellular communication. They are active in the control of proliferation, maturation, and differentiation of hematopoietic cells and also in the regulation of inflammatory and immunologic responses. They exercise their regulatory activity through an autocrine, paracrine, juxtacrine, and endocrine mechanism via the membrane receptors present on focus cells. In the field of immunology, there exist two groups of cytokines: pro-inflammatory cytokines such as interleukins 1, 6, 8, and 18 (IL-1, IL-6, IL-8, IL-18), TNFα and anti-inflammatory cytokines such as interleukins 10, 4, and 13 (IL-10, IL-4, IL-13) transforming growth factor β (TGFβ). The balance between pro-inflammatory and anti-inflammatory cytokines regulates the local intensity of an inflammatory reaction and its duration. Among pro-inflammatory cytokines, IL-1β and TNFα have the central role in the initiation and chronicity
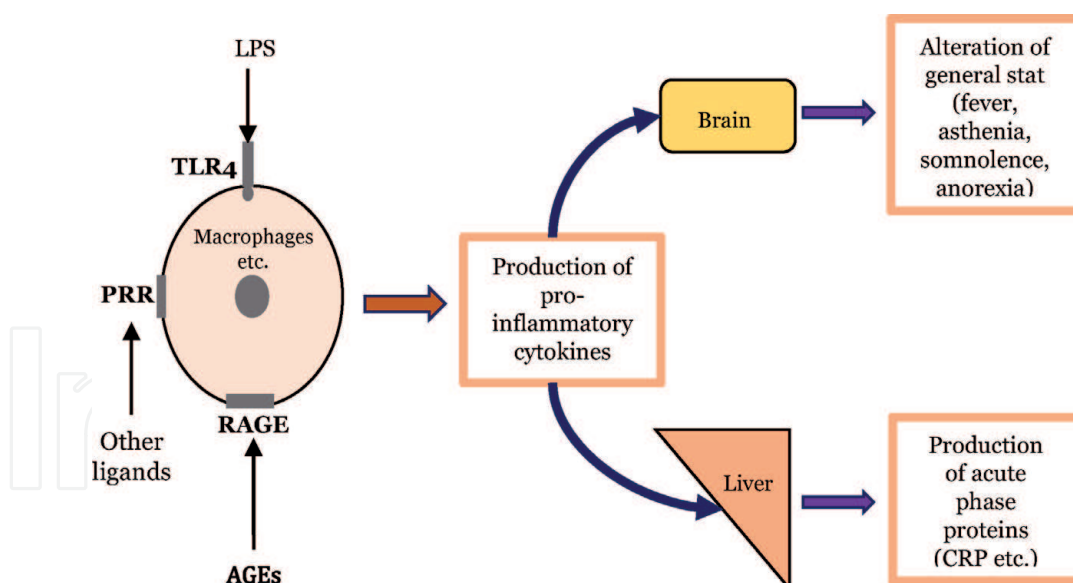
Figure 2.
Role of sentinel cells in the inflammatory response (modified from [8]). Sentinel cells (macrophage in this case) detects in its environment a potential danger by the pattern recognition receptors (PRR). This recognition active the inflammation signalization ways with the liberation of pro-inflammatory cytokines. PRRs considered in this example are toll like receptor 4 (TLR4) which recognize the lipo-poly-saccharide (LPS) of Gram negative bacteria and RAGE which recognize the ends products of glycation (AGEs).

of inflammation. These cytokines are synthetized in an inactive precursor form: pro-IL-1β and pro-TNFα. Activation of pro-IL-1β is done by a cysteine/aspartate-type membrane protease named caspase-1 or IL-1β converting enzyme (ICE). Concerning TNFα, its liberation and activation require an adamalysine family enzyme called TNFα- converting enzyme (TACE). Interleukin-1β and TNFα have a synergetic action at the inflammation focal point; they are implicated in the expression of cyclooxygenase 2 (COX2); production of PGE2, NO, and PAF; expression of adhesion molecules at the endothelium level membrane; production of other pro-inflammatory cytokines; liberation of chemotactic peptides and metalloproteases; etc. The activities of these major pro-inflammatory cytokines are under the control of many natural inhibitors. These inhibitors can be classified regarding their mode of action into three categories:

- The pro-inflammatory cytokine receptor antagonists: they compete with pro-inflammatory cytokines on their receptors.

- The pro-inflammatory cytokine soluble receptors: they inhibit pro-inflammatory cytokine activities binding them; this family is represented by truncated receptors of IL-1β (IL-1 R1 and R2) and TNFα (TNF R55 and R75).

- The anti-inflammatory cytokines: they act by inhibition of pro-inflammatory cytokine biosynthesis; this family is represented by IL-4, IL-10, IL-11, IL-13, and TGFβ.

Chemokines constitute another group of pro-inflammatory cytokines; they have chemotactic properties for the leukocytes. They are produced by all leukocytes, platelet, and connective tissue cells following stimulation by bacterial or viral products, IL-1β, TNFα, fragment C5a of complement, and leukotriene. Chemokine release leads to the degranulation and activation of leukocytes which provoke a massive release in the inflammatory focal point of lysosomal enzymes, oxidant, and lipid mediators [7].

2.3 Particularities of inflammation in the central nervous system

In the central nervous system (CNS), the same inflammatory mechanism previously described remains valid. However, because of the blood–brain barrier, the actors and kinetic of inflammation in the CNS are particular [9]. Furthermore, in the CNS, the immune reactions are molded by the presence of cellular and molecular factors slowing the immune response [9]. In the physiologic conditions, the blood–brain barrier is not permeable to blood constitutes including immune cells. This immune isolation of the CNS brings up the question about the actors implicated in an inflammatory reaction in this particular organ. Many studies prove that the microglial cells located in the periventricular spaces express the class II molecules of the major histocompatibility complex (class II MHC) and can play the role of macrophages in the initiation and amplification of inflammation [9, 10]. Hence, microglial cells can be activated in CNS by three ways: pathogen-associated molecular patterns (PAMPs), missing self, or danger-associated molecular patterns (DAMPs) [11, 12]. This microglial cell activation leads to phagocytosis, antigen presentation, and production of pro-inflammatory cytokines [13]. Furthermore, the active microglial cells express the co-stimulant molecules including CD45, B7–1, B7–2, LFA-1, CD40, ICAM-1, and VCAM-1 which increase the permeability of the blood–brain barrier resulting in the penetration of immune cells in the CNS [9, 13]. It is possible for the active T lymphocytes to cross the blood–brain barrier and penetrate into the brain parenchyma [14]. If these infiltrated T lymphocytes recognize their specific antigen, they will produce pro-inflammatory cytokines that further increase the permeability of the blood–brain barrier [9]. However, this inflammatory activity caused by activated microglial cells or activated T lymphocyte in the CNS remains strongly modulated and inhibited by many cells and molecular immunosuppressing factors present in the CNS.

In the CNS, they are unappropriated conditions for the development and amplification of an inflammatory reaction. Indeed, we observe in the CNS a reduction of the expression of class I and class II molecules of the major histocompatibility complex on the cells, a local production of anti-inflammatory cytokines and a continuous elimination, by apoptosis, of the active T lymphocytes that have crossed the blood–brain barrier [9]. This apoptotic elimination of infiltrated T lymphocyte is the result of an interaction between receptors Fas/Apo-1 (CD95) on the active T lymphocytes and ligands FasL (CD95L) on the CNS cells [15, 16]. This "inflammo-resistance" state of the CNS is not necessarily an advantage. Indeed, low expression of class I molecules of the major histocompatibility complex on the CNS cells leads to two potential consequences. Firstly, it may be possible for the active immune cells if they cross the blood–brain barrier to attack the self CNS cells following the "missing self" principle [11]. Secondly, it may be difficult for active cytotoxic T lymphocyte when they cross the blood–brain barrier to destroy infected CNS cells in the case of CNS viral infection [17]. These consequences make the CNS particularly susceptible to persistent inflammatory states once the pathogen or other cause of inflammation has circumvented all the anti-inflammatory processes present in CNS [17]. Furthermore, even if apoptotic elimination of infiltrated active T lymphocytes leads to a modulation of inflammation in the CNS, it also delays the elimination of the cause of inflammation and therefore prolongs the inflammatory state in the CNS. Apoptosis of infiltrated active T lymphocytes also leads to the release, in the CNS parenchyma, of anti-inflammatory cytokines notably IL-10 and TGFβ which inhibit the cytotoxic activity of active T lymphocytes and thus might perpetuate an eventual CNS viral infection [18, 19]. It appears that it is difficult for an inflammatory process to begin in the CNS, but if for one reason or the other an inflammatory process does begin in the CNS, it becomes very difficult to avert it completely and rapidly.

3. Inflammasome molecular platform

3.1 Description of an inflammasome

Inflammation is amplified and maintained by the activities of pro-inflammatory cytokines principally IL-1β and IL-18. However, the previously described inflammatory mechanism leads to the formation of these cytokines in an inactive form. In this part, we focus on the analysis of the molecular platform implicated in the activation of these cytokines called inflammasome. An inflammasome is an innate immune complex that recognizes pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) and leads to the activation of an inflammatory caspase: caspase-1 [20]. It is a macromolecule complex formed by oligomerization of a specific type pattern recognition receptor, an adaptor protein and caspase-1. This association results from the interaction between homotypic domains [20]. Pattern recognition receptors (PRRs) implicated in the inflammasome's structure are particular. Their activation leads specifically to the activation of caspase-1 rather than the activation of transcription factors such as nuclear factor kappa-B (NF-κB) or IFN regulatory factor 3/7 (IRF3/7) as well as protein synthesis [20]. Three receptors' families are actually described as principal activators of the inflammasome: nucleotide-binding domain and leucine-rich repeats containing receptors (NLR), AIM2 {absent in melanoma 2}-like receptors (ALR), and RIG {retinoic acid inducible gene}-I-like receptor (RLR) [20]. The implication of the RLR in the activation of inflammasome is still debated.

Twenty-two NLR types have been identified in humans. They have a structural organization with a leucine-rich repeat (LRR) domain, which interacts with the ligand; a nucleotide-binding domain (NBD), which permits the ATP depending oligomerization of NLR into an hexameric form that activates the inflammasome; and an effector domain, which permits the transduction of signals (**Figure 3**) [21]. The effector domain is different for each NLR receptors and aids in their distinction. The NLRP have as effector domain the pyrin domain (PYD); the NLRC have as
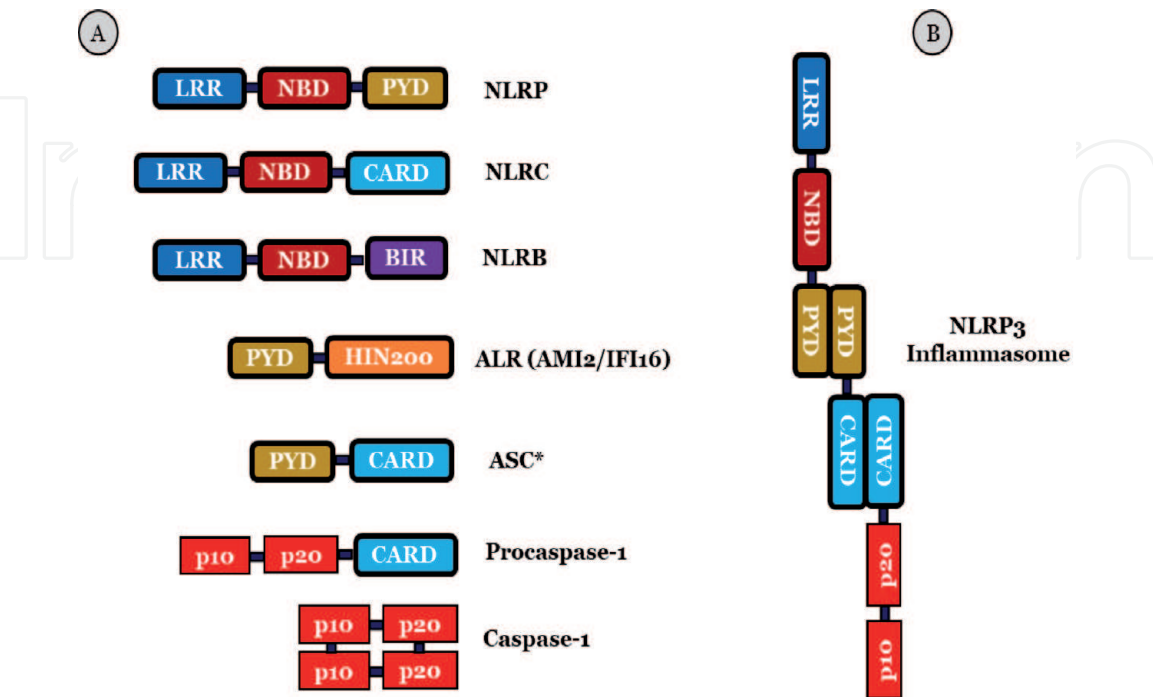

Figure 3.
*Inflammasome structure (modified from [20]) (A) structure of Inflammasome domains (B) NLRP3 Inflammasome. *Apoptosis-associated speck-like protein containing a CARD plays the role of adaptor protein.*

effector domain the caspase activation and recruitment domain (CARD); and the NLRB or NAIP (NLR family apoptosis inhibitory protein) have as effector domain the baculoviral inhibitor of apoptosis protein repeat (BIR) [21]. AIM2-like receptors (ALR) are formed by four receptors: the AIM2, interferon-γ- inducible antigen 16 (IFI16), myeloid cell nuclear differentiation antigen (MNDA), and interferon-inducible protein X (IFIX). The end carboxyl extremity of these receptors is formed by an HIN200 domain which reacts with double-stranded DNA, and the end amino extremity is formed by a pyrin domain [20].

3.2 Activation of the inflammasome

Activation of inflammasome requires the interaction between its receptors and the specific ligands grouped in the name of pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [11, 12]. A large number of inflammasome ligands have been identified; the major ones are presented in **Table 1**. Receptors implicated in the inflammasome structure are located on the intracellular site of cell membrane. This localization means that the inflammasome's receptors are activated by ligands present on the inner aspect of the cell [20]. In other words, an inflammasome is activated in a cell only if the considered cell is infected, mutated, or damaged. The most studied inflammasome platform is the NLRP3 or cryopirine; its activation can be mediated by a double stimulus. The first is the stimulation of a toll-like receptor (TLR) which leads to the activation of the transcription pathway of pro-IL-1β that raises the transcription of the genes of NLRP3 and its deubiquitination [22]. The second stimulus is

Receptors	Stimuli	DAMPs/PAMPs
NLRP1	Anthrax toxin	PAMP
	Myramyl dipeptide of peptidoglycan bacterial wall	PAMP
NLRP3	Extracellular ATP	DAMP
	Reactive oxygen species	DAMP
	Asbestos fiber	DAMP
	Potassium ions efflux	DAMP
	Urate crystal	DAMP
	Silica crystal	DAMP
	Aluminum salt	DAMP
	Cholesterol crystal	DAMP
	β-amyloid protein	DAMP
	Pore forming bacteria toxin	PAMP
NLRP6	Unknown	Unknown
NLRP7	Bacteria lipopeptide	PAMP
NLRP12	*Yersinia pestis* unknown pattern	PAMP
NLRC4	Flagellin	PAMP
	Type 3 and 4 secretion system	PAMP
AIM2	Bacterial and viral DNA	PAMP
IFI16	Viral nuclear DNA	PAMP

Table 1.
Major Inflammasome activators (modified from [20]).

done directly on the NLRP3 through its receptors by a DAMP expressed by the cell secondary to the first stimulus and linked to a cell membrane damage, trouble of cell ionic or metabolic homeostasis, etc. Another activation mechanism of NLRP3 is described in Alzheimer's disease and implicates the β-amyloid protein [23]. Beta-amyloid proteins activate the inflammasome pathway in the microglial cells and thus provoke the liberation of IL-1β and its pyropoptosis which lead to neural cell death. Inflammasomes are also activated by reactive oxygen species resulting from mitochondrial malfunctioning or destruction [20].

Regardless of the inflammasome receptor activating stimulus, it causes a conformational modification of the receptor with liberation of the NBD domain. This liberation of the NBD domain permits the oligomerization of the inflammasome receptor into a hexamer or heptamer and recruitment of an adaptor protein by homotypic PYD-PYD interaction in the case of NLRP3. The recruited adaptor protein also recruits the procaspase-1 by homotypic CARD-CARD interaction. The obtained conformational two-by-two rapprochement of procaspase-1 leads to their autoproteolytic cleavage and their autoactivation [20]. On active form, caspase-1 is a tetramer formed by two pairs P10 and P20 subunits. Active caspase-1 produces activation of IL-1β and IL-18 and the outbreak of pyropoptosis by induction of cell membrane pore formation, which leads to water influx into the cell, swelling, and then osmotic lysis. Interleukin-1β and IL-18 amplify inflammation reaction and activities of all types of lymphocyte. Pyropoptosis, defined as inflammatory programmed cell death, has been found in macrophages, dendritic cells, and neurons [24]. So, in the CNS, inflammation through inflammasome and caspase-1 activation leads to pyroptosis of neurons and microglial cells that play the role of macrophages. This cellular death occurs indirectly in the case of microglial cell death or directly in the case of neuronal death resulting in significant neurotoxicity observed in many diseases.

4. Inflammation in neurotoxicity and neuroprotection

4.1 Inflammation in neurotoxicity

At the level of the central nervous system (CNS) as we have shown previously, the inflammasome effects are much more detrimental than beneficial for its homeostasis. This detrimental effect has been observed in many neurological disorders where inflammasomes seem to provoke neurotoxicity, both directly or indirectly [2]. Among these disorders we have Alzheimer's disease, bacterial meningitis, mouse's equivalent multiple sclerosis, depression, etc. [2, 23, 25]. This evidence, built from clinical and experimental researches, is more often based on the observation of a rise in the expression of inflammasome NLRP3 in the CNS or in the peripheral blood or on the discovery of an anti-inflammasome activity of the drugs used in the treatment of these disorders. **Table 2** summarizes for each neurological disorder the role played by inflammasome and inflammation in its pathogenesis. Another fact is that a unique neuron culture treatment with IL-1β does not produce deleterious effect; however, when the administration is prolonged for several days, it leads to neurotoxicity [34]. The negative impact of pro-inflammatory cytokines on the CNS is also seen on glial cells. Indeed, glial cells are the targets of pro-inflammatory cytokines and are activated by an inflammatory stimulus (PAMPs or DAMPs). This glial cell activation leads to the production of cytokines responsible of a local inflammatory response. Astrocytes activated by inflammation produce neurotrophins and growth factors like nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell

Neurological pathologies	Inflammasome actors	Experimental justifications	References
Alzheimer's disease	NLRP3, IL-1β	Activation of inflammasome NLRP3 by β-amyloid protein and production IL-1β by microglial cell leading to neuro-inflammation and neurons death.	[23, 25]
Multiple sclerosis	NLRP3, ASC, IL-1β	Presence of SEP-like lesions in Muckle-Wells syndrome. Rise of gene's expression and concentrations of caspase-1, IL-18 in peripheral mononuclear cells. Gene's polymorphisms of caspase-1 is associated with SEP.	[26–28]
Amyotrophic lateral sclerosis	Caspase-1, IL-1β	Activation of caspase-1 and IL-1β by a mutant of superoxide dismutase in microglial mouse cell provokes neuro-inflammation.	[29]
Parkinson's disease	NLRP3, IL-1	Activation of inflammasome NLRP3 by α-synuclein protein. Neuro-degenerescence is accelerated by excess IL-1.	[30, 31]
Pneumococci meningitis	NLRP1, NLRP3, CARD8, ASC, IL-1β, IL-18	Gene's polymorphisms of NLRP1 and CARD8 and spinal fluid concentration of IL-1β and IL-18 are associated to clinical prognostic of meningitis. Low severity of meningitis in mouse's models deficient to NLRP3and ASC or after inhibition of IL-1 or IL-18.	[32, 33]

Table 2.
Implication of inflammasome in neurological pathologies (modified from [2]).

line-derived neurotrophic factor (GDNF) [34]. These trophic factors have a neuroprotective effect. In contrast, microglial cell activation leads to the release of neurotoxic factors such as pro-inflammatory cytokines, chemokines, free radicals, nitric oxide, and metalloproteases [34]. For example, in the case of stroke, vascular interruption provokes an ischemia with neural lysis. This neural lysis is associated with a massive release of intracellular contents into the extracellular compartment, among which is glutamate. At this stage two neurotoxicity pathways are triggered: the excitotoxicity pathway by massive glutamate release and the inflammation pathway by activation of microglial cells. Microglial cells are activated by the ischemic danger signal or through N-Methyl-D-aspartate (NMDA) receptors on their surface membrane that are sensible to glutamate [34]. This microglial cell activation leads to the production and release of pro-inflammatory cytokines and other molecules as specified previously. The consequences are neurotoxicity and in stroke an increase of the core ischemia at the expense of ischemic penumbra.

4.2 Metabolic syndrome as a cause of inflammation in neurotoxicity

Neurotoxicity as we aforementioned results from multiple biochemical processes including inflammation. Whether it is initiated and amplified at the level of the CNS or at the periphery, inflammation remains harmful to the CNS. As a matter of fact, when it comes to inflammation, there is a communication between the periphery and the CNS [34]. Before addressing, at the end of this section, this connection between CNS and periphery, we would first of all want to present the metabolic syndrome as a cause of peripheral inflammation that could have an impact on the CNS. The metabolic syndrome is in fact a metabolic disorder characterized by a group of conditions that increase the risk of developing cardiovascular diseases and type 2 diabetes mellitus. Two mechanisms are suggested in an attempt to explain

the genesis of inflammation in metabolic syndrome. The first is a dysfunction of the organelles of adipocytes, observed in obesity; the second is adipose tissue hypoxia also observed in obesity [35]. The first mechanism suggests that hypertrophic adipose tissue found in obesity undergoes excessive lipolysis resulting in hyperlipidemia and an increase in circulating fatty acid levels. This increase in circulating levels of fatty acids, coupled with an abundance of carbohydrates, results in an increase in the oxidative activity of mitochondria that produce excess energy. As time goes by, this state results in a dysfunction of the mitochondria freeing a large quantity of electrons responsible for an increased production of reactive oxygenated compounds. This oxidative stress can subsequently activate the innate immune system and thus cause inflammation. Furthermore, the excess of nutrients overruns the endoplasmic reticulum, resulting in a faulty plication of proteins which activates the response to faulty plication of proteins. This response stimulates the activation of three membranous proteins: PKR-like eukaryotic initiation factor 2-alpha kinase (PERK), inositol requiring enzyme-1 (IRE-1), and activating transcription factor-6 (AFT-6). PERK, IRE-1, and AFT-6 significantly enhance inflammation by activating the signaling pathway NF-kB [35].

Concerning the second mechanism, it is suggested that a localized hypoxia could initiate a dysregulation of adipokines in obesity. As a matter of fact, adipose tissue is mainly made up of adipocytes, but also preadipocytes, resident macrophages, fibroblasts, and endothelial cells. With the increase in adipose tissue observed in obesity, there is a need for a significant angiogenesis. The hypoxic signal present during this expansion results in the activation of transcription factors like the hypoxia-inducible factors which are required in the activation of genes associated with angiogenesis, glucose metabolism, stress, and inflammation. Moreover, in vitro data reveal that human preadipocytes, when exposed to hypoxia, increase their expression of leptin and reduce their expression of the peroxisome proliferator-activated receptor gamma (PPARγ). Yet, agonists of the PPARγ stimulate insulinosensitivity and reduce inflammation. Furthermore, exposed to hypoxia, resident macrophages produce pro-inflammatory cytokines [35]. In type 2 diabetes, coupled with the mechanisms mentioned above, chronic hyperglycemia maintains a vicious circle. In fact, chronic hyperglycemia is responsible for an increase in glycation end products (AGEs) whose receptors belong to the family of PRRs. So, glycated plasma proteins, glycated lipids, or nucleic acids bind to AGE receptors present at the surface of macrophages and provoke a pro-inflammatory and pro-oxidative response [35].

Therefore, the metabolic syndrome induces a state of peripheral inflammation that becomes chronic because it is maintained by its causative process. This peripheral inflammation can directly affect the CNS through produced and circulating inflammatory mediators. These mediators penetrate the CNS via areas without a blood–brain barrier like the periventricular choroid plexuses following which they cause the aforementioned neurotoxic effects [34]. Furthermore, the blood–brain barrier is capable of transmitting an inflammatory message from the vascular endothelium to the CNS via active mechanisms involving cyclooxygenases [34]. Through these mechanisms, an inflammation at the periphery, if it lasts long enough, can extend to the CNS and result in neurotoxicity and subsequent neurologic disorders.

4.3 Inflammation and neuroprotection

Actually, even if some anti-inflammatory strategies have proven their efficacy in animal models, none have demonstrated efficacy in humans in the prevention or treatment of neurological diseases associated with neurotoxicity. However, with conclusive experimental results on the use of anti-inflammatory drugs in neuroprotection, this therapeutic approach presents encouraging prospects for clinical

research. In doing so, after bringing out the negative impact of inflammation on the central nervous system (CNS), it seems appropriate to present some strategies explored or still to be explored in an attempt to inhibit neuro-inflammation and prevent or treat neurotoxicity associated with many neurological disorders. Glucocorticoid and general anesthesia products have stimulated a strong interest in neuroprotection in the cases of stroke on experimental animal models; this has not been demonstrated yet in humans [34]. Indeed, glucocorticoids have been found to be ineffective in stroke, head trauma, and meningeal hemorrhage [34]. And classic hypnotic agents like thiopental, midazolam, or propofol have peripheral immune-modulatory effects and are capable of inhibiting inflammatory response. They inhibit chemotaxis, adherence of neutrophils, phagocytosis, and liberation of free radicals and pro-inflammatory cytokines like IL-1β and TNFα in experimental mouse model; however, these activities have not been demonstrated in humans yet [34]. In general, having in mind previously described inflammation and inflammatory neurotoxicity mechanisms, we can conclude that neuroprotection strategies based on modulation of inflammation have to maintain the beneficial roles of immunological defense and healing of inflammation while neutralizing its neurotoxic consequences. Thus, three anti-inflammatory strategies for neuroprotection axis can be developed: the modulation of the communication between peripheral inflammation and CNS, the modulation of interaction between pro-inflammatory cytokines and their intracerebral targets, and the modulation of inflammasome expression in CNS cells.

In relation to the first axis, namely, the modulation of the communication between peripheral inflammation and CNS and the COX inhibitors (nimesulide and indomethacin) has shown a neuroprotective activity in baby mice with brain lesions. This neuroprotective activity is made possible by inhibition of the communication through the blood–brain barrier between activated peripheral inflammatory cells and the CNS [34]. With the same idea, the COX inhibitors have been presented as potentially beneficial in the treatment of major depression and other psychiatric disorders. Indeed, celecoxib has presented a beneficial effect in the treatment of major depression and schizophrenia especially in early stages [36]. Acetyl salicylic acid in particular seems to have both a preventive and therapeutic effect on schizophrenia [36]. Communication between peripheral inflammation and the CNS does not occur solely via the blood–brain barrier as it can also be done through the parasympathetic and sympathetic systems. Indeed, immune cells present at their surfaces nicotinic receptors for acetylcholine and β-adrenergic receptors for catecholamine [34]. These receptors link immune cells to parasympathetic and sympathetic systems respectively. Thus, a pharmacologic vagal or noradrenergic stimulation could represent a potential target for neuroprotection. For this purpose, vagal stimulation potentially passing through the modulation of lipocalin prostaglandin D2 synthase (L-PGDS) has shown in rat models with ischemic stroke a neuroprotective effect against ischemia reperfusion [37]. Also, a noradrenergic stimulation has shown, in Parkinson's disease, a neuroprotective effect by inhibition of inflammation [38].

Concerning the modulation of interaction between pro-inflammatory cytokines and their intracerebral target strategy, specific receptor antagonist of IL-1 appears to be the most conclusive therapeutic approach. This antagonist is produced endogenously following brain injury, and its administration by systemic or intracerebral route leads to a reduction in the size of lesions in mouse models [34]. Furthermore, Veltkamp et al. report the use, via general route of anakinra, of an antagonist of IL-1 receptors in a clinical trial on a patient having stroke [39]. This clinical trial has shown a great reduction of national institute of health stroke scale (NIHSS), and it also shows more patient with modified Rankin score (mRS) of 0–1 in 3 months [39].

Also based on this axis, sitagliptin, a molecule used in the treatment of type 2 diabetes since the discovery of incretin effect, has shown a great anti-inflammatory capacity. This anti-inflammatory activity of sitagliptin is linked to the inhibition of synthesis of pro-inflammatory cytokine and a raise in anti-inflammatory cytokine synthesis [40]. This property has been exploited in the treatment of Alzheimer's disease in mouse models, and the results were conclusive [40]. In humans, the administration of sitagliptin was associated with an amelioration of the mini-mental state examination (MMSE) score used to evaluate dementia [40]. All these axes remain focused on more or less advanced stages of inflammation. For this reason, they carry the risk of possibly altering the beneficial effects of inflammation. Thus, to reduce this intrinsic risk, it seems necessary to develop more specific methods to modulate the inflammation. One method could be the inhibition of inflammasomes. However, because of the lack or incomplete knowledge on inflammasome structure and activation, this approach remains difficult. Nevertheless, the inhibition of NLRP3, the most studied inflammasome, has been subjected to several studies in psychiatric disorders [41]. A specific inhibitor of NLRP3 has been developed which lays the foundation for further exploration of this axis [42].

5. Conclusion

Neuroprotection is both a topical problem and a realistic dream for the researchers and clinicians. By this analysis, the immune system no more seems to only be a tool useful in the protection against endogenous and exogenous offenders. As a matter of fact, its role could be understood as defense against all sorts of disorders, including infectious, metabolic, degenerative, etc. and even aging. Indeed, the role of the immune system and inflammation in disease-associated neurotoxicity is more and more highlighted in present literature. This evidence justifies the outbreak of an inflammatory approach to develop a neuroprotection strategy in the fight against neurotoxicity. All this evidence does not only provide hope for the future development of neuroprotective strategies, but also invite us to reflect on the possibility that failure of the immune system may be implicated as primary cause of any human pathology. In experimental research, this is in the process of being demonstrated for neurologic and psychiatric disorders. Even though clinically the results of the researches are not yet irrevocable, the inflammatory pathway in neuroprotection remains a good approach in the fight against these main neurological ailments.

Acknowledgements

Conflict of interest

The authors declare that they have no competing interests.

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