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Acute Phase Protein's Levels as Potential Biomarkers for Early Diagnosis of Neurodegenerative Diseases

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1. Introduction

1.1 Inflammation

Inflammation is a response of the organism that facilitates the immune response and/or repair after a harmful stimulus, such as pathogens, damaged cells, or irritants. The inflammatory process is necessary for the healing of the tissues. However, the uncontrolled chronic inflammation can also lead to harmful diseases, such as atherosclerosis or rheumatoid arthritis, among others (Eming et al., 2007; Tabas, 2010; Libby, 2008).

The cause of inflammation may be of different origin. An inflammatory response could be stimulated by chemical or physical damages, but also by pathogens or immune reactions (Moore et al., 2010).

The cardinal signs of inflammation in the majority of the tissues include pain, redness, immobility, swelling and heat. These signs usually encompass the increase of blood flow in the inflamed area and the accumulation of fluids that help to increase the possibilities of tissue repair. However, inflammation of particular tissues, such as in the central nervous system (CNS), those characteristics are not fully applicable (Carson et al., 2006).

Many cells are implicated in the inflammatory process. One of the initial players is the resident macrophages, that are able to respond rapidly to damage. Particularly in the CNS, the macrophage-analogue cells are the resident microglia but their role is not fully understood and it is some how different from macrophages (Schwartz, 2003). Other tissue resident cells, like Dendritic cells or Kupfer cells, not present in the CNS, may also be initial responders to inflammation but other cells, entering in the CNS and coming from the systemic circulation, such as natural killer (NK) cells, leukocytes, and lymphocytes are also implicated in the inflammatory response (McMahon et al., 2006; Haskill et al., 1992).

Inflammation also comprises a complex biological response implicating vascular tissues and the activation of the endothelium to facilitate the specific entrance of blood cells (Trepels et al., 2006).

After a specific insult, several cascades of factors are activated. The plasma derived inflammatory mediators such as the complement and the coagulation system, together with

the cell-derived inflammatory mediators (Pesce and Dosekun, 1983). In the latter case, resident inflammatory cells start to release different factors that trigger and amplify the local inflammatory response. Among these factors, the cytokines and chemokines are the crucial players in the inflammation cascade (Luster, 1998) and, as we describe in depth in following sections of this chapter, are important mediators of the Acute Phase Protein (APP) response. Pro-inflammatory cytokines are proteins able to induce specific inflammatory responses in the tissue. Each type of cytokine participates in a particular function and it is specifically stimulated in particular scenarios and pathologies (Kopf et al., 2010). In the CNS, the cytokines play very important roles and their deregulation may result in neurological disorders. In fact, cytokines has been many times proposed as biomarkers for neurodegenerative diseases (Reale et al., 2009). The most studied cytokines, with clear effects in the CNS are the tumor necrosis factor alpha (TNF- α), the interferon gamma (IFN- γ), interleukin (IL)-6, IL-1 β IL-17, and transforming growth factor beta (TGF- β) among many others.

TNF- α is a cytokine involved in many inflammatory processes, with fundamental roles in inflammation and lymphoid organogenesis as well as in neuro-degenerative diseases (Idriss and Naismith, 2000). It is expressed by several cell-types including macrophages, lymphocytes and NK cells. Its deficiency or exacerbation may cause inflammatory and autoimmune diseases. The blockade of TNF- α with specific antibodies has been largely developed with therapeutic purposes as for example anti tumor activity, but also it has been developed for brain disorders.

IFN- γ is produced mainly in lymphocytes and NK cells and its expression by macrophages is still controversial. It has a crucial role in maintaining the host defense against pathogens and has been linked with the progression of many autoimmune diseases including those in the brain. Surprisingly, mice lacking IFN- γ or IFN- γ receptor (IFN- γ R) develop an exacerbated inflammation in models autoimmune diseases, which suggest that Th1 T cells, that produce IFN- γ , may be indirectly involved in these diseases (Jacob, 1992; Olsson, 1992).

IL-1 is produced by several types of cells and it is involved in many inflammatory responses (Dinarello, 2006). The overproduction of IL-1 β has been associated with a group of inflammatory disorders. Mice lacking the receptor for IL-1 or lacking both IL-1 α and IL-1 β are protected from the development of autoimmune alterations. IL-1 β promotes dendritic cell maturation and Th-17 cell clonal expansion, contributing to autoimmunity in brain diseases. The blockade of IL-1 β has also been developed as a possible anti-cancer treatment (Dinarello, 2010; Curti et al., 1995) and may be beneficial to treat some brain degenerative disorders.

IL-6 is produced by various cell types in response to infection or tissue alteration. Importantly, it is a crucial mediator of the immune system inducing a liver APP response and the B cell and T cell effector responses to pathogens (Hirano, 1992). Its target has therapeutic potential, since it is directly involved in some inflammatory diseases such as arthritis or colitis (Dayer and Choy, 2009; Atreya et al, 2000). As we describe below IL-6 is critically involved in the APP regulation.

Chemokines also contribute to the specific inflammatory responses in the tissue. There are many types of chemokines involved in particular scenarios and pathologies similarly to cytokines. Importantly, chemokines play crucial roles in recruiting factors and cells into the parenchyma, contributing to enhance the local inflammatory response (Semple et al., 2010). Chemokines also may be considered biomarkers for tissue alteration. One of the most

important subfamily of chemokines is the subgroup so called CC chemokine ligand (CCL). Examples of CC chemokine include the CCL2, formerly called monocyte chemoattractant protein-1 (MCP-1), which is involved in the extravasation and recruitment of macrophages and lymphocytes into the tissue. CCL5 or RANTES also contributes to the entrance of T cells, basophils and eosinophils (Ge et al., 2008). In the CNS, CCL2 seems to play a key role in some neurodegenerative diseases. Accordingly, in other neuro-inflammatory processes, such as acute brain trauma, stroke, as well as during chronic affections like multiple sclerosis or Alzheimer's Disease (AD), prolonged and sustained inflammation mediated by CCL2 may have cytotoxic effects, aggravating the incidence and the severity of the disease (Conductier *et al*, 2010). Therefore, the CCL2 modulation may be considered as an interesting potential therapeutic target to control local inflammatory responses.

This complex inflammatory response, driven by cytokines and chemokines, and consequently by APP, although it is necessary for the repair of the tissue, if is not controlled may contribute to the development of pathological conditions. Particularly in the CNS, increasing evidences show that the inflammatory response may be a crucial contributor to the neurodegenerative process.

1.2 Inflammation and neurodegenerative diseases

The inflammatory response in the CNS is very different from the rest of the systems. The particular anatomical location, inside the cranium, and the crucial importance of the brain function has shaped the need for a particular immune response. These characteristics have lead many scientists to think that the brain is an immune privileged tissue. The special brain blood barrier (BBB) and the absence of dendritic cells, or clear analogous cells, makes difficult to understand the mechanisms of the immune responses in the brain keeping in mind the standards of other tissues (Yong and Rivest, 2009). Glial cells, and in particular microglial cells, has been widely known as the initial responders of the immune response in the brain, however, there are many questions that remain unanswered regarding their function in neurodegenerative diseases (Henkel et al, 2009).

The glial activation is a histological hallmark in many neurodegenerative diseases. *Post mortem* histopathology of brains from patients with Parkinson's disease (PD) and AD show activation of microglial cells and astrocytes, which suggests that the neuronal degeneration is associated with inflammatory response (McGeer et al., 1988). However, it is still unclear whether glial activation precedes or is secondary to the neuro-degeneration. Previous studies in experimental Parkinsonism have shown that exacerbated microglial activation lead to the degeneration of dopaminergic neurons (Mount et al., 2007, Barcia et al., 2004). In line with this, when the microglial cells are activated locally with lipopolysaccharide (LPS), a large molecule found in the outer membrane of Gram-negative bacteria that elicits a strong immune response in animals, the local dopaminergic neuronal loss is exacerbated (Saijo et al., 2009). However, the endogenous and constitutive factors responsible of the local glial activation that may lead to degeneration in neurodegenerative disorders are still uncertain. Cytokines and chemokines are clear candidates to be directly involved in the activation of glial cells in the brain. Recent studies performed in our laboratory have shown in experimental models of PD that cytokines, specifically IFN- γ and TNF- α , are responsible of the local glial activation in the brain parenchyma. Importantly, the levels of cytokines in the brain correlates with the neuronal degeneration and are persistently increased along the years, which suggest that the perpetuation of the neuronal loss may be mediated by certain cytokines (Barcia et al., 2011). Moreover, and most importantly for this review, the cytokines

are also increased in the circulating plasma demonstrating that the inflammatory response goes beyond the brain parenchyma in neurodegenerative processes. In addition, other studies have demonstrated that the artificial induction of increasing circulating levels of specific cytokines in the blood exacerbates the neuronal death in experimental models of neuro-degeneration *in vivo* (Pott Godoy et al., 2008). Coherently with this evidences, patients with neurodegenerative disorders also show increased levels of cytokines in the blood and cerebrospinal fluid (CSF), which suggests a general and systemic inflammatory response involving the whole organism (Reale et al., 2009). This generalized inflammatory response could certainly activate many other inflammatory cascades in other organs. One of the general responses that may be activated is the APP reaction. However, there are many proteins that are included in the APPs, and each disorder may have a particular response involving different proteins. Unfortunately, one of the caveats to keep in mind for this kind of measurements is the putative variation of these proteins that individuals may have when they are under pharmacological treatment. Nevertheless, the clinical significance of specific APP levels in serum or plasma of patients for specific neurological symptoms may be crucial in order to find biomarkers that may help for the early and accurate diagnosis of neurodegenerative diseases.

1.3 Acute phase response and acute phase proteins

The first reaction of the body to immunological stress is the innate, non-specific response preceding specific immune reactions. The acute phase response (APR) is a prominent systemic reaction of the organism as a result of this innate response to local or systemic disturbances in its homeostasis and may be caused by infection, tissue injury, trauma or surgery, neoplastic growth or immunological disorders (Gordon and Koy, 1985; Gruys et al., 1999).

This response takes place at the very beginning of the inflammatory process and lasts for 1-2 days. After that, the host returns to normal functions. However, the systemic response can also be prolonged, if acute inflammation becomes chronic (Kushner et al., 1981).

The purpose of acute-phase reaction is to counteract the underlying challenge in order to restore rapidly the homeostasis. This phenomenon is accomplished by isolating and destroying the infective organisms, or removing the harmful molecules, and activating the process of repair. Their function in neurodegenerative disorders is unclear but there are evidences that suggest their involvement and may be important for diagnosis. Acute-phase reaction includes a wide range of neuroendocrine (Fever, anorexia, decrease of thyroxine, increase of cortisol), hematopoietic (Anemia, leukocytosis, thrombocytosis), and metabolic changes (muscle atrophy, increase of lipolysis) that can be reflected systemically (Woo and Gorman, 1992; Whicher and Westacott, 1992).

Precisely, one of the most interesting features of the acute-phase is the change in the concentrations of many plasma proteins, known as the acute-phase proteins, which can be easily detected in the blood. The APP has been defined as one whose plasma concentration increases (positive acute-phase proteins) or decreases (negative acute-phase proteins) by at least 25 percent during inflammatory reactions (Gabay and Kushner, 1999). The very first APP to be described, C-reactive protein (CRP), was discovered in 1930 in the plasma of patients during the acute phase of pneumococcal infection. In some pathologies CRP may even increase more than 1000 times (Gabay and Kushner, 2001) being an excellent marker for diagnosis.

1.4 The regulation of the acute-phase expression and activation

The synthesis and release of plasma APP takes place in the liver and it is regulated by inflammatory mediators. These mediators fall into four major categories: IL-6-type cytokines, IL-1-type cytokines, glucocorticoids, and growth factors. Cytokines mainly stimulate the APP gene-expression, while glucocorticoids and growth factors modulate the cytokine activity (**Figure 1**). Binding of the inflammatory mediators to their respective receptors on hepatocytes and the transduction of this signal induce changes in APP gene expression that are primarily regulated at transcriptional level (Gauldie et al., 1987).

As we stated above, cytokines are a group of proteins acting as extracellular and intercellular signaling molecules. The role of cytokines during inflammation is both initiation and fine-tuning of the whole process: some cytokines initiate and amplify the response, others sustain or attenuate it, and some of them cause it to resolve (Martínez-Subiela, 2001, Heinrich et al., 1990).

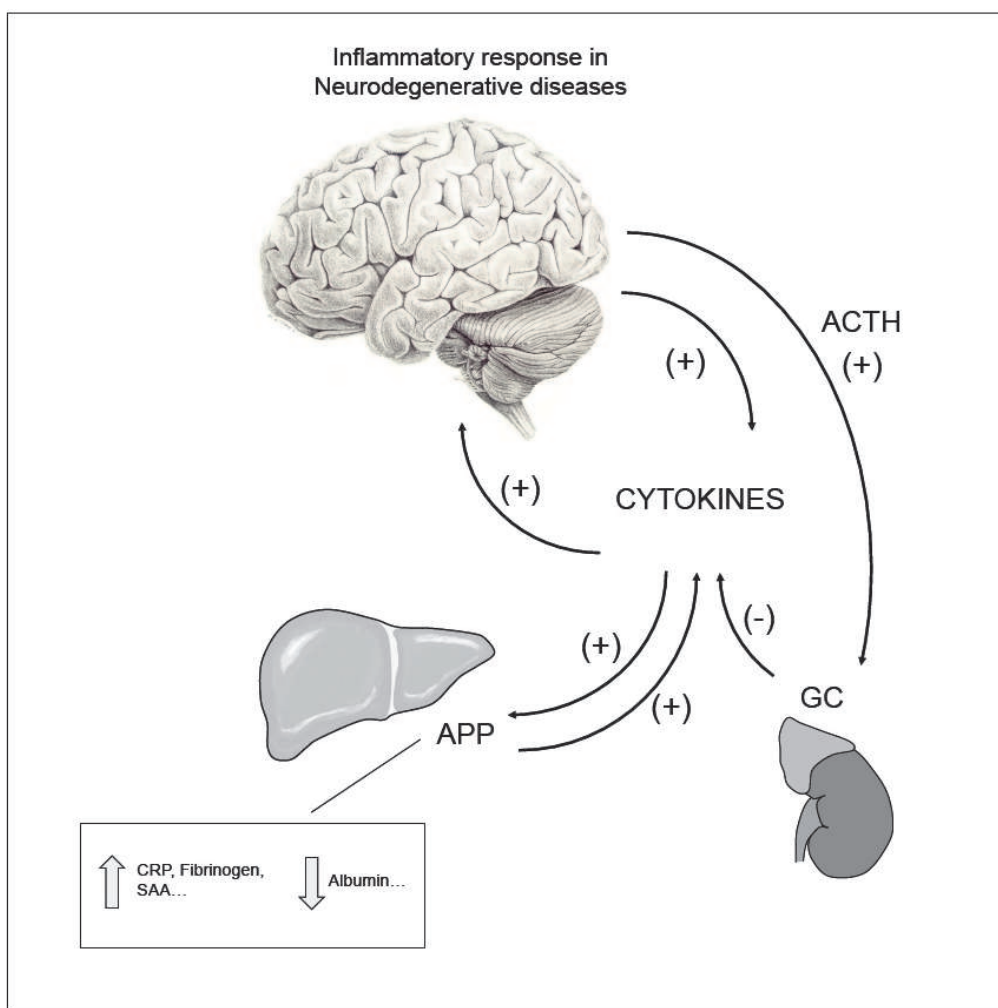


Fig. 1. Local inflammation in neurodegenerative diseases induces a Serum amyloid A (SAA) APP peripheral inflammatory responses in a cytokine-dependent fashion. This APP response is orchestrated in the liver, and it is characterized by the increase of some factors such as CRP, fibrinogen or SAA and the reduction of some others like albumin. Furthermore, this response may contribute to the general inflammatory response and may exacerbate the local neuro-degeneration.

During inflammation, inflammatory cells, mainly macrophages and neutrophils that assemble at the site of challenge, together with endothelial cells, secrete the so-called pro-inflammatory cytokines TNF- α , IL-1 β , and IL-6, in that order. This order is important, since each cytokine fulfills a precise role in up-regulating or down-regulating the expression of the others. TNF- α released by T cells and macrophages precedes the release of IL-1 β and both stimulate the anti-inflammatory or proinflammatory cytokines (Feldmann, 2002).

Pro-inflammatory cytokines induce a number of local and systemic responses like: a) the expression of selectins on local endothelial cells, that recruit inflammatory cells from the bloodstream; b) the activation of recruited cells in developing their optimal defensive activity, i.e. increased expression of receptors (Complement receptors), or cell metabolism, such as oxidative burst, and c) expression of other cytokines, such as chemokines, that recruit more and more defensive cells to the inflammation site (Richards *et al.*; 1992) and importantly d) the production of APPs.

Then, cytokines are clear inducers of the APP response and both, cytokines and APP, may vary by the same pattern. However, changes in cytokines are less evident and more difficult to be measured while APPs changes are usually higher and clearly identifiable, which makes them suitable for early diagnosis.

1.5 Classification of APP

Since their discovery several classifications of acute phase proteins have been proposed. All the up-regulated proteins have been called "positive APP", in order to differentiate them from the so-called "negative APP", that are down regulated. Importantly, the most physiologically expressed proteins, albumin and several other proteins, usually present in blood, belong to the latter group, which makes the positive ones suitable for diagnosis.

Another interesting classification differentiates the APPs for the rate of their expression. For example, the apolipoproteins serum amyloid SAA1 and SAA2 (commonly called SAA) are considered "major acute-phase proteins" and their concentration, as we have stated above, can increase as much as 1000-fold. Other major APPs are CRP and Alpha-1-acid glycoprotein (AGP) (Gabay and Kushner, 2001) which are important for degenerative disorders.

Relevant APPs for CNS disorders

C-Reactive Protein (CRP)

CRP is an acute phase protein that circulates as a pentamer (pentameric CRP) in plasma and with serum levels rising as much as 1000-fold following injury or infection. It is increased by bacterial infections and generally less elevated in viral infections (Jaye and Waites, 1997).

The name derives from its ability to react with the C polysaccharide of *Streptococcus pneumoniae*, but it may also bind to chromatin in nuclear DNA-histone complexes. Once bound, it is able to activate the classical complement pathway (Woo and Gorman, 1992).

An increased CRP may be due to: (i) inflammatory disorders, e.g. inflammatory arthritis, vasculitis, Crohn's disease, (ii) tissue injury or necrosis, e.g. burns, necrosis, myocardial infarction, pulmonary embolus, (iii) Infections, especially bacterial, (iv) malignancy, and (v) tissue rejection.

CRP concentrations typically return to normal level after 7 days of appropriated treatment for bacterial meningitis, if no complications are developed. Thus, serial monitoring of CRP concentrations in serum and CSF concentrations may be clinically useful.

However, CRP is non-specific and its clinical usefulness is therefore limited, especially in diagnosis. CRP is useful in monitoring inflammatory disease activity, including rheumatoid arthritis, infections or malignancy and can also be useful as a prognostic marker for some conditions (e.g. acute pancreatitis). There is also evidence that CRP has a stronger predictive value for the risk of coronary heart disease and stroke events than low-density lipoprotein (LDL) cholesterol (Ridker *et al.*, 2002), in contrast its predictive value for neurodegenerative diseases is still under development.

Homocysteine

Homocysteine (Hcy) is an amino acid formed from the metabolism of the essential amino acid, methionine. It is a homologue of the amino acid cysteine, differing by an additional methylene (-CH₂-) group. It is biosynthesized from methionine by the removal of its terminal C methyl group. Homocysteine can be recycled into methionine or converted into cysteine with the aid of B-vitamins (Selhub, 1999).

High dietary consumption of methionine, which can be found in meats and dairy products, can result in the overproduction of homocysteine. Once homocysteine is produced it is metabolized in the body through one of two possible pathways - remethylation or trans-sulfuration. Re-methylation is a process that utilizes folate, vitamin B12 or betaine (trimethylglycine) to convert homocysteine back to methionine. Alternately, trans-sulfuration utilizes vitamin B6, pyridoxal-5-phosphate, to catabolize excess homocysteine into a number of metabolites for eventual excretion from the body (Graham *et al.*, 1997) and it can be increased in some neurodegenerative diseases, as we will describe below.

Plasma homocysteine concentrations may differ, depending on which metabolic homocysteine pathway is defective. An abundance of research indicates that an increased homocysteine level may indicate an increased risk of cardiovascular disease like coronary heart disease, stroke and peripheral vascular disease (Boushey *et al.*, 1995)

Fibrinogen

Fibrinogen is a soluble plasma glycoprotein, with high molecular weight of 340 kDa, synthesised by the liver that is converted by thrombin into fibrin during blood coagulation. This is achieved through a process in the coagulation cascade that activates the zymogen prothrombin to the serine protease thrombin, which is responsible for converting fibrinogen into fibrin. Fibrin is then cross-linked by factor XIII to form a clot (Weisel, 2005).

Fibrinogen normal plasma levels are between 150 and 450 mg/dl. More than 300 mg/dl are related with the risk of heart attack. It is still controversial the role of fibrinogen as an atherosclerotic vascular disease risk factor; epidemiological evidences seem to be coincident about its role as a marker or predictor of new or reiterated atherothrombotic events (Paterno, 2000).

The reasons by which fibrinogen is elevated in cardiovascular disease and atherosclerosis are, in general, only incompletely understood; but all cells involved in the atherogenetic process are able to produce cytokines, which induce an acute phase reaction that increases fibrinogen levels in plasma (Canseco-Ávila *et al.*, 2006).

Recent research has also shown that fibrin also plays a key role in the inflammatory response and the development of rheumatoid arthritis. In addition, it has been related with AD as we will discuss in following sections.

Serum amyloid A proteins (SAA)

SAA constitutes a protein family related to the A proteins of secondary amyloidosis (Bausserman et al, 1980, 1982; Betts et al, 1991; Strachan et al, 1989).

SAA is one of the major APPs (encoded by SAA1 and SAA2; collectively referred to also as A-SAA (acute phase serum amyloid A). Its level in the blood increases dramatically (up to 1 000-fold; 1 000 micrograms/mL) in response to various stimuli, which suggests an important short-term beneficial role in responses to tissue injury and inflammation. Although the liver is the primary site of synthesis of both A-SAA and C-SAA, extrahepatic production has also been reported for most family members in most of the mammalian species studied. Bacterial lipopolysaccharides and several cytokines (mainly IL-1 β , IL-6 and TNF- α but also LIF, CNTF, oncostatin M, IL-11, and cardiotrophin-1) are involved in the induction of SAA synthesis and some of these cytokines act synergistically (Benigni et al, 1996).

Although the precise role of A-SAA in host defense during inflammation has not been defined, many potential clinically important functions have been proposed for individual SAA family members. These include involvement in lipid metabolism/transport, induction of extracellular-matrix-degrading enzymes, and chemotactic recruitment of inflammatory cells to sites of inflammation. A-SAA is potentially involved in the pathogenesis of several chronic inflammatory diseases: it is the precursor of the amyloid A protein deposited in amyloid A amyloidosis, and it has also been implicated in the pathogenesis of atherosclerosis, rheumatoid arthritis and, importantly, PD.

2. Neurodegenerative diseases and Acute Phase Protein

2.1 Alzheimer's disease and APP

AD is a complex neurodegenerative disorder characterized by progressive loss of cognitive function and subsequent death. Since the first case of this disease was diagnosed one century ago, much effort has been dedicated to find a cure. However, even though progress has been made in the knowledge of the pathogenesis of this disease, its ultimate cause remains unknown. An effective treatment has not yet been found and the efforts to prevent the neuronal death are crucial. Therefore, new approaches are urgently needed regarding the early diagnosis.

The relevance of APP measurements in the diagnosis of neurodegenerative diseases like AD is actually under evaluation. Obviously, the inflammatory response generated in these kinds of illnesses is less noteworthy than the inflammatory response that may be observed in other pathological conditions such as viral or bacterial infections.

A large number of proteins, peptides and aminoacids, other than β -amyloid, have been examined in plasma, based on their putative role in AD pathology. Perhaps the two most consistent findings are the increase in total Homocystein (tHcy) and CRP seen in AD. First reported by Clarke and colleagues, an increase of tHcy in plasma has been widely reported and a recent systematic review of large and prospective studies, found a relative risk of AD in individuals with elevated tHcy. Increased tHcy and CRP are both associated with a risk of cardiovascular disease but it is worth noting that neither contributes to risk estimation, even in cardiovascular disease, enough to warrant recommendation for use in clinical practice. Given that the association with AD may well be weaker than

cardiovascular disease, this emphasizes the gap between finding an association with disease and proof of utility as a biomarker. Nonetheless, CRP and tHcy may have independent effects on the risk of developing AD. Regarding CRP, the studies are somewhat controversial and complex. Some studies reported that an elevation in CRP has been associated with the rate of progression of AD but also with MCI and Down's syndrome. However, other large longitudinal studies found that markers of inflammation, such as TNF- α but not CRP, were associated with the risk of dementia while others found an association between CRP and vascular dementia (VD).

Accordingly, a recent study by O'Bryant and colleagues (2010) analyzing a combined pool of 192 patients diagnosed with probable AD and 174 non-demented controls show that mean CRP levels were found to be significantly decreased in AD (2.9 mg/mL) versus controls (4.9 mg/mL; $P < .003$). These findings, together with previously published results, are consistent with the hypothesis that these changes in CRP may be time-dependent, therefore, midlife elevations in CRP may be associated with increased risk of AD development, although elevated CRP levels may not be useful for prediction in the immediate prodrome years before AD becomes clinically expressed.

There is significant evidence that AD patients suffer from inadequate circulation and cerebrovascular pathology, and one theory that is gaining evidence is the importance of vascular factors in the onset and progression of this disease (Farkas et al., 2001; Iadecola C, 2004; de la Torre 2004). In line with this, AD patients have an abnormal cerebral vasculature and brain hypoperfusion, and a large body of research, implicates cerebrovascular dysfunction as a contributing factor to AD. Some recent studies show how reducing fibrinogen, a circulating protein critical in hemostasis, provides a significant decrease in the neurovascular damage, blood-brain barrier permeability and neuroinflammation present in AD. These studies involve fibrinogen as a possible contributor to AD (Cortes-Canteli and Strickland, 2009).

On the other hand, some other studies show increased levels of tHcy in patients with probable AD and established negative correlation between serum tHcy concentrations and cognitive damage tested by Mini-Mental State Examination (MMSE) scores, suggesting a potential role for tHcy in the pathogenesis of AD and cognitive impairment (Lepara et al., 2009).

These findings imply that the serum tHcy level may be a potential biomarker for AD, as well as a marker of cognitive damage associated with this disease.

2.2 Parkinson's disease and APP

PD is a neurodegenerative disorder characterized by the loss of dopaminergic neurons of the Substantia Nigra *pars compacta* (SNpc). A big problem with this particular disease is that the neurological symptoms only appear when more than 60% of the neurons are already lost. For this reason the early diagnosis is crucial to prevent the neuronal degeneration. The areas of neurodegeneration are accompanied by local inflammation characterized by a strong glial response mediated by cytokines. These proinflammatory compounds also travel outside the brain and can be detected in the blood.

It is known that some cytokines, such as IL1- β , TNF- α and IFN- γ , are increased in the blood and cerebrospinal fluid (CSF) of patients with PD. These cytokines are able to reactivate the local inflammation in the CNS but they are also able to induce the activation

of other peripheral inflammatory pathways such as the activation of APP. Then, the measurement of blood APP levels may be a valuable tool for assessing and confirming the early diagnosis in Parkinsonism, and the secretion of these anti-inflammatory markers such as cytokines or APPs could be utilized to help the diagnose of the disease (de Pablos et al., 2009).

There are very few studies regarding the levels of APP in PD and some of the results are apparently in conflict. Dufek and coworkers (2009) only found sporadic and slight abnormalities in the concentration of CRP and SAA in the serum of PD patients but McGeer and coworkers (2004), however, observed an increase of CRP in the affected dopaminergic areas of the brain. This apparent contradiction may be explained since the patients studied by Dufek and colleagues were moderately impaired and were all taking antiparkinsonian drugs, which may interfere in the peripheral APP measurements. In fact, a study of our laboratory shows that tHcy is increased in PD patients under L-dopa treatment (Martín-Fernández et al., 2010). On the other hand, other study regarding the APP levels in the blood of PD patients show an increase of CRP in the plasma according with the Hoehn-Yahr stages of PD severity (Seet et al., 2009). Importantly, in the study of Seet and coworkers the patients were advised to refrain from consuming their anti-parkinsonian medications 4 h before collection of the samples suggesting that a previous wash out of drugs may be needed in order to detect changes in these proteins. These results suggest that the dopaminergic loss in the brain is able to induce an increase of the peripheral APP that can be detected in the serum. In line with this, previous studies of our group have demonstrated that the specific degeneration of dopaminergic neurons induced by MPTP administration in non-human primate, stimulates an increase of CRP, SAA and Haptoglobin (HP) in plasma (de Pablos et al., 2009). This increase is very fast and transient, except for HP, which suggest that this response is related with the immediate effect of the toxin. On the other hand, a persistent increase of APP in the plasma suggests a persistent damage, which can be related with chronic degeneration.

The role of APP in PD is still unclear but increasing evidences show that the local inflammatory response in the brain is also reflected by several markers systemically and may be easily detected in the blood by well-established techniques. CRP seems to be a clear candidate as a PD biomarker but further studies are needed to soundly determine the specific factors that are increased in PD, which APPs are particularly increased and how are they correlated with the dopaminergic degeneration and the level of Parkinsonism.

2.3 Vascular dementia and APP

Several inflammatory proteins, such as cytokines are linked with AD and some APP, such as tHcy and CRP, has been associated with the disease (Clarke et al., 1998). However, the relation between the APP and the presence of absence of dementia is still unclear. Very few studies report changes in the APP levels in VD and some of them present inconclusive results. Mancinella and coworkers (Mancinella et al., 2009) described that CRP levels are elevated in patients with VD respect to controls but still they show lower levels than patients with AD, which makes difficult to distinguish both disorders based in the peripheral biomarkers. Other authors did not find any differences in the CRP levels in VD but they however found an increase in tHcy (Davis et al., 2009). Importantly, high blood levels of tHcy have been related with cardiovascular diseases and may be also related with similar alterations in the VD (Lepara et al., 2009).

A. Proteins whose plasma concentrations increase
Complement system
C3
C4
C9
Factor B
C1 inhibitor
C4b-binding protein
Mannose-binding lectin
Coagulation and fibrinolytic system
Fibrinogen
Plasminogen
Tissue plasminogen activator
Urokinase
Protein S
Vitronectin
Plasminogen-activator inhibitor 1
Antiproteases
α -1 -Protease inhibitor
α -1 -Antichymotrypsin
Pancreatic secretory trypsin inhibitor
Inter α -trypsin inhibitors
Transport proteins
Ceruloplasmin
Haptoglobin
Hemopexin
Participants in inflammatory responses
Secreted phospholipase A2
Lipopolysaccharide-binding protein
Interleukin-1-receptor antagonist
Granulocyte colony-stimulating factor
Others
C-reactive protein
Serum amyloid A
α -1 -Acid glycoprotein
Fibronectin
Ferritin
Angiotensinogen
B. Proteins whose plasma concentrations decrease
Albumin
Transferrin
Transthyretin
Alpha-2-HS glycoprotein
Alpha-fetoprotein
Thyroxine-binding globulin
Insulin-like growth factor I
Factor XII

Table 1. Human Acute-Phase proteins.

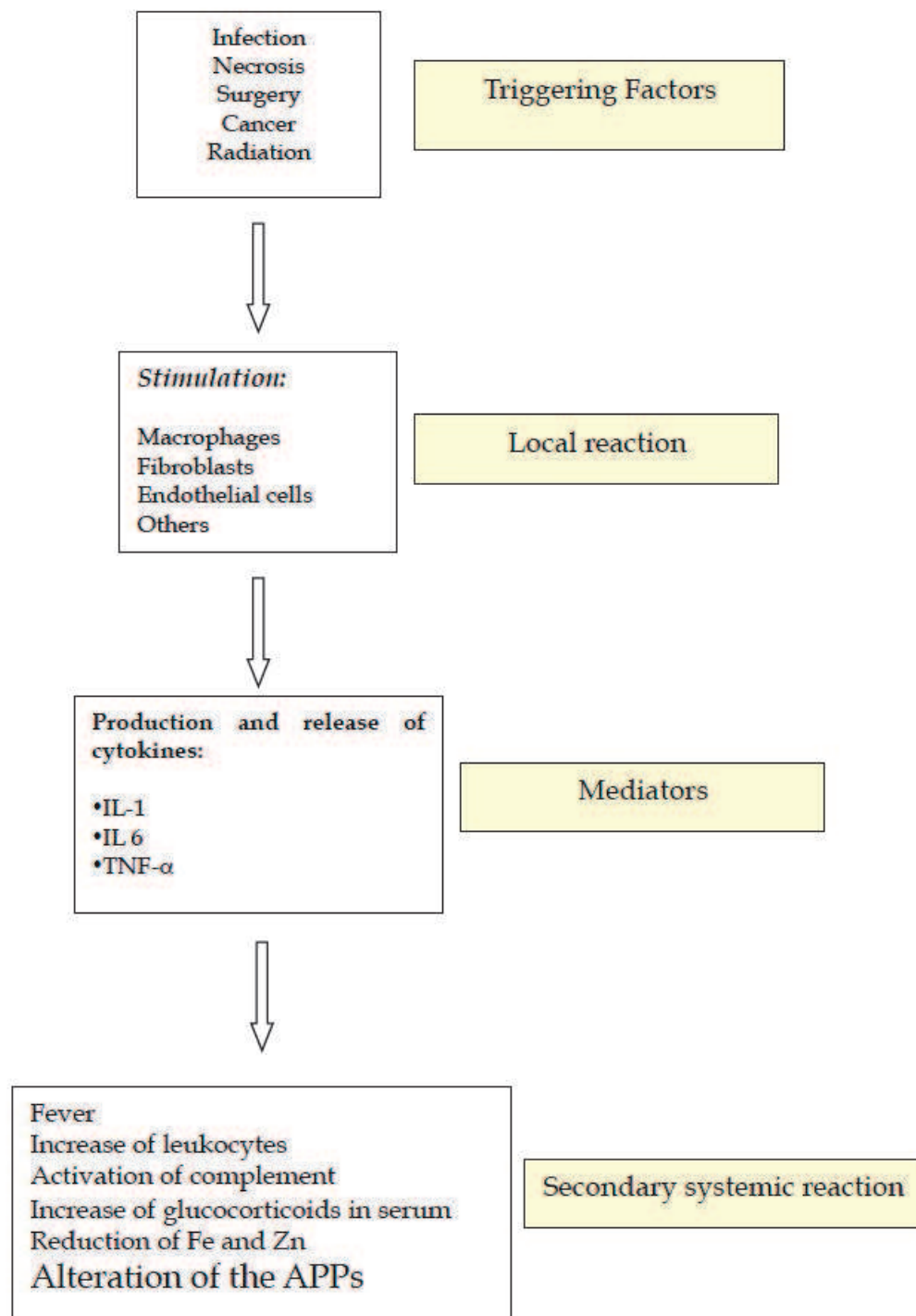


Fig. 2. Different inflammatory triggering factors activate cells to stimulate local reactions. This response is mediated by different cytokines that are able to provoke a secondary systemic reaction characterized by the increase of leukocytes, activation of complement, increase of glucocorticoids in serum, reduction of Fe⁺⁺ and Zn⁺ and the cascade of APPs.

Acute Phase Protein	Normal concentration in plasma (mg/l)
GROUP 1 (50% increase)	
Ceruloplasmin	150-600
C3-Complement	800-1700
C4-Complement	150-650
GROUP 2 (2-5-fold increase)	
Haptoglobin	400-1800
α 1-glycoprotein	550-1400
α 1 antichemotrypsin	300-1600
α 1 protease inhibitor protease	2000-4000
Fibrinogen	2000-4500
GROUP 3 (1000 -fold increase)	
C-Reactive Protein	< 5.0
Serum Amyloid A	<10.0

Table 2. APP Classification production depending on the rate of their expression and normal concentration in human.

3. Conclusions and therapeutic perspectives

In neurodegenerative diseases changes observed blood parameters could be considered as putative hallmark of diseases evolution that might be helpful for personalized diagnosis, prognostic and/or progression diseases monitoring.

Obviously, the inflammatory response triggered in neurodegenerative diseases such as PD or AD is less easily detectable than those observed in other pathological conditions such as viral or bacterial infections. Accordingly, the APPs increase observed in neurodegenerative diseases is of less extent than the increase observed in infectious pathologies. Therefore, it is to be expected that the increase in APPs in patients exhibiting neurodegenerative diseases will be low as compared with other diseases. Although the relevance of APP measurements in the diagnosis of neurodegenerative diseases should need further evaluations, we believe that the prospects for blood-based biomarkers may be useful in the near future. We suggest that blood-based APP markers, perhaps in association with other biomarkers, will be useful tools for diagnosis of neurodegenerative diseases such as AD or PD and it is very likely that plasma markers will become part of the armamentarium for the investigation of CNS disorders.

The measurement of blood APP levels will be a safe and valuable tool for assessing and confirming the diagnosis of some disorders; the secretion of anti-inflammatory markers such as cytokines or APPs could be used to help to diagnose and evaluate the progression of the neurodegenerative process. However, more sensitive techniques of APP detection are needed, in particular to be used as putative diagnosis marker of neurodegenerative disorders.

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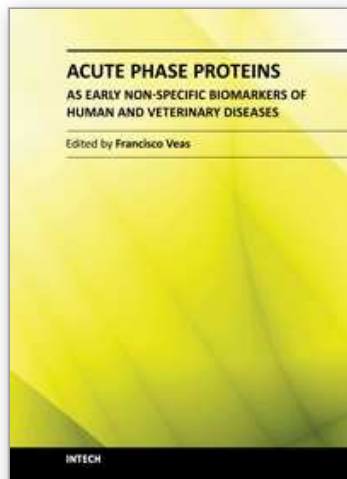
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