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Post-Myocardial Infarction Depression

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1. Introduction

Prospective studies show that persons with depression are at increased risk for coronary artery disease, myocardial infarction (MI) and cardiac death (Anda et al. 1993; Barefoot and Schroll 1996; Ferketich et al. 2000; Penninx et al. 2001). This high rate is at least partly related to a greater activation of platelets resulting in an increased risk of thrombosis, which can partly explain the relation between these events (Laghrissi-Thode et al. 1997). Moreover, clinical depression can occur in 30-60% of MI patients and 15-20% develop major depression (Guck et al. 2001; Meneses et al. 2007) following MI. Evidence for a poor prognosis is particularly strong in MI patients with depressive symptoms (Ahern et al. 1990; Forrester et al. 1992; Frasure-Smith et al. 1993; Frasure-Smith et al. 1995; Bush et al. 2001; Lespérance et al. 2002): the risk of cardiac death in the 6 months after acute MI is approximately 4 times greater in patients with depression compared to non-depressed control subjects (Frasure-Smith et al. 1993). A 3.5-fold risk is still present years after MI (Lespérance et al. 2002).

Despite a lower quality of life and poor prognosis for survival, only a few patients with post-MI depression are treated for their affective disorder (Schleifer et al. 1989; Frasure-Smith et al. 1993; Lespérance et al. 1996; Honig and Maes 2000). This unfortunate situation has been attributed either to the fact that symptoms of depression are unrecognized because of the overlap with sequelae of hospitalization for MI (e.g., sleep disturbances, fatigue, feelings of guilt, loss of appetite, preoccupation with death) (Katon and Sullivan 1990; Freedland et al. 1992; Frasure-Smith et al. 1993), or because symptoms of depressive disorder in post-MI patients are not always typical (Honig et al. 1997). It has also been suggested that physicians may hesitate to treat a depression considered to be a normal and transient reaction to a life-threatening event and the associated hospitalization period (Fielding 1991; Littman 1993). Furthermore, some physicians may avoid prescribing antidepressant medication for patients who have sustained an MI, because of the potential interaction or unwarranted adverse cardiac events reported for classic (i.e., tricyclic) antidepressants (Glassman et al. 1993). Still, the mechanisms by which MI is so often followed by depression is little investigated and poorly understood. For this reason, we have undertaken the task to develop an experimental animal model to advance the knowledge on post-MI depression.

2. An experimental model of post-myocardial infarction depression

On a pathophysiological point of view, the occurrence of post-MI depression lead us to search for common threads between the ischemic heart and the brain structures associated with depression. More specifically, we designed our experimental strategy toward documenting biochemical modifications in the brain limbic system as well as the behavioral modifications following an acute MI.

2.1 Myocardial infarction and pro-inflammatory processes

Ischemia occurs when coronary arteries blood flow is interrupted, which leads to reversible changes at the cellular level (swelling of mitochondrial matrix, intracellular fluid accumulation, etc). If ischemia persists, irreversible damage appears: membrane integrity is affected and intracellular substances are released, leading to an inflammatory reaction associated with a significant influx of neutrophils in the ischemic myocardium (Chatelain et al. 1987) and ultimately will be replaced by macrophages (Yu et al. 2003). After a prolonged period of ischemia, almost all the cells present in the ischemic region will die which can lead to heart failure if myocardial damage is extended.

Reperfusion of cardiac ischemic tissue is associated with a massive inflammatory response characterized by the release of chemotactic and inflammatory substances. The accumulation of neutrophils is rapid for the first six hours of reperfusion and diminishes to insignificant levels after 24 hours of reperfusion (de Lorgeril et al. 1990). The inflammatory response observed during the reperfusion period is more intensive that the one observed during the ischemic period (Chatelain et al. 1987). The reperfusion period of ischemic cardiac tissue is also associated with apoptosis, i.e., programmed cell death. This may appear paradoxical at first hand since apoptosis induces cell death without inflammation. It is known, however, that pro-inflammatory substances are released by jeopardized myocardium, which leads to the apoptotic process. Indeed, acute MI is associated with high production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-8) by monocytes, and inflammatory mononuclear cells infiltrate the border zone, cardiomyocytes and endothelial cells (Francis et al. 2004). This represents parts of an intrinsic myocardial stress response system to tissue injury that may contribute not only to wound healing but also to secondary injury (Marx et al. 1997; Gwechenberger et al. 1999; Irwin et al. 1999; Kato et al. 1999; Pudil et al. 1999; Deten and Zimmer 2002; Hillis et al. 2003; Tziakas et al. 2003).

The rapid increase in pro-inflammatory cytokine expression after MI is accompanied by a simultaneous local and systemic increase of catecholamines (Bürger et al. 2001), which can contribute to cytokine expression. Recent confirmation has been obtained with the attenuation of IL-1β mRNA expression in cardiac tissue in presence of propranolol, a β-adrenergic receptor antagonist (Deten et al. 2003). This shows that MI can elicit a quick and intensive inflammatory response that may alter the blood-brain barrier (Wann et al. 2004) or intestinal permeability (Arseneault-Bréard et al. 2011). It has been reported that increased cytokine synthesis (mainly TNF-α) may be observed in the brain following MI, and this could be prevented by the intraperitoneal administration of pentoxifylline (Francis et al. 2004). In parallel, we have observed that MI affects the integrity of the intestinal barrier and this could be prevented by the administration of probiotics, possibly by altering the balance between pro- and anti-inflammatory cytokines (Arseneault-Bréard et al. 2011).

Because reperfusion needs to be performed upon cardiac arrest and since there is an inflammatory response observed early after the onset of reperfusion, we used the reperfused MI as the basis of our model. Smaller infarct size, better survival rate, rapidly recovering animals, and great clinical relevance are among the different advantages of using a short period of ischemia followed rapidly by reperfusion compared to a permanent occlusion.

2.2 Post myocardial infarction depression and apoptosis

Post-mortem brains of depressed patients show DNA fragmentation and neuronal apoptosis, suggesting enhanced neuronal vulnerability in depression (Lucassen et al. 2006). Neuronal loss and reduced neurogenesis have also been observed in animal models of mood disorders (Gould and Tanapat 1999; Czeh et al. 2001; Lucassen et al. 2006). A decrease in the volume of the hippocampus, amygdala and prefrontal cortex is one of the neuropathological signs described in depression in which apoptosis may play a role (Sapolsky 1996; Drevets 2000; Strakowski et al. 2002). Neuronal cell death may occur via 2 mechanisms: a) an acute form, or necrosis, that is rapid; and b) a delayed form, through apoptosis (Yuan and Yankner 2000). The former cannot be prevented efficiently because it tends to be prominent after more extreme conditions, such as ischemic insults or mechanical injury while the later is tightly regulated and dependent of the presence of energy (Yuan and Yankner 2000). Apoptotic cells are characterized by a reduction of volume, cytoplasmic shrinkage, DNA fragmentation, cell rounding and membrane bledding (Kerr et al. 1972). Apoptotic cells can ultimately break into membrane-contained apoptotic bodies, which can be phagocytosed by neighboring cells or phagocytes, which explains the difficulty of documenting apoptosis in vivo (Wyllie et al. 1980).

Clinical evidence has demonstrated the presence of apoptosis in the brain of persons with depression. In one investigation, cell death was observed in the entorhinal cortex, subiculum, dentate gyrus and hippocampus (CA1 and CA4) in 11 out of 15 depressed patients without obvious massive cell loss (Lucassen et al. 2001). An imbalance between neurogenesis and cell death may thus contribute to some extent to the brain volume changes in depression or, alternatively, cell death may be present for a limited time followed by regeneration (Malberg et al. 2000). In another study, the same authors suggested that the contribution of cell death may have been underestimated, since antidepressant treatments are now known to be anti-apoptotic (Lucassen et al. 2004). Since then, 3 investigations have responded to this comment: a) The antidepressant Desipramine is associated with cultured hippocampal neural stem cell neuroprotection against lipopolysaccharide-induced apoptosis by inhibiting inflammatory processes in vitro (Huang et al. 2007); b) Desipramine and Fluoxetine increase Fibroblast Growth Factor-2 activity, a growth factor involved in maturation, synaptic connectivity, neurogenesis and survival of catecholamine neurons in the cortex and hippocampus (Bachis et al. 2008); c) Our own data, showing that Sertraline, an antidepressant with selective serotonin reuptake inhibition properties, blocks early post-MI apoptosis in the limbic system (Wann et al. 2009). The anti-apoptotic effect of antidepressants was also reported in 2 other recent studies in rats (Huang et al. 2007; Bachis et al. 2008). Although apoptosis is difficult to document in human clinical cases (because patients are usually treated with antidepressants), another set of evidence indicates that the lymphocytes (Ivanova et al. 2007) or blood leukocytes (Szuster-Ciesielska et al. 2008) of depressed patients manifest a higher proportion of apoptotic elements compared to healthy

controls. It is also observed that proapoptotic serum activity is elevated in depressed patients (Politi et al. 2008), again suggesting a link between apoptosis and depression. Moreover, it has been found that mood-regulating molecules, such as Lithium and Valproate, increase the expression of Bcl_2, an anti-apoptotic cytoprotective protein. Bcl_2 shuts off the apoptotic signal transduction pathway upstream of caspase activation (Chinnaiyan et al. 1996). It is also reported that antidepressant treatments themselves can increase neurogenesis in the rat hippocampus (Malberg et al. 2000) and prevent apoptosis (Lucassen et al. 2004; Nahon et al.). Apoptosis thus holds a key position in our experimental strategic plan to better understand the pathophysiology of post-MI depression.

2.2.1 Intracellular mechanisms of apoptosis

Multiple cellular pathways can trigger apoptosis, involving caspase activation or not (MacFarlane and Williams 2004) and two pathways of caspase activation have been described: extrinsic and intrinsic (figure 1). The extrinsic and intrinsic pathways of caspase activation differ according to the mechanism by which initiator caspases (see below) are activated, whereas effector caspases (caspase-3, -6 and -7) are common in both pathways (Adams 2003).

The extrinsic pathway is initiated by ligand binding to death receptors, such as tumor necrosis factor (TNF), Fas or TNF-related apoptosis-inducing factor receptors (TRAIL) (Thorburn 2004). The formation of death-inducing signaling complexes (DISC) is the key element. These complexes are formed by the activated receptor FAS-associated death domain protein (FADD) or TRAIL-associated death domain protein (TRADD). Pro-caspase-8 is then recruited to the complexes to form DISC, resulting in auto-cleavage and caspase-8 activation (Wang and El-Deiry 2003). Activated caspase-8, in turn, cleaves and activates downstream effector caspases, such as caspase-3, leading to the cleavage of cellular proteins and cell death. Active caspase-8 can cleave Bid, a member of the Bcl-2 family, and cleaved Bid can amplify the death signal by promoting the release of apoptogenic proteins from the mitochondria (Luo et al. 1998).

The intrinsic pathway or mitochondria-dependent pathway can be activated by chemicals, drugs, irradiation and cell stress such as hypoxia (Jeong and Seol 2008). Independently of signals that trigger the intrinsic pathway, mitochondria in the target organelle, resulting in the release of cytochrome c and the loss of mitochondrial membrane potential (Reyland 2007). Cytochrome c, together with apoptotic protease activating factor 1 (Apaf-1), ATP and pro-caspase-9, forms apoptosomes and elicits caspase-9 activation (Jeong and Seol 2008). Apoptosis is suppressed through heterodimerization of anti-apoptotic Bcl_2 proteins, such as Bcl_2 and Bcl-xL, with pro-apoptotic proteins, such as Bak and Bax; thus, the ratio of pro- and anti-apoptotic proteins is an important determinant of cell fate (Reyland 2007). Apoptotic stimuli alleviate the Bcl_2-mediated suppression of pro-apoptotic Bax and Bak, allowing these proteins to oligomerize into transmembrane pores in the mitochondria, induce cytochrome c release and activate caspases.

Caspase activation is also regulated by the release of mitochondrial proteins, such as the inhibitor of apoptosis proteins (cIAP1, cIAP2, XIAP) that suppress activated caspases, and Second Mitochondrial Activator of Caspases SMAC/DIABLO that binds and reduces IAPs (Salvesen and Duckett 2002; Shi 2002). Finally, a group of mitochondrial proteins that induce

apoptosis independently of caspase activation has been identified (Lorenzo and Susin 2004; Bras et al. 2005). These include apoptosis-inducing factor (Lorenzo and Susin 2004; Bras et al. 2005) and endonuclease G (Li et al. 2001), which are released from the mitochondria in response to an apoptotic signal and translocate to the nucleus to trigger nuclear condensation and DNA fragmentation (Lorenzo and Susin 2004).

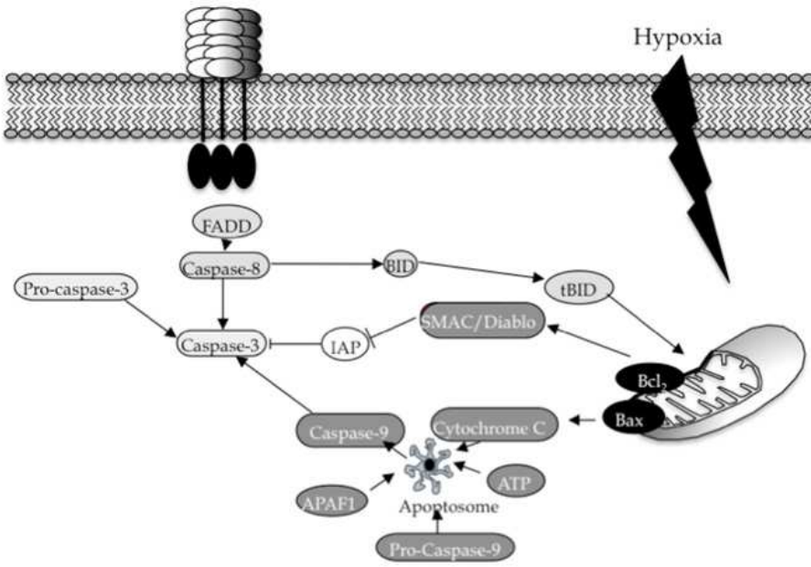

Fig. 1. Intrinsic and Extrinsic pathways of apoptosis. The extrinsic pathway involves receptor-mediated caspase-8 activation with subsequent effector caspase-3 activation. Within the intrinsic apoptosis pathway, caspase-3 is activated after cytochrome c release from the mitochondria and the formation of complexes called apoptosome that consist of caspase-9, Apaf1, ATP and cytochrome C. The release of apoptogenic factors from the mitochondria, such as cytochrome c, is regulated by Bcl_2 family proteins.

2.3 Apoptosis in the limbic system after myocardial infarction

Apoptosis has been observed in the limbic system after myocardial infarction (Wann et al. 2006; Kaloustian et al. 2009). We have documented the presence of apoptotic cells in the limbic system mainly in the amygdala, 3 days after the onset of reperfusion whereas no substantial apoptosis was observed in the sham group. In presence of MI, amygdala presents an increase in the activity of caspase-3 as compared to the sham group, as well as a higher Bax/Bcl2 ratio and a significant number of TUNEL positive cells. In order to be more precise in the localization of the presence of apoptosis at 3 days post-MI, we evaluated the presence of apoptosis in 9 different regions of the brain, using the cerebellum as a control structure (Wann et al. 2009): prefrontal and frontal cortices, CA1, CA3 and dentate gyrus of the hippocampus, lateral and medial amygdala and anterior and posterior hypothalamus. Our data indicate an increase of apoptosis in 7 of these regions (prefrontal and frontal cortices, CA1, dentate gyrus, lateral and medial amygdala and anterior hypothalamus). The next step of our investigation was to determine the kinetic of apoptosis in these regions during the first week after the onset of reperfusion (Kaloustian et al. 2008). Apoptosis was detected in the CA1 region as soon as 15 minutes

after the onset of reperfusion, followed 24 hours later by the medial amygdala. Seven days after the onset of reperfusion, the frontal cortex is the only region where apoptosis is present.

As explained above, apoptosis can be triggered via intrinsic and extrinsic pathways. In a series of experiments designed to dissect the respective contribution of these two pathways, we found that caspase-9 activity was increased as soon at 15 minutes after the onset of reperfusion in the CA1, indicating that the intrinsic pathway is rapidly activated in this region (Rondeau et al. 2011). This result can be explain by the sensitivity of this region to hypoxia (Sugawara et al. 1999) which can be induced by MI. However at the same moment, the dentate gyrus presents an activation of caspase-8, (extrinsic pathway) but no activation of caspase-9 or caspase-3, indicating that: 1) intrinsic pathway is not activated in this region; 2) apoptosis is beginning in dentate gyrus at this moment. At three days post-MI, caspase-3 and -8 are activated in the hippocampus and amygdala regions. Overall, these data indicate that apoptosis is rapidly triggered in the CA1 region after the onset of reperfusion by an intrinsic pathway mechanism whereas apoptosis is induced in the other regions, such as dentate gyrus, by an extrinsic pathway mechanism.

An interesting observation from these series of experiments is that apoptosis does not occur at the same time throughout the limbic system. One hypothesis could be that cell death observed in a region can affect other regions later. Indeed, it has been observed that neurons which have no trophic support or electrical activity die by apoptosis (Jacobson et al. 1997). Thus, it can possible that the loss of neurons in a region may affect the neurons in other part by a reduction of trophic support or electrical activity.

Although the characterization of the cells that undergo apoptosis has not been fully completed yet, we have used the fluorojade labeling technique to verify if neurons are affected in the limbic system after myocardial infarction. Positive fluorojade staining cells indicate the presence of degenerating neurons (figure 2).

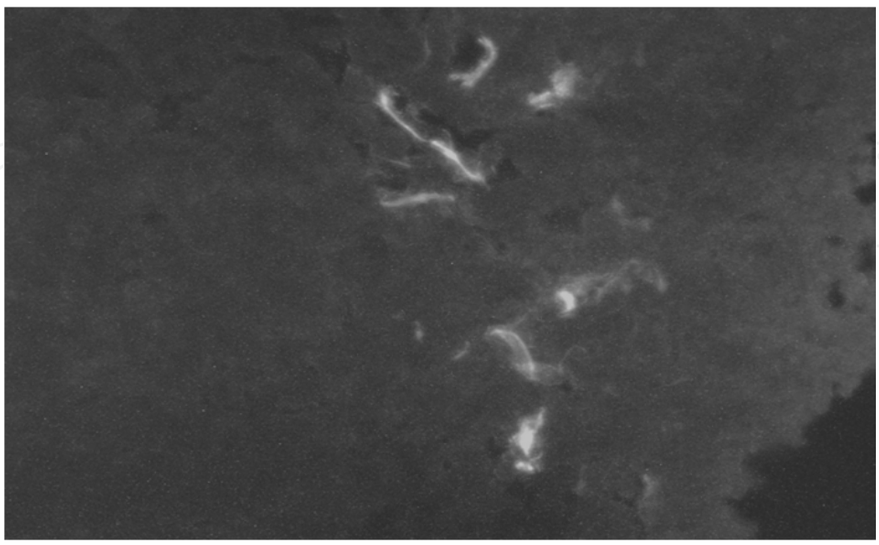

Fig. 2. Example of positive fluorojade staining cells in amygdala after myocardial infarction indicating the presence of degenerating neurons.

2.4 Cytokines, depression and post-myocardial infarction

Since the extrinsic mechanism of apoptosis is activated in the limbic system after MI and because apoptosis can be attenuated by pentoxifylline (Wann et al. 2006), an inhibitor of cytokine synthesis, we hypothesized that pro-inflammatory cytokines could be involved in the pathophysiology of post-MI depression. The following paragraphs summarize some of the supporting evidence.

Cytokines are a heterogeneous group of short-acting soluble proteins, glycoproteins and peptides. These regulatory proteins are secreted by a variety of cell types including white blood cells (lymphocytes and monocytes or macrophages) and somatic cells (O'Brien et al. 2004). Cytokines are multipotent and have pleiotropic effects not only in the immune system but also the CNS (Oprica et al. 2005); they contribute to immune responses of the body, help maintaining homeostasis, and mediate inflammation. Cytokines are associated with the membrane or the extracellular matrix, and toggle between the soluble and membrane forms (Sprague and Khalil 2009). Different cell types can secrete the same cytokine and a single cytokine can act on several cell types (pleiotropy), producing multiple biological activities depending on cell type, time and context (Hirano 1999) or inducing the synthesis of additional cytokines. Cytokines are redundant in their activity, meaning that similar functions might be stimulated by different cytokines (Ozaki and Leonard 2002). Because of the redundancy, the pathophysiological role of cytokines may be difficult to assess. In addition, cytokines are often produced in a cascade of events engaged in diverse modes of action: autocrine (when acting on cells that secrete), paracrine (when acting on cells near those that secrete) and endocrine (when acting on cells far from those that secrete) (Sprague and Khalil 2009). Cytokines can also act synergistically (two or more cytokines acting together) or antagonistically (cytokines causing opposing activities).

Cytokines bind to specific receptors at picomolar to nanomolar concentrations to activate and modulate functions at the cellular and tissular levels. Cytokine receptors are present in different structures of the limbic system. For example, IL-1 receptors are found in the hypothalamus and the hippocampus; IL-6 receptors are located in the hippocampus, hypothalamus, the dentate gyrus and piriform cortex (Vitkovic et al. 2000); TNF receptors are located in the hippocampus, cortex, amygdala, the basal ganglia (Vitkovic et al. 2000) and are also expressed by oligodendrocytes (Tchelingerian et al. 1995).

Recent advances in the field of psychoneuroimmunology suggest that major depression may alter immune function. Conversely, abnormal immune system may play a role in the etiology of depression (Maes et al. 1993). The immune system function in depressed patients involves both the hyperactivity of pro-inflammatory cytokines and anti-inflammatory cytokines (Grippo and Johnson 2002).

The administration of endotoxins in humans increases serum levels of pro-inflammatory cytokines and induces anxiety, mood changes and decreased memory skills, (Reichenberg et al. 2001). In rodents, pro-inflammatory cytokines induce the so-called "sickness behavior", which includes aspects of depression such decreased appetite, weight loss, fatigue, loss of libido, sleep disturbances and reduced social contacts (Krueger et al. 1984; Yirmiya et al. 2000; Dantzer 2001). In humans, the direct administration of pro-inflammatory cytokines such as TNF-α (Spriggs et al. 1988), IFN-γ (Niiranen et al. 1988) and IL-1β (Cunningham and De Souza 1993) leads to symptoms of depression such as irritability, fatigue, lethargy, loss of appetite psychomotor retardation and sleep disturbances. In patients with depression, the

activation of the immune system translates into an augmentation in the number of circulating lymphocytes and phagocytic cells, immune cells by-products such as prostaglandin E2, complement proteins and increased concentrations of pro-inflammatory cytokines (Maes 1995; Irwin, Mak et al. 1999; Maes 1999; Maes, Song et al. 1999; Nunes, Reiche et al. 2002; Zorrilla, Valdez et al. 2001; Tuglu, Kara et al. 2003; (Maes 1995; Zorrilla et al. 2001; O'Brien et al. 2004).

Another potential action of the pro-inflammatory cytokines that may contribute to depression is by an action on indoleamine 2,3-dioxygenase (IDO) (Wirleitner et al. 2003). IDO is an enzyme induced by pro-inflammatory cytokines (IL-1, IFN-γ and TNF-α) and that is involved in the catabolism of tryptophan, the precursor of serotonin (Russo et al. 2003; Wirleitner et al. 2003). The net result is a reduced synthesis and availability of serotonin in the brain, thus facilitating depression (Heyes et al. 1992; Wichers and Maes 2002).

Blocking cytokine synthesis with PTX (Wann et al. 2006) or, more recently, with a TNF-α blocker (Kaloustian et al. 2009) significantly reduced apoptosis in the limbic system. The presence of pro-inflammatory cytokines at the limbic level can be explained by different mechanisms. The first possibility refers to modifications in endothelial permeability. Indeed, it has been reported that TNF-α disrupts endothelial cell lining integrity in various organs, including the anterior cingulate gyrus (Worrall et al. 1997). The pattern of selective plasma protein extravasation induced by TNF-α injection is similar to the pattern of MI-induced leakage (ter Horst et al. 1997). A second possibility is that circulating pro-inflammatory cytokines trigger the transcription of genes in cells of the blood-brain barrier, including NF-kB and cyclooxygenase-2 (COX-2), the limiting enzyme for the formation of prostaglandins (Laflamme and Rivest 1999). Prostaglandins, such as PGE_2, can diffuse across the brain parenchyma and stimulate the hypothalamic-pituitary-adrenal axis and corticotropin-releasing-factor activity (Rivest 2001; Banan et al. 2002). Moreover, it has been reported that COX-2 expression is associated with increased PGE_2 tissue levels and neuronal apoptosis (Li et al. 2003; Sasaki et al. 2004). In another study, PGE_2 induced caspase-dependent apoptosis in rat cortical cells (Takadera et al. 2002). Our results (Wann et al. 2006) show biochemical changes in the hippocampus and amygdala, limbic regions that express high levels of PGE_2 receptors. This suggested that COX-2 inhibition can be a significant element in our model (Zhang and Rivest 1999). A third possibility is the presence of a carrier that mediates the transport of cytokines into the brain across the blood-brain barrier (Banks et al. 1995; Kronfol and Remick 2000; Banks 2001). The fourth possibility refers to "central cytokines induced by peripheral cytokines" via afferent nerves activated by myocardial ischemia (Francis et al. 2004). It was derived from the fact that cytokines are relatively large protein molecules (≈15 kDa for interleukin-1 (IL-1) and TNF-α), the hydrophilic nature of which does not allow crossing of the blood-brain barrier. According to these authors, transmission of the cytokine signal to the brain could be due to epicardial afferences, since destruction of these nerves by phenol prevents the induction of brain cytokine expression in the hypothalamus and hippocampus (Layé et al. 1995; Hansen et al. 1998; Francis et al. 2004). Among these different hypotheses, we believe that neurotransmission, via afferent nerves, is probably the more interesting: 1. we observed apoptosis, via activation of the caspase-8 pathway (extrinsic pathway) as early as after 15 min of reperfusion in some specific regions of the limbic system (dentate gyrus); 2. pro-inflammatory cytokines increased in the brain as early as 30 min after the onset of myocardial ischemia, but could be blocked by the destruction of afferent epicardial nerves with phenol (Francis et al. 2004).

2.5 Hypothalamic-pituitary adrenal axis-dependent mechanism

The regulation of the hypothalamic-pituitary adrenal (HPA) axis plays a major role in metabolic homeostasis and its overactivation by stress is associated with deleterious effects to the brain (Bluthe et al. 1999; Bluthe et al. 2006). Dysregulation of the HPA axis is part of the pathophysiology of depression.

The classic description of the HPA axis includes 3 main components (Bao et al. 2008): 1) The hypothalamus, that secretes the corticotropin-releasing hormone (CRH) upon a stressful situation; 2) the pituitary gland that reacts to CRH by producing growth hormone, prolactin and the adrenocorticotropic hormone (ACTH); 3) the adrenal glands (also named suprarenal glands), that react to ACTH by producing and releasing glucocorticoid (GC), mainly cortisol in humans and corticosterone in rodents (Carvalho and Pariante 2008), epinephrine and norepinephrine. A feedback loop makes the hypothalamus capable of monitoring cortisol blood levels and inhibits the release of CRH when cortisol levels are too high; in depression, this feedback mechanism may be altered so that CRH is still released despite high amounts of circulating cortisol (Pariante and Lightman 2008). Cortisol activates two types of receptors, the high-affinity mineralocorticoid receptors (MRs) and the low affinity glucocorticoid receptors (GRs); MRs are thus activated by low (basal) levels of GC while GRs are activated as GC concentrations increase, i.e. after stress. MRs and GRs apparently activate different genes and elicit different, sometimes opposing, actions: high levels of corticosterone induce apoptosis through the activation of GRs via the direct regulation of the extrinsic and intrinsic apoptosis pathways while low doses of corticosterone can prevent cell death through MRs activation, conferring a neuroprotective role for these receptors (Crochemore et al. 2005; Herr et al. 2007; Krugers et al. 2007; Yu et al. 2008). More specifically, studies revealed that activation of the GRs mediates hippocampus neuron- and volume-reducing actions of GC whereas stimulation of the MRs abrogates the neurodegenerative actions of the GRs agonists (Yu et al. 2008). High levels of GC can affect the survival of immature neurons, decreasing neurogenesis in the dentate gyrus (Wong and Herbert 2004).

Hyperactivity of the HPA leads to depression because dysregulation of GC can affect brain regions involved in the physiopathology of depression (Herbert et al. 2006). Activation of GRs by the agonist dexamethasone induces apoptotic death of neurons, while activation of MRs would tend to induce neuronal survival (Crochemore et al. 2005). The hypotheses to explain the effect of antidepressants on the HPA is that such treatment could increase the expression and the function of GRs, and promote its nuclear translocation (Pariante 2006). No effects of antidepressants on MRs are noted (Lai et al. 2003). The administration of tricyclic antidepressants or serotonin reuptake inhibitors (SSRIs) are accompanied by an increase in mRNA of GRs in various tissues and neurons (Pepin et al. 1989). Desipramine (a tricyclic antidepressant) showed an increase in function and nuclear translocation of GRs (Pariante et al. 1997). The tricyclic antidepressant imipramine and the SSRI fluoxetine inhibit the CRH gene promoter (Budziszewska et al. 2002). With effective antidepressant treatment, 75% of patients who did not respond to the dexamethasone suppression test now do (Heuser et al. 1996), while remaining unresponsive often suffer a relapse (Zobel et al. 2001).

We now know that growth hormone and prolactin stimulate the immune response while cortisol inhibits the immune response, the inflammatory response and natural killer cells (NKC). Depression is associated with an increase of secretion of IL-1β, TNF-α and IFN-α (Smith 1991; Maes et al. 1993; Maes 1995). Hyperactivity of the HPA axis accompanies this

phenomenon (Connor and Leonard 1998) and, in turn, IL-1, IL-6, interferon and TNF activate the HPA axis (Turnbull and Rivier 1995).

Cytokines are also released following MI and they will reach the paraventricular nucleus of the hypothalamus, stimulating the synthesis and secretion of stress-related glucocorticoids (Turnbull and Rivier 1995). Increased plasma levels of pro-inflammatory cytokines such as IL-1 and IL-6 in patients with depression are correlated with hyperactivity of the HPA axis and the severity of symptoms (Maes 1995; Maes 1999).

The immune system can also influence the HPA axis response through various mechanisms involving pro-inflammatory cytokines: for example they may contribute to resistance to GC (cortisol unable to induce the negative feedback loop) by a decrease in GR function or sensitivity to GC (Miller et al. 1999) or inhibit GR translocation to the nucleus and decreases the transcription of genes induced by GR (Pariante et al. 1999). GC resistance following exposure to cytokines can be induced via the MAP kinase pathway: 1) ERK and JNK can inhibit GR function directly, by phosphorylation, or indirectly, through cofactors (Rogatsky et al. 1998); 2) NF-kB can directly interact with GR at the nuclear level or may decrease its function indirectly by competing for the same coactivators (McKay and Cidlowski 1999). Cytokines also activate the JAK-STAT pathway, which can GR functions by a direct protein-protein interaction (Rogatsky and Ivashkiv 2006; Pace and Miller 2009).

We have measured the level of corticosterone in our model, 2 weeks post-MI and we have observed that myocardial infarction induces an increase in plasmatic concentrations of corticosterone. However, the contribution of HPA axis in our model seems to be modest since attenuation of the depressive behavior has been observed with Escitalopram whereas no significant effect was detected in the plasmatic concentration of corticosterone (Bah et al. 2011).

2.6 Neurotrophic factors in depression

The reduction of hippocampal volume in depression is related to a dysregulation of neurogenic and neurotrophic factors (Duman and Monteggia 2006). The chronic administration of antidepressants increases neurotrophic factors and facilitates neurogenesis in the hippocampus, thus reducing the damage described above (Dranovsky and Hen 2006). The brain-derived neurotrophic factor (BDNF) is more particularly frequently cited as playing a significant role in that respect.

BDNF belongs to the family of Nerve Growth Factors (NGF). Physiologically, neurotrophins are initially synthesized as precursor protein (or pro-neurotrophin) and transformed into mature proteins (Mowla et al. 2001). All neurotrophins have a common structure and a structure variable that determines their specific receptors and their biological action arising (Heumann 1994).

BDNF mRNA is expressed in the hippocampus, septum, hypothalamus, cortex and noradrenergic brainstem nuclei (Castren et al. 1995; Katoh-Semba et al. 1997). This distribution overlaps with immunohistochemical localization of BDNF itself in the rat cerebral cortex, hippocampus, basal forebrain, striatum, hypothalamus, cerebellum (Kawamoto et al. 1996) as well as in the parietal and entorhinal cortices, amygdala and in the somatic nuclei (Wetmore et al. 1991).

BDNF is decreased in patients with depression (Karege et al. 2002) and antidepressants regulate the transcription of its mRNA (Dias et al. 2003). Moreover, the chronic administration of

antidepressants increases BDNF in the limbic system, including the hippocampus (Nibuya et al. 1999). The mRNA expression of TrkB, the BDNF receptor, is altered in the rat hippocampus or cortex after repeated stress (Nibuya et al. 1999) and after treatment with antidepressants (Saarelainen et al. 2003). Impaired BDNF or TrkB signaling in rats does not lead to behavioral signs of depression, but lessened the behavioral response to antidepressants (Saarelainen et al. 2003). In addition, increased neurogenesis in the hippocampus is required to find behavioral effects of antidepressants in animal models of depression (Santarelli et al. 2003).

In our rat model of post-MI depression, BDNF levels were found to be increased in the dentate gyrus of the hippocampus 2 days post-MI and in the medial amygdala 7 days post-MI, suggesting a potential role of BDNF in this model (Kaloustian et al. 2008).

3. Behavior observed in experimental model of post-MI depression

One of the major challenges in developing a model of a mental health disorder is at the behavioral level, trying to establish variables that mimic the clinical picture found in humans. In the particular case of post-MI depression, the challenge is increased by the fact that physical fitness should not interfere with the behavioral dependant variables. The major concern is that the damage induced to the heart by the ischemia may affect the performance of the animals and, with these constraints in mind, we elected to use an acute model of heart infarct, thus by-passing the physical impact of chronic heart failure. Moreover, since experimental acute MI involves thoracotomy, sham operated rats are used as controls and tasks involving physical fitness are tested. In our model, reperfusion is rapidly reinstated and the surgical procedure can be summarized as follows. A left thoracotomy is performed and the left anterior descending coronary artery is occluded. Ischemia is confirmed by ST segment alterations and ventricular subepicardial cyanosis. After 40 min of occlusion, the ligature is loosened so that the myocardial tissue can be reperfused. Reperfusion is confirmed by the disappearance of cyanosis. This procedure induces an infarct size that routinely approximates 25% of the left ventricle. A control (sham-operated) group of rats is submitted to the same thoracotomy protocol but without actual coronary artery occlusion.

Behavioral tests that we have chosen were selected on the basis of face validity with regards to the human clinical picture and proven to be reliable and sensitive to antidepressant treatments as shown by previously published results from other groups using different models of depression. In the present model, this is a rather long process that has started less than 10 years ago and will obviously need a few more years before it is firmly established. Nonetheless, we believe we have accumulated enough converging evidence to suggest that our model replicates a significant portion of the human post-MI depressive syndrome. In the following paragraphs we will describe behavioral tasks that are commonly used in behavioral models of depression and that were included in the test battery for our own post-MI depression model. Like most models of depression, the post-MI syndrome appears 2-3 weeks after the experimental procedure aimed at inducing depression and tests are now routinely administered in that interval following reperfusion.

3.1 Forced swim test

This test was first developed by Porsolt (Porsolt et al. 1977; Porsolt et al. 1978a; Porsolt et al. 1978b) as a procedure for validating antidepressant efficacy. It models behavioral despair and learned helplessness, as rats are natural swimmer. In our experiments, rats are

individually placed in a clear plastic cylindrical pool (45 cm tall x 25 cm diameter) filled with 30 cm of water maintained at 22-25°C. Rats are tested for two consecutive days (15 min. on the first day and 5 min. on second day). Time spent swimming, trying to escape and being immobile on day 15 post surgery are the dependant variables. During the initial period of this test, rats will usually present an intense activity followed by a characteristic immobile posture, moving occasionally to keep at least their nose above the waterline. Depression has been positively correlated with the length of immobility during the second trial on the test. The Forced swim test has a good predictive validity to detect antidepressant-like activity (Arunrut et al. 2009). Antidepressants usually decrease immobility.

In our model, we observe that 14 days after the onset of reperfusion, the animals with MI present more immobility than the group of sham-operated control animals (figure 3A). This effect can be reversed by different interventions, as we will discuss later. We also determined if the myocardial infarct size influenced the behavioral results. Plotting swimming time against MI size, expressed as percent of the left ventricle, showed no relation between the two variables (figure 3B). This is further evidence that infarct size observed in our model had no influence on motor performance in the Forced Swim test.

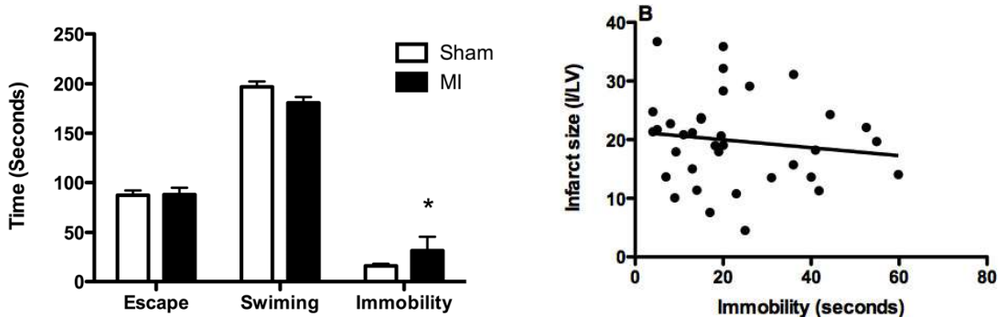

Fig. 3. A: Performance of rats in the forced swim test. Escape and swimming time is similar between groups whereas the time of immobility is significantly higher in the MI group. * indicates $p < 0.05$. n=16-18 per group. B: Relationship between infarct size (expressed as the proportion of infarcted tissue in the left ventricle) and immobility time in the forced swim test. The slope of the relationship is non-significant, $p = 0.44$ with a $r^2 = 0.02$.

3.2 Morris water maze

This is a test of motor performance and spatial memory requiring an intact hippocampus (Morris 1984). Rats are placed in a pool (150 cm diameter, 50 cm deep) filled to 25 cm with water maintained at 22°C–25°C and made opaque with powder milk. A submerged platform is placed just below the surface of the water. The rats are tested on 4 trials each day, 5 minutes apart, for 6 consecutive days (i.e., 14–19 days after surgery). The number of quadrants crossed, the number of successful trials and the time taken to reach the platform are recorded. Our results indicate no significant difference between MI and sham group, suggesting that MI: a) has no effects on hippocampus-dependant spatial memory; b) has no effects on the swimming capacity of experimental rats (Wann et al. 2007).

3.3 Sucrose preference

The sucrose preference test is classically used to define anhedonia in rat models of depression (Willner et al. 1987; Stock et al. 2000; Redei et al. 2001). For this test, rats have free access to two

250 ml bottles for five consecutive days (i.e., 14-18 days postsurgery): one containing tap water and the other containing a 1% sucrose solution. The position of the bottles is alternated each day. Volume intake (in ml) is estimated by weighing bottles each morning, at light onset. Contrary to most publication, rats are not deprived of water before running the test because we fear it might interfere with bodily functions. Anhedonia is operationally defined as a reduction in sucrose intake compared to a control group and untreated MI rats are found to take less sucrose solution than sham animals. In this case, it can be assumed that the physical condition of the animal has no significant effects on the results.

3.4 Social interaction test

It is known that depressed individuals have fewer interactions with congeners. In this test, two rats are placed together in a new, clean shoebox for 10 min. During this period, the following measures are taken for each of the two rats: duration and number of interactions with the other rat, number of grooming events and number of rearings. Sham rats are found to interact more with congeners than MI rats (figure 4).

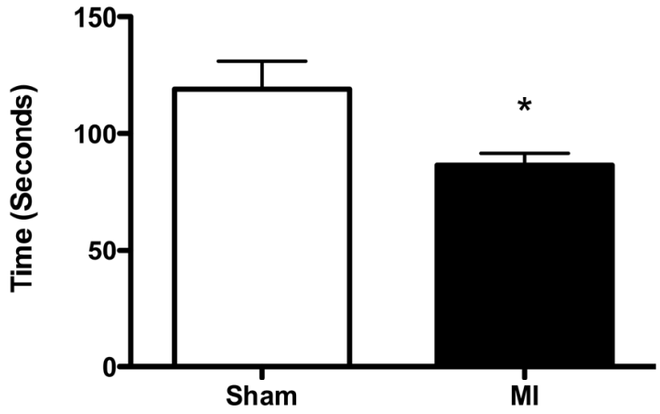

Fig. 4. Social interaction test. The data indicate that MI rats interact less than the sham group with their congeners. Time is expressed in seconds. n = 16 per group. *indicates $p < 0.05$ for Sham vs MI.

3.5 Passive avoidance step-down foot shock

This test is based on contextual memory and emotional memory, and depressed rats are known to show a decreased efficiency in response to a repeated aversive stimulus. It is a reliable behavioral indicator of depression in rats and it is also sensitive to the therapeutic action of antidepressants (Joly and Sanger 1986; van Riezen and Leonard 1991). For this test, the rat is placed on a plexiglass platform (14 X 19 cm). An electrifiable grid (14 X 14 cm) is alongside and 2.5 cm lower than the plexiglass platform. Initially, both sham and MI rats begin to wander around immediately, exploring the platform and the grid. When the animal places four feet on the electrifiable grid, it receives a mild, brief shock (5 mA for 1 sec) and is removed from the test box. After 30 sec, the rat is placed again on the platform. If the rat remains on the platform without going onto the grid for one minute, it is removed from the test box for 30 sec. Criterion is reached when the rat avoids going onto the grid for three consecutive trials. We have found that the number of trials and the time to succeed the test is significant higher in the MI rats compared to sham animals (figure 5).

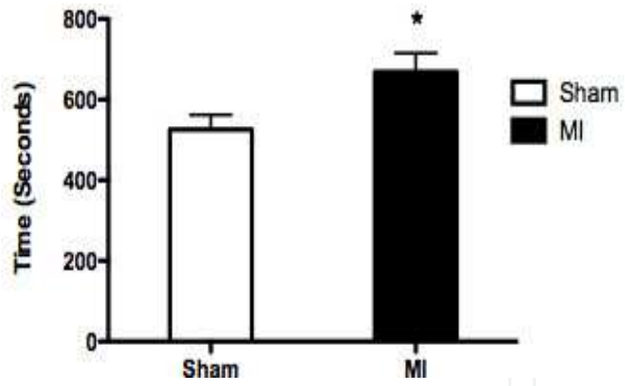

Fig. 5. Passive avoidance step-down foot shock test. In the passive avoidance step-down foot shock test, MI rats take more time to succeed in the test than the sham group (*$p < 0.05$). n = 16 per group.

3.6 Voluntary exercise-training cage

As an additional test to determine if MI affects the physical condition of experimental animals at baseline, we used a voluntary exercise-training cage (threadmills), using the distance travelled by 24 hours as the dependent variable. Measures were taken before and 2 weeks post-MI and the results indicate no differences between tests, i.e., more than 2 km/day (figure 6). Moreover the distance travelled at different moments of the day is similar between the two conditions. These results suggest that: 1) MI does not interfere with total spontaneous locomotion per 24 hour; 2) that circadian patterns may not be affected either.

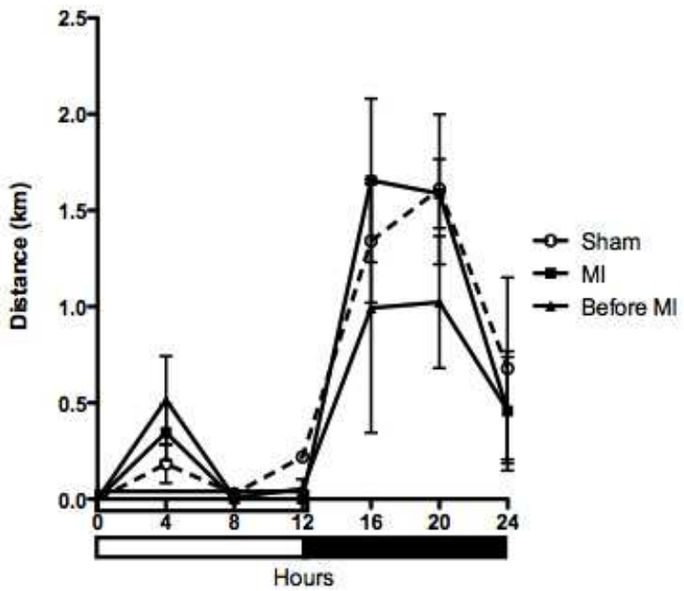

Fig. 6. Distance in km travelled by rats during a day in voluntary exercise-training cage. Open circles represented the distance travelled by the rats 2 weeks after the thoracotomy but without myocardial ischemia. The square represents the distance travelled by MI rats, 2 weeks post-MI whereas the triangle represented the same MI rats but before any manipulations. No significant difference are observed between conditions.

3.7 Sleep

In humans, depression is accompanied by sleep disorders, including difficulties initiating and maintaining sleep, less slow-wave sleep (SWS) together with a facilitation of rapid eye movement (REM) sleep, also known as paradoxical sleep (PS) (Benca et al. 1992). These sleep disorders have also been documented in rat models of depression, such as learned helplessness (Adrien et al. 1991), chronic, mild stress (Willner 2005), olfactory bulbectomy (Song and Leonard 2005), Flinders Sensitive Line (Overstreet et al. 2005), and the neonatal clomipramine model of endogenous depression (Vogel et al. 1990). Compared to sham rats, MI rats displayed a longer latency to sleep onset and to PS and fewer minutes in PS. The number of cholinergic neurons in the pedunculo-pontine tegmentum (PPT) area of MI rats, an area known to control PS, was decreased by 20% compared to sham rats while the number of latero-dorsal tegmentum (LDT) cholinergic neurons was not different (Bah et al. 2010).

These results partially replicate the sleep disorders observed in clinical depression and reveal that acute MI is accompanied, within 2 weeks, by PS-specific insomnia.

4. Treatment of post-MI depression

The pathophysiology of depression has been classically associated with monoamines, with more emphasis on serotonin (Leonard 2000; Delgado 2004): impaired serotoninergic neurotransmission is thought to be a major element in the pathophysiology of depression and SSRI antidepressants restore central serotoninergic neurotransmission. Monoaminergic theories of depression appear today, however, to be only one part of the story. It is known, for example, that pro-inflammatory cytokines influence serotonin metabolism in the central nervous system (Dunn 1992; Palazzolo and Quadri 1992; Cho et al. 1999) and studies have shown that antidepressants suppress the action of pro-inflammatory cytokines (Bengtsson et al. 1992; Xia et al. 1996). Moreover, pro-inflammatory cytokines such as IL-1, IFN-α, IFN-γ and TNF-α upregulate the serotonin transporter, thus causing a depletion of extracellular serotonin (Ramamoorthy et al. 1995; Morikawa et al. 1998; Mossner et al. 1998; Wichers and Maes 2002), whereas IL-4 (an anti-inflammatory cytokine) induces a reduction of serotonin reuptake like antidepressants do (Mossner et al. 2001; O'Brien et al. 2004). It is therefore not surprising that inhibition of pro-inflammatory cytokines is not only beneficial for the remission of depressive symptoms, but also to reduce the inflammation caused by myocardial infarction (Frangogiannis et al. 2002).

In animal models, administration of cytokines or cytokine inducers is associated with depressive symptoms (Dunn et al. 2005). Conversely, the administration of anti-inflammatory cytokines such as IGF-1 or IL-10 antagonizes the effects of cytokine inducers and lowers the symptoms of depression (Bluthe et al. 1999; Bluthe et al. 2006). Patients with depression have high levels of circulating inflammatory cytokines, including IL-1, IL-6 and TNF-α (Dowlati et al. 2009), and low levels of anti-inflammatory cytokines (Sutcigil et al. 2007). Despite the fact that small amounts of peripherally-released pro-inflammatory cytokines make it to the brain, it seems sufficient to induce depression in humans (Wilson and Warise 2008). It has been shown in patients with Cushing's syndrome that infliximab, a TNF-α inhibitor, reduces symptoms of depression before improving disease-specific symptoms (Lichtenstein et al. 2002).

The following paragraphs will review therapeutic strategies we have used in order to control for symptoms of depression in our animal model.

4.1.1 Tricyclic antidepressant (desipramine)

Desipramine is a tricyclic molecule that inhibits norepinephrine and serotonin reuptake, together with antidepressant properties (Katz et al. 2004). In our model, desipramine also reduces depressive-like symptoms such as behavioral despair as assessed by the Forced swim test as well as anhedonia as assessed by the Sucrose preference test. Interestingly, desipramine reduces apoptosis in models of stress-induced depressive disorders (Bachis et al. 2008) and we have found a significant negative correlation between swimming time on the Forced swim test and the Bax/Bcl2 ratio, a pro-apoptotic index, in the prefrontal cortex of MI depressed rats, suggesting again a link between apoptosis and depressive behavior (Wann et al. 2007).

4.1.2 Selective serotonin reuptake inhibitors (SSRIs)

4.1.2.1 Sertraline

The antidepressant SSRI fluoxetine inhibits apoptosis by blocking mitochondrial permeability transition pores (Nahon, et al., 2005) in vitro and we have shown that sertraline blocks post-MI apoptosis in vivo at three days post-MI, in different regions of the limbic system (Wann et al. 2009). At the behavioral level, MI rats showing signs of anhedonia (i.e., decreased sucrose intake) and despair (decreased swimming, increased immobility) improved with sertraline as they do in other models like chronic mild stress (Grippo, et al., 2006), social defeat or subordination (Rygula, et al., 2005).

4.1.2.2 Escitalopram

Escitalopram, an enantiomer of citalopram, is another SSRI antidepressant (Wu et al. 2009; Pan et al. 2011). In our model, we observed that escitalopram reduces the levels of pro-inflammatory cytokines (see above) and attenuates depressive-like behavior in MI rats without modifying their sleep (Bah et al., 2011).

These results with antidepressants together with the evidence cited in the previous sections suggest that cytokines and apoptosis could involve in the pathophysiology of depression, including after a MI.

4.2 Pentoxifylline

Pentoxifylline (PTX), a methylxantine-derivative and non-specific phosphodiesterase inhibitor with combined anti-inflammatory and anti-fibrogenic properties (Gutierrez-Reyes et al. 2006; Danjo et al. 2008), lowers circulating pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 (Raetsch et al. 2002), via a cyclic adenosine monophosphate (cAMP)-dependent mechanism. Systemically administered PTX in MI rats reduce apoptosis in the limbic system at three days post-MI (Wann et al. 2006) and attenuates depressive-like behavior at 14 day, indicating the importance of pro-inflammatory cytokines in both events (Bah et al., 2011b).

4.3 Nutritional interventions

A loss of equilibrium between pro-and anti-inflammatory proteins could be involved in the pathophysiology of depression (Szelenyi and Vizi 2007). Our previous work has shown that

a reduction of circulating pro-inflammatory cytokines attenuates post-MI depressive-like behavior. Since diet can be used to modify the balance between pro- and anti-inflammatory cytokines, we hypothesized that targeted diets could attenuate post-MI depression.

4.3.1 Probiotics

The probiotics *Lactobacillus helveticus and Bifidobacterium longum* can reverse MI-induced apoptosis in the limbic system (Girard et al. 2009) by a mechanism that could include a reduction of pro-inflammatory cytokines. It has been observed that of *L. helveticus R0052* reduces IL-1β, IL-6 but not significantly TNF-α (Cazzola et al. 2010) whereas *B. longum R0175* can reduce IL-8 and TNF-α (Wagar et al. 2009) indicating that each strain has a specific effect on pro-inflammatory cytokines synthesis while they possibly are ineffective against stress (Diop et al. 2008; Girard et al. 2009; Messaoudi et al.). We combined both strains and found significant therapeutic effects on post-MI behavior, including behavioral despair (Forced swim test), passive avoidance and socialization Arseneault-Bréard et al. 2011).

4.3.2 Polyunsaturated fatty acids omega-3

Polyunsaturated fatty acids (PUFA) omega-3 are found mostly in the retinal and neuronal membranes. The lack of adequate levels of PUFA omega-3, and more particularly DHA, during brain development results into cognitive deficits (McNamara and Carlson 2006). Altered membrane concentration of PUFA omega-3 is also observed in depression (Peet et al. 1998; Mamalakis et al. 2006). Moreover, a recent study by Lespérance et al (2011) observed a clear benefit of PUFA omega-3 supplementation among patients with a major depressive episode but without comorbid anxiety disorders. Another study found that PUFA omega-3 had a similar effect on depression as the SSRI antidepressant fluoxetine, while the combination (EPA and fluoxetine) resulted in a superior effect than either of them alone (Jazayeri et al. 2008). The influence of PUFA omega-3 on psychiatric disorders has yielded mechanistic hypotheses, one of which involves the anti-inflammatory properties of fatty acids, in accordance with the fact that increased cytokine levels are associated with depression (Orr and Bazinet 2008; Kiecolt-Glaser 2010). A second hypothesis, based on PUFA omega-3 depletion studies, involves a modulation of monoaminergic neurotransmission (Chalon 2006) since a profound PUFA omega-3 deficiency is able to alter several neurotransmission systems such as dopaminergic and serotonergic. PUFA omega-3 may also improve depression via an anti-apoptotic neuroprotective mechanism. Indeed, DHA facilitates the activation and translocation of Akt, an anti-apoptotic protein (Akbar et al. 2005). Moreover, PUFA omega-3 induces the expression of the Bcl-2 anti-apoptotic protein and reduces the activation of caspase-3 (Bazan 2009; Sinha et al. 2009). In the more specific case of post-MI depression, it can be mentioned that omega-3 fatty acid levels were found to be lower in plasma and red blood cell membrane of depressed patients with acute coronary syndromes than non-depressed patients (Schins et al. 2007; Amin et al. 2008). Our own results show that an PUFA omega-3-rich diet reduces post-MI apoptosis in the limbic system (Rondeau et al. 2011) and depressive behavior (unpublished observations).

5. Conclusions

The data obtained over the last few years indicate that post-MI apoptosis occurs in the limbic system rapidly after the onset of reperfusion and our working hypothesis is that

increased cytokines levels in the CNS are involved. Whether neurogenesis or HPA axis plays a significant role in the picture of post-MI depression is not yet clearly established and needs to be further investigated. In Figure 7 we propose a model to explain the etiology and consequences of post-MI depression. It is our hope that converging evidence will eventually lead to a better knowledge of how the heart and brain connection operates to allow post-MI occurring and possibly show the way for effective treatment strategies.

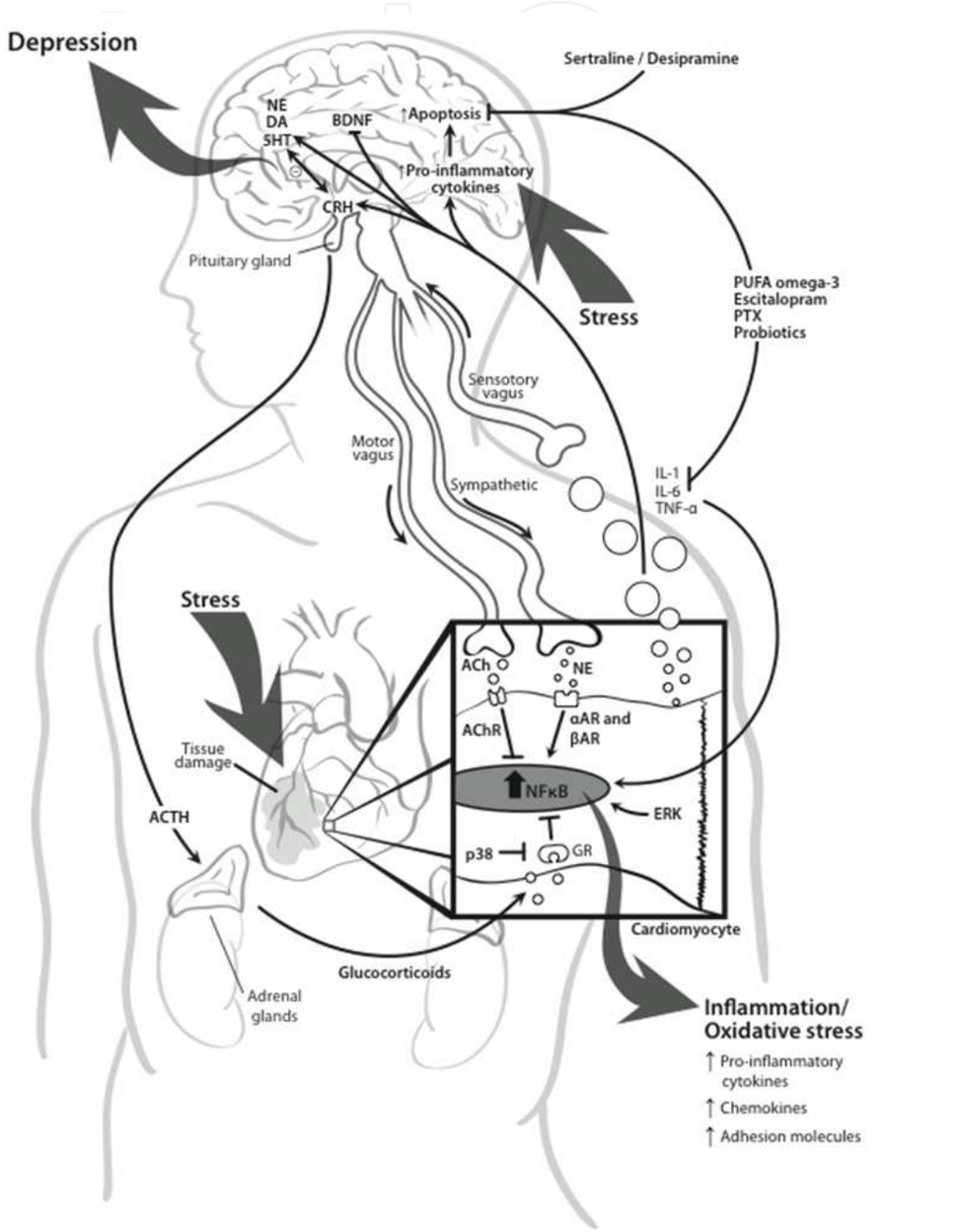

Fig. 7. Myocardial ischemia induces an increase in pro-inflammatory cytokines in the circulation and the limbic system. These cytokines may have access to brain via several routes (see text). Pro-inflammatory cytokines modulate different signaling pathways known to be involved in the development of depression including:

1. Presence of apoptosis and degenerating neurons;
2. Altered metabolism of neurotransmitters;
3. Reduction of neurogenesis by an action on BDNF.

Stress acting on heart, intestine or brain tissue contributes to the augmentation of pro-inflammatory cytokines by the activation of the NF-kB or the increase of the release norepinephrine.

Activation of different kinases such as P38 or MAP kinase inhibit the function of glucocorticoid receptor, releasing NF-kB from negative regulation by glucocorticoids released as a result of the HPA axis in response to stress.

PUFA-omega-3, PTX, escitalopram, probiotics reduce the circulating level of pro-inflammatory cytokines and apoptosis in the limbic system. These treatments as well as sertraline and desipramine could also attenuate the depressive-like behavior observed after myocardial infarction.

NE: Norepinephrine; DA: Dopamine; 5HT: Serotonin; BDNF: Brain-derived NEurotrophic Factor; CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone; GR: Glucocorticoids receptor; AchR: Aceylcholine receptor, αAR; A-adrenergic receptor; βAR: b-adrenergic receptor, PTX: Pentoxifylline

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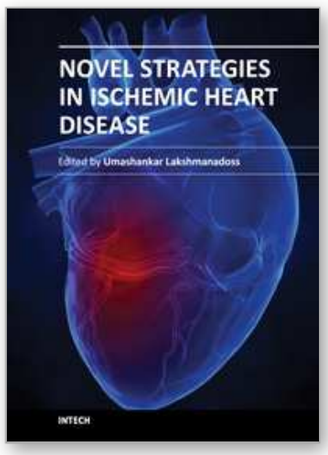

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The first edition of this book will provide a comprehensive overview of ischemic heart disease, including epidemiology, risk factors, pathogenesis, clinical presentation, diagnostic tests, differential diagnosis, treatment, complications and prognosis. Also discussed are current treatment options, protocols and diagnostic procedures, as well as the latest advances in the field. The book will serve as a cutting-edge point of reference for the basic or clinical researcher, and any clinician involved in the diagnosis and management of ischemic heart disease. This book is essentially designed to fill the vital gap existing between these practices, to provide a textbook that is substantial and readable, compact and reasonably comprehensive, and to provide an excellent blend of "basics to bedside and beyond" in the field of ischemic heart disease. The book also covers the future novel treatment strategies, focusing on the basic scientific and clinical aspects of the diagnosis and management of ischemic heart disease.

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