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Stress, ageing and their influence on functional, cellular and molecular aspects of the immune system

Running Head: Stress, ageing and immune system

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Abstract

The immune response is essential for keeping an organism healthy and for defending it from different types of pathogens. It is a complex system that consists of a large number of components performing different functions. The adequate and controlled interaction between these components is necessary for a robust and strong immune response. There are, however, many factors that interfere with the way the immune response functions. Stress and ageing now consistently appear in the literature as factors that act upon the immune system in the way that is often damaging. This review focuses on the role of stress and ageing in altering the robustness of the immune response first separately, and then simultaneously, discussing the effects that emerge from their interplay. The special focus is on the psychological stress and the impact that it has at different levels, from the whole system to the individual molecules, resulting in consequences for physical health.

Keywords: Stress; Ageing; Immune response; Caregiving

Ageing is a physiological process that emerged as a side-product of normal development and the metabolic processes involved in the reproductive potential of the species (Cutler 1982). It has been developed most likely as a non-adaptive phenomenon with no biological function (Partridge and Gems 2002) and allowed to evolve through a trade-off mechanism (Williams 1957), reviewed in (Partridge and Barton 1993). According to Thomas Kirkwood's modification of Orgel's (1963) theory, ageing can also be linked to the attempt of the body to reduce energy expenditure when switching off from germ line to somatic cells, which is achieved by making protein production less accurate (Kirkwood 1977). Therefore, ageing is a dysdifferentiation (Cutler 1985), phenomenon that emerged from the by-products of development (such as growth or sexual hormones), oxygen metabolism (active oxygen species), but also the by-products of stress (glucocorticoids, GC). Among these, development and oxygen metabolism are constant and necessary involuntary forces, and hence unchangeable, but the stress response in humans and other primates has changed over time, gaining another characteristic; the capacity to be chronic and detrimental (Sapolsky 2007).

This review will present the mechanisms by which stress can influence different aspects of immunity, as well as the interaction between ageing and stress and the consequences of this for immune health. It will first present stress as an adaptive phenomenon, and explain its relationship with immune system generally. Second, we will focus on how psychological stress affects the immune system, with particular emphasis on the chronic stress of caregiving. In the latter part of the review, the influence of ageing will be discussed, firstly describing the interplay between ageing and stress and then their additive effect on immunity. Finally, the review will discuss the pathophysiological consequences of the interaction between stress, ageing, and immunity. Although the focus is mainly on humans, where applicable, studies using small animal models are included.

Stress

A challenging life demands tough reactions and has led to the development of a number of physiological changes that constitute the stress response in animals and humans. In a hostile environment more complex organisms like vertebrates develop a response that Walter Cannon (1929) first introduced as 'fight or flight'. The main function of this response is maintaining body homeostasis. The key site involved in this process is the hypothalamus (Barrett 2005), a part of the brain that communicates by sending nerve impulses to other parts of the body. In this way, the hypothalamus acts within seconds and via sympathetic nervous system stimulates medulla of the adrenal gland to release catecholamines (adrenalin and noradrenalin). In addition, the hypothalamus also produces chemical messengers that act more slowly and in the next minutes travel through the hypothalamic-pituitary-adrenal (HPA) axis (Sapolsky et al. 2000). Chemical messengers in this pathway include corticotrophin releasing hormone (CRH) which stimulates anterior pituitary gland to release another hormone, adrenocorticotropic hormone or ACTH, into general circulation. The target organ of ACTH is again the adrenal gland, but this time it is the cortical cells that synthesise and release species-specific GC into the blood. The tight control of these GC (mainly cortisol in humans) is sustained via negative feedback that controls and, in the end, terminates the release of CRH (Griffin and Ojeda 2004).

Clear distinction is made today between two types of stress, acute and chronic stress. From an evolutionary point of view, the acute component is beneficial in that it provides organisms with the mechanisms of the protection from the changeable and threatening environment. In that context, an interaction such as one between lion and zebra, even though there is no common interest for the outcome between these two animals, will trigger the same cascade of events in the body of both. Adrenalin and noradrenalin mainly, but with glucocortiocoids potentiating the effects, will increase arousal, alertness and vigilance, focus attention and elevate core temperature, and also increase the

pain threshold (Kulkarni 1980), cardiovascular output, respiratory rate (Coles et al. 1956), and blood flow to the brain and skeletal muscle (Brown et al. 1979; Charmandari et al. 2005; Coles et al. 1956; Dowd et al. 2009; Kulkarni 1980). Skeletal muscle will gain the supply of the energy from the adipose and hepatic cells stores, whereas all other activities that are inessential in that moment, such as digestion, reproduction, feeding and growth, will be decreased through the action of GC (Cannon 1929; Selye 1956; Sorrells and Sapolsky 2007). Although acute stress and the events that follow have evolved as an adaptation, and are therefore beneficial, too great or too long of a response can be detrimental to the body. For example, synaptic plasticity in adult rats was negatively affected by prolonged stress exposure (Trentani et al. 2002). In humans, continuous or repeated psychological stress is strongly associated with detrimental effects on the cardiovascular system, and through it, with obesity and hypertension (McEwen 1998; Phillips et al. 2012; Sedova et al. 2004). However, despite the seemingly direct relationship between stress and different physiological functions, the general rule regarding the particular effects of GC alone on other organ systems is not sufficient to explain their action on the immune system, as described below. In other words, the negative effect of stress on the immune system is actually a non-adaptive phenomenon, as, using the analogy of Sapolsky, an injured animal would not survive and propagate the species if it escaped a predator only to then die of sepsis soon afterwards (Sorrells and Sapolsky 2007).

Stress and the immune system

GC and CA effects of acute and chronic stress

It was previously thought that the stress response, through the action of GC, strictly suppresses immunity. There are several sources of evidence for this anti-inflammatory action of GC, such as: involution of the thymus explained by Selye in 1930s (Selye 1936; Viner 1999); the shift from a cellular Th1 to a humoral Th2 phenotype; limitation of the capacity of dendritic cells (DC) to

interact with immature T-cells by preventing upregulation of MHC class II and co-stimulatory molecules (Akdis et al. 1997; DeKruyff et al. 1998; Franchimont 2004; Ramirez et al. 1996); and inhibited production of the proinflammatory cytokines (IL-12, IFNγ, TNF-α) (Franchimont et al. 2000; Hu et al. 2003; Steer et al. 2000), accompanied by the increased secretion of anti-inflammatory cytokines (IL-4 and IL-10) by Th2 cells (Elenkov and Chrousos 2002; Mozo et al. 2004; Wu et al. 1991). It is now known, however, that the way stress impacts immunity is not always straightforward, and can be highly influenced by the duration of the stressor (Sorrells and Sapolsky 2007).

Initially in the acute stress-response, the immune system is activated rather than suppressed (Sorrells and Sapolsky 2007), and only after this first reaction, in the following stages of the stress-response, when levels of GC further rise, their anti-inflammatory effects come on the scene (Munck et al. 1984). Higher concentrations of GC will then help the organism to recover from the early phases of the stress response (Munck et al. 1984). However, it is certain that upon repeated stimulation by stress, or through prolonged, chronic stress, the immune system is suppressed, and this is, at least in part, mediated by the action of GC (Sorrells and Sapolsky 2007). The explanation for this dual behaviour of GC could be in the way they transmit their effects through steroid hormone signalling (Sorrells and Sapolsky 2007). The actual mechanism by which GC exert these different effects is yet to be elucidated. However, a potential explanation is that mineralocorticoid receptors, which paradoxically have much higher affinity for GC than GC receptors, completely bind GC when they are present in lower levels, so during the initial acute stress phase, and are thus responsible for much of the initial pro-inflammatory effects, as seen in the brain (De Kloet et al. 1998). In the following stages of the stress response, when mineralocorticoid receptors get saturated, GC receptors become increasingly occupied and can govern some of the anti-inflammatory action. On the other hand, it is uncertain if the same explanation could apply to the immune system in the periphery. For example, even though expressed in macrophages,

mineralocorticoid receptors do not seem to be involved in modulating immune cells function by GC. Instead, that action is strictly confined to the concentration-dependent binding of the GC to the GC receptors (Lim et al. 2007). Nevertheless, it seems likely that a similar type of concentration-dependent effect of GC could be responsible for the difference in the effect of acute and chronic stress on the peripheral immune system, too (Sorrells and Sapolsky 2007). It is important to note here that GC are neither the only, nor the primary inducers of immune alterations during the chronic stress response (Moynihan 2003). For example, the suppression of mitogen responses by rat lymphocytes was dependent only upon the production of β-endorphin and without any influence by corticosterone levels (Panerai 1997). Similarly, Shi et al. (2003), showed that the apoptosis of lymphocytes during restraint stress was dependent on the state of opioid receptors only. The adrenergic receptor (β_2-AR) after binding catecholamines through two different signalling pathways triggers DNA damage as well as degradation of an important tumour suppressor in the brain of rats (Hara et al. 2011). Similar results were obtained after exposing rats to chronic restraint stress, whereas, the administration of propanolol, a β-blocker, diminishes this effect (Hara et al. 2013). Finally, the mutual action of GC and cateholamines (CA) during chronic restraint stress will simultaneously affect migration of mononuclear cells in the peripheral blood of a specific mouse strain (Hermann et al. 1995), largely reduce cytokine expression from the lymph nodes and spleen (Dobbs et al. 1996), delay cytokine gene transcription in the lungs and lymph nodes (Sheridan et al. 1998), as well as diminish activation of cytotoxic T lymphocytes in the lymph nodes (Dobbs et al. 1993; Sheridan et al. 1998). However, it was also shown that chronic stress-induced changes in the concentrations of GC alone can have different effects on different proinflammatory cytokines, TNF-α, IL-1β and IL-6 (DeRijk et al. 1997). For example, daily fluctuations of these hormones were able to strongly affect TNF-α concentrations, whereas IL-1β responded only after exercise-induced increases in the levels of cortisol, and lowering IL-6 demanded pharmacological concentrations of GC (DeRijk et al. 1997). All three of these cytokines are predominantly produced by monocytes,

but IL-6 can be produced by endothelial cells, fibroblasts and keratinocytes (Heinrich et al. 1990). Finally, while TNF-α, IL-1β are strictly pro-inflammatory, IL-6 can have both pro-inflammatory and anti-inflammatory effects (Scheller et al. 2011). Therefore, perhaps, the differential effects of stress hormones on TNF-α, IL-1β, and IL-6 are largely caused by the different roles of these cytokines.

Immuno-enhancing and immunosuppressive effects of acute and chronic stress

There is a well established difference in the effects that acute and chronic stress exert on the immune response, being immuno-enhancing and immunosuppressive, respectively. The acute stress response and its associated immunological changes closely resemble those related to infection, and involve both energy mobilization, and activities of cytokines and neurotransmitters (Maier and Watkins 1998). Acute brief restraint stress, applied before surgical sponge implementation into the rats has lead to more prominent increase in all blood leukocyte count comparing to the non-stressed group (Viswanathan and Dhabhar 2005). Similarly, the same type of acute stress administered before the immunisation increased the number of memory and effector helper T (Th) cells following immunisation (Dhabhar and Viswanathan 2005). This also seems to influence more robust immune response upon repeated stimulation with the same antigen months later (Dhabhar and Viswanathan 2005). This can be beneficial in cases when increased immunoprotection is needed, but detrimental in the cases of immunopathology such as allergic conditions and autoimmune disease(Atanackovic et al. 2013; Dhabhar 2009; Dhabhar and Viswanathan 2005).

Chronic stress is generally accepted as being immunosuppressive. However, if it was strictly immunosuppressive, it would not be able to negatively influence disease outcomes in infectious and neoplastic disease (associated with inadequate immunity) on the one hand, and allergic and autoimmune disease (that emerge from an excessive immune response) on the other, as explained

by Segerstrom and Miller (Segerstrom and Miller 2004). One possible explanation for these seeming mutually exclusive consequences of chronic stress was given by Marshall et al. (1998), who suggested that chronic stress drives the Th1-to-Th2 shift by altering patterns of cytokine expression. In that way, stress-induced suppression of Th1 cytokines (such as interferon gamma, IFN-γ) involved in the defence against many kinds of infection and some neoplastic diseases, would lead to activation of Th2 cytokine production, involved in allergies and different autoimmune diseases, such as interleukin (IL)-10 (Marshall et al. 1998). In addition, it has been shown that chronic stress caused by immobilisation affects the number of lymphocytes in rats, but impacts on different subsets in different ways (Dominguez-Gerpe and Rey-Mendez 2001). The overall decrease in the number of circulating lymphocytes was accompanied by the increase in the number of mainly immature T lymphocytes, suggesting one of the potential mechanisms by which stress associated immunosuppression can affect and exacerbate autoimmune diseases (Moroda et al. 1997).

In summary, acute stressors usually, with the exceptions of natural killer (NK) cell function (Cunnick 1988) and neutrophil superoxide production (Khanfer R. 2010; Khanfer et al. 2012) boost the immune system, particularly its innate component which is the one able to act quickly(Bosch et al. 2003; Dhabhar and McEwen 1997; Sapolsky 1998). The majority of chronic stressors, on the other hand, are associated with global immunosuppression and have an impact on both innate and adaptive component of the immune system (Kiecolt-Glaser et al. 1991a; Phillips et al. 2006; Segerstrom and Miller 2004; Thaker et al. 2006) to mention a few.

Beneficial and detrimental effects of acute and chronic stress

Both the immune response and the fight-or-flight response provide an adequate defence for survival and further protection against infection after the injury occurs. In that context, the relationship between acute stress and immune up-regulation can be viewed as an adaptive trait. On the other

hand, chronic exposure to stress appears to have detrimental effects on immunity through continual activation of the same mechanisms. This overlap between the stress response and the immune response to infection could be the answer to some of the seemingly contradictory processes that arise as the consequence of different durations of the same stressor. For example, in response to acute stressors, T cells in the rat react by redistributing into the skin, which is the organ that is the most likely to be affected in a life threatening situation when fighting the attackers. On the other hand, prolonged action of the same type of stressor will lead to the progressive decrease in this stress-induced redeployment of T cells, as well as to the suppression of delayed type hypersensitivity in the skin (Dhabhar and McEwen 1997). Similarly, surgical operation in cancer patients after oesophagectomy has been associated with an increase in peripheral blood lymphocytes apoptosis (Kono et al. 2001). The mechanism used to explain this rise was increased Fas expression (Oka 1996), and changes in T lymphocyte signal transduction through down-regulation of T cell receptor ζ with a crucial influence of activated post-operative monocytes on the process overall (Kono et al. 2001). Negative effects on lymphocytes associated with surgical stress were also observed in combination with psychological (daily life hassles) and physiological (cold pressor) stress upon stimulation of lymphocytes with phytohemagglutinin (PHA) and pokeweed mitogen, respectively (Linn et al. 1988). Through altering IFN-γ production and the ability to respond to both interferons and proinflammatory cytokines, e.g., IL-2, chronic restraint stress affects the activity of NK cells, components of the innate immunity important in resolving viral infections such as infection with herpes simplex virus (HSV) (Bonneau et al. 1991).

Psychological stress and immunity

A relationship between the central nervous system (CNS) and immune system was first discovered in early animal experiments where it was revealed that immunosuppression could be induced through classical conditioning (Ader 2003; Ader and Cohen 1975; Garcia et al. 1955). A large

number of studies have emphasised the behavioural changes that accompany chronic stress situations (such as alcohol consumption (Nguyen et al. 2012; Silva and Madeira 2012)), smoking (Lee et al. 2007), nutrition (Thompson et al. 2013), and sleep disturbances) that are already known to have direct and serious health consequences and could mediate the negative effect of stress on health indirectly (Dallman et al. 2003; Hussain 2010). Other indirect effects might be via changes in social roles and social support associated with stress at the same time affecting health and quality of life (Baron et al. 1990; Pressman et al. 2005; Rutledge et al. 2004; Segerstrom and Miller 2004). However, many direct effects on immunity have also been demonstrated. Several studies reported changes in cytokine profile in students during an academic examination period. The general pattern seems to be the emphasis of Th2 response through the decrease in proinflammatory cytokines (tumour necrosis factor alpha (TNF-α), IL-6, IL-1, INF-γ) and higher levels of anti-inflammatory cytokines (IL-10 and IL-4) (Kang and Fox 2001; Marshall et al. 1998). Similar to these studies, delayed wound healing and a decrease in IL-1β, a key interleukin involved in this process, has been demonstrated in young healthy students during an examination period compared to a non-stressful holiday period (Marucha et al. 1998). The opposite is the case in students with higher anxiety where levels of proinflammatory cytokines rise just before the important exam (Kamezaki et al. 2012; Maes et al. 1998). The explanation for this seemingly contradictory effect of examination stress is seen in its duration, as it can be divided into examination stress, its acute (i.e. immediately before the exam, as in Kamezaki, 2012, Maes, 1998), and its prolonged, chronic component (i.e. during the examination period, as in Kang, 2001, Marshall, 1998), for a review see Bosch, 2002. In one of the first studies that examined the relationship between psychological stress and the immune system in humans, the strong psychological stressor of bereavement was associated with decreased function of T lymphocytes (Bartrop et al. 1977). In a similar way, neutrophils' killing ability was suppressed in the bereaved, the effect that was accompanied by the increase in cortisol:DHEAS (dehydroepiandrosterone sulphate) ratio (Khanfer et al. 2011), a parameter

previously used as a measure of the effect stress hormones have upon immune system components (Butcher et al. 2005). Further, homeless people who reported higher stress levels had lower density of lymphocyte beta-adrenergic receptors (Dimsdale et al. 1994). This could indicate either a down-regulation of receptors due to higher stress hormone levels (CA or GC) or simply a change in the lymphocyte subsets, both of which could be a consequence of prolonged exposure to a stressful lifestyle. In addition, in children with a history of recurrent colds and 'flu who demonstrated higher levels of psychological stress, salivary IgA/albumin ratio was lower, indicating a potential link between stress and colds and 'flu (Drummond and HewsonBower 1997).

Loneliness affects NK cell activity not only in psychiatric patients (Kiecolt-Glaser et al. 1984b), but also in young and healthy medical students indicating general importance of social relationships for individuals' wellbeing (Kang et al. 1998; Kiecolt-Glaser et al. 1984a). Marital quality and recent separation among young women were associated with depressive symptoms and poorer immune function, seen through poorer proliferation of lymphocytes after stimulation with different mitogens (concavalin A and phytohemaglutinin) (Kiecolt-Glaser et al. 1987). More frequent marital concerns were associated with flatter cortisol profile (Barnett et al. 2005), an indicator of non-adaptive cortisol metabolism during chronic stress exposure.

One commonly studied model of the impact of stress on immunity is role of caring for someone, be it a spouse or child with a physical or mental illness or disability. Caregiving is now well established as having a serious effect on psychological well being, physical health and self-efficacy among caregivers when compared to matched non-caregiving individuals (Pinquart and Sorensen 2003). For example, parents of cancer patients when compared to control parents had a decreased sensitivity to the anti-inflammatory effect of GC which could potentially contribute to the development of asthma, different cardiovascular and autoimmune diseases, as well as indicate dysregulation of the immune system that may become incapable of resolving infections (Miller et al. 2002). This is where we see the other side of stress effects on immune function where it

exacerbates excessive immune response. Another study of adaptive immunity in mothers of children with developmental disabilities showed a lower T helper: suppressor ratio, indicating again potentially less effective adaptive immunity for fighting the pathogens among the older age cohort of caregivers (mean age = 50.3 years) (Pariante et al. 1997).

A common approach for assessing the severity by which psychological stress affects the immune system is assessing antibody titres to latent viruses. Generally, latency is the ability of a virus to lie dormant in the host cell after the initial infection, and emerge as an acute infection once the immune surveillance of the host weakens (Nowak 1991). Therefore, even though asymptomatic in the immunocompetent hosts, these infections could cause serious harmful and even fatal effects in the immunocompromised (Pawelec et al. 2005; Rasmussen 1991). In that context, separated women also had higher antibody titre against Epstein-Barr (EBV) virus, indicating poorer control of the virus, as well as lower number of both NK cells and helper T lymphocytes when compared to married women, with worse depression and immune outcomes seen in those with greater attachment to their ex-husband (Kiecolt-Glaser et al. 1987). In the case of married and separated men, those who went through divorce were more depressed, lonelier, and had a higher antibody titre against both EBV and HSV (Kiecolt-Glaser et al. 1988). Finally, more negative behaviour in marriage has been shown to adversely affect endocrine responses in women and immunological activation, seen through antibody titres to EBV and the blastogenic response to T-cell mitogens, in both genders (KiecoltGlaser et al. 1997). Another study also demonstrated higher antibody titres against cytomegalovirus (CMV) in a group of caregiving individuals when compared to the controls, indicating poorer latent virus control (Pariante et al. 1997).

Vaccination produces immune memory against specific pathogens, ready to respond to a real infection. An inadequate response and failure to provide required protection after vaccination, measured in terms of antibody titre, is indicative of a poorer immune response in the recipient. Unmarried older adults and those who had poor marital quality had a weaker antibody response to

the influenza vaccination than happily married older adults (Phillips et al., 2006). Life events stress and perceived stress were also related to a lower antibody response after vaccination against flu and meningitis in students (Burns et al. 2003; Burns et al. 2002; Phillips et al. 2005), while greater social support enhanced antibody titres for some vaccine strains (Phillips et al. 2005). However, studies that have examined the antibody response to medical vaccination in younger caregivers have reported inconsistent results. The first study of this type compared hormonal and immune status between 41 partner of multiple sclerosis patients and 62 controls (Vedhara et al. 2002). Multiple sclerosis was chosen as serious chronic and degenerative illness that usually causes physical and cognitive complications (Barcellos et al. 2002), and as such thought to cause equivalent level of burden for caregivers as seen in spouses and partners of dementia patients. Despite reporting higher levels of stress, but not anxiety and depression, caregivers showed no difference in either antibody response to an influenza vaccination, nor their IFN-γ and IL-4 levels. Similarly, cortisol and DHEAS ratio was not different between the groups, supporting previously shown preserved immune response in stressed, caregivers group. In contrast, a study conducted by Gallagher et al. (Gallagher et al. 2009a) showed a poorer antibody response to pneumococcal vaccination in caregiving parents of children with developmental disabilities when compared to age and sex matched control parents at both one and six months follow up. These findings were further supported by Gallagher et al. (Gallagher et al. 2009b) which showed inability of caregiving parents to mount equally good antibody response as control parents after vaccination against the influenza virus. It was argued that the difference in immune response in these studies could be due to characteristics of the care-recipient such as challenging behaviours, rather than the caregiving role *per se*, and that perhaps the caregiving experience, reported as more challenging in case of parents of children with developmental disabilities, is what drives this changes in immune function (Gallagher et al. 2009b). Indeed within the caregiving group, those parents who reported higher

child problem behaviours had a poorer antibody response to the pneumococcal vaccine (Gallagher et al. 2009b).

Stressed individuals also show significant changes in the DNA repair process. Changes in DNA repair processes have been associated with different types of cancer such as cutaneous malignant melanoma (Wei et al. 2003), lung cancer (Wu et al. 2003), and breast cancer (Sharan et al. 1997). One of the theories of ageing suggests that the accumulation of DNA damage is a potential cause of gradual disruption in living organisms (Freitas and de Magalhaes 2011), emphasising the involvement of the repair mechanism in this process (de Boer et al. 2002). Several studies have shown correlations between stress and the action of the DNA repair machinery (Yang and Glaser 2003). This is also a demonstration of the complicated relationship between stress and body mechanisms, as it shows that in addition to the duration of stressor, the consequences of its action depend also upon the capacity of the organism to adapt to change and maintain homeostasis. The effect of stress was different depending on the population tested, with a decrease seen in the DNA repair mechanism after X-irradiation in psychiatric compared to non-psychiatric patients (Kiecolt-Glaser et al. 1985), whereas in young and healthy medical students, stress during an examination period influenced the increase in the extent of DNA repair after UV radiation (Cohen et al. 2000). As examination stress increases DNA damage and hence the need for its repair, it could be that the increase in the repair process in young and healthy students indicates their ability to meet this criteria, an ability that is not present in psychiatric patients who exhibit a decrease (Yang and Glaser 2003). Forlenza et al. (2000) confirmed this in a study that showed an increased rate of nucleotide exchange repair in medical students during an examination period when compared to the low stress holiday period. Further evidence can be found in the rat studies where sister chromatide exchange, a process that is known to occur with higher incidence in the presence of agents with oncogenic potential (Banerjee and Benedict 1979), showed a doubling potential in the bone marrow cells of rats subjected to different types of behavioural stressors, such as swimming, white noise, and foot

shock (Fischman and Kelly 1987). On the other hand, a decreased DNA repair capability was reported after carcinogen administration in rats exposed to the rotational stress compared to a non-stressed group (Glaser et al. 1985).

When considering factors, tightly regulated and controlled, related to both maintaining and disturbing homeostasis on intracellular level, structures that emerge as one of the key controllers of the cell cycle are telomeres. Telomeres are complexes of repetitive DNA sequences located on the very end of each chromosome surrounded by a large number of proteins. They have several functions, but are mainly involved in maintaining chromosome stability (Dahse et al. 1997). Due to the nature of DNA replication process, telomeres protect the core of DNA from shortening with every cell cycle, but at the same time, due to their own shortening, they are limiting factors that determine number of cell division in physiological conditions (Dahse et al. 1997). As such, they are an attractive target for process of tumorigenesis, but at the same time essential for understanding processes that are part of normal cell cycle, like senescence and apoptosis. Indeed, a large number of studies proved telomeres as an important factor in the process of ageing, as well as diseases such as HIV, hepatitis, Alzheimer's, inflammatory bowel disease, and cancer (Jiang et al. 2007). The importance of adequate telomere length is a key to the immune system, particularly adaptive immunity, as cell division in lymphocytes is necessary for their response to antigenic challenge (Kaszubowska 2008). Studies have indicated that chronic stress might in this case mimic immunosenescence. For example, telomere length was shorter in parents caregiving for a chronically ill child and experiencing higher stress levels compared to those in the low stress caregiver group, even though there was no difference in telomere length between caregiving parents generally and their age and sex matched controls (Epel et al. 2004).

Another very important mechanism inside the cell that needs to be carefully regulated and kept in balance in order for the cell to function normally is programmed cell death or apoptosis. Apoptosis is essential for proper embryonic development, functioning of the immune system, as well as

maintaining of the homeostasis in response to different physiological and pathological stimuli (Elmore 2007). Therefore, it is not surprising that different conditions, such as cancer, autoimmune diseases, neurodegenerative diseases, and ageing are all linked to imbalance in the regulation of apoptotic processes (Elmore 2007). Apoptosis is one of the main mechanisms in the regulation of neutrophil function. Neutrophils are key effector white blood cells in defending the host from bacterial infection by producing various cytokines and reactive oxygen species (Lloyd and Oppenheim 1992). However, neutrophils are also important factors in regulating inflammatory processes, and the existence of an adequate regulatory mechanism is necessary to prevent these protective components becoming a dangerous enemy. This is the reason for a very tight relationship between these cells and apoptosis (Sendo et al. 1997). With a half-life of 5-6 hours, these cells are given enough time to perform their protective role and fight bacterial infection, but prevented from any deleterious effect on surrounding tissue that no longer requires their activity (Sendo et al. 1997). Intense exercise stress prolongs the survival of neutrophils, whereas longer lasting examination stress inhibits the process (Sendo et al. 1997). This, considered in the light of both aspects of neutrophil function, fighting infection and inflammation, indicates the variety of ways in which stress can affect health, and emphasises the complexity that lies behind that relationship.

Ageing, stress and the immune system

One of the important components that should to be taken into account when considering the effect of stress on immunity is age. Even in the cases where the effect of stress on the immune system is strong, such as in the case of caregiving, this might be even more evident or might change once the immune system is challenged by both ageing and stress simultaneously (Segerstrom and Miller 2004). Ageing is considered to weaken body's ability to respond to stress, and with stress affecting organisms in the similar way as ageing, it may lead to accelerated ageing (Sapolsky 1999). It has

been suggested that one of the factors contributing to this exacerbated effect of stress in the aged organisms is their inability to terminate the production of GC in response to stress (Sapolsky et al. 1986). According to the GC cascade hypothesis, failure of the control mechanism that should stop the production of GC after the effect of the stressor has ended is caused by the age-induced degeneration of the region of the brain responsible for communication with the endocrine system cascade (Sapolsky et al. 1986). In that way, excessive amounts of GC further damages the target brain region, starting a positive feedback cascade (Sapolsky et al. 1986). Functional connections between the immune and neuroendocrine systems stems from the existence of the interplay between their components, cytokines and hormones, on various levels (Ottaviani and Franceschi 1997), thus the GC response to stress and ageing has a significant impact on immune function.

The way ageing and stress simultaneously act to affect the immune response seems to be influenced not only by the way organisms age, but it could be highly influenced by early life event experience (Graham et al. 2006). Long-term effects seem to emerge not only after negative maternal behaviours, such as poor prenatal nutrition, but also following external, psychological and environmental stress in mothers (reviewed in (Graham et al. 2006)). For example, early life stress through the excess of maternal stress hormones, mainly GC (Painter et al. 2012) has been shown to relate to emotional problems and learning deficits, and it could lead to the conditions such as type 2 diabetes and general depression and anxiety symptoms in the adulthood (Weinstock 2008).

A theory of ageing known as a 'disposable soma' hypothesis emphasises the difference between the efficiency of the translational machinery in reproductive and somatic cells, where the latter have traded accuracy in order to save energy for other more important functions (Kirkwood 1977). In the same manner, this theory explains longevity through the presence of the 'more successful' alleles of the genes involved in the protective mechanisms of the cellular response to a variety of physical

stressors such as oxidative stress, radiation, and heat (Kapahi et al. 1999). Further, it has been suggested that the immune system has been developed as a response to pathogens which are a specific type of stressors (i.e. antigenic stressors) (Ottaviani and Franceschi 1997). In that way, immunosenescence in more complex organisms such as vertebrates will be the product of the continuous accumulation of damage due to lifelong exposure to antigenic stress (Franceschi et al. 1999).

A typical consequence of ageing on immunity is involution of the thymus where T cells mature, but also changes in bone marrow stem cells that shift the number of circulating T cells from naive to a relative increase in memory T cells(Castle 2000; Miller 1996). NK cells show decreased activity per cell (Castle 2000), and dendritic cells show decreased ability to reach T cells as their target and promote adequate production of cytokines such as IFN-γ and IL-10 by influenza-specific T cells (Castle 2000). Toll-like receptors, membrane proteins that recognise conserved structure from microbes, are present in lower levels on macrophages from aged mice than young mice (Renshaw et al. 2002). Further, neutrophils from elderly donors have poorer phagocytic function, and diminished ability to fight of infections caused by Gram positive bacteria, such as pneumonia, which is one of the major causes of death in the older population (Butcher et al. 2001).

The existence of compromised immunity in both younger stressed individuals (Cohen et al. 1997; Gallagher et al. 2009b, a), and older adults (Arora Duggal et al. 2013; Butcher et al. 2000; Butcher et al. 2001; Hazeldine et al. 2012; Hazeldine and Lord 2013; Pawelec et al. 2005) suggests a potential common mechanism that may be shared between stress and ageing in relation to the immune system. Some forms of immunosuppression seen in response to stressors are also present with age. One example would be the change in cytokine production in the elderly, with cytokines from the Th2 response, such as IL-10 and IL-4, taking over from those typical for Th1 response,

such as IFN-γ and IL-12 (Rink et al. 1998). Others are stress induced thymus changes in both animals (Kioukia-Fougia et al. 2002) and humans (Gruver and Sempowski 2008), that are characteristic of normal ageing (Singh and Singh 1979), but also molecular changes seen as telomere shortening in chronically stressed (Epel et al. 2004) that also progressively occur with age (Cherif et al. 2003; Mikhelson 2008).

There is also an interesting association between age-related changes and stress in the pattern of sex steroid production (Arlt and Hewison 2004). Even though its exact effect on immunosenescence is yet to be established, DHEAS, a sex steroid, is considered to have immune-enhancing capacity (Phillips et al. 2007). Another characteristic of this hormone is that it reaches its peak in the third decade of human life and then gradually declines with age (Orentreich et al. 1984). On the other hand, cortisol, a GC with known immunosuppressive effects, does not change with age, although it might be that its availability in the intracellular compartment of certain cells, including immune cells, does. This idea comes from the fact that activity of the enzyme capable of converting cortisone to active cortisol, 11β-hydroxysteroid dehydrogenase Type 1 (11β-HSD1), is increased with the higher proinflammatory status, which is considered typical in the ageing process (Tomlinson et al. 2004). The result of this is a higher cortisol:DHEAS ratio, with the immunosuppressive effect of cortisol overcoming the immuno-enhancing effect of DHEAS (Phillips et al. 2007).

Many of the complex processes of ageing and the stress response remain unclear; nevertheless, research continues to suggest common pathways between them on all organisational levels, from those as big as organ systems or even the whole body, to those as small as intracellular pathways and their gene candidates. One component also involved in and frequently related to processes of ageing and the stress response is a transcriptional factor, nuclear factor-kappa B (NF-κB). NF- κB is a whole family of transcription factors (Gilmore 2006), involved in regulation of both innate and

adaptive immunity. Its dysregulation leads to autoimmune diseases and cancer, but it is also studied as an ageing- and stress-related factor. The suggested mechanism through which psychological stress can be transferred onto intracellular level to affect NF-κB functioning and increase its binding activity, involves a signalling pathway that is activated through binding of increased concentrations of noradrenalin to α_1- and β-adrenergic receptors during stress (Bierhaus et al. 2003). Another possible link between NF-κB and stress response is its interaction with GC receptors in a way that is yet to be elucidated (De Bosscher et al. 2003). It is not a surprise that a transcriptional factor that is involved in the response to so many key processes, such as oxidative stress, growth, immune function, DNA damage, like NF-κB, is also considered one of the components affected by ageing. Other molecular factors with the role in ageing, immunity and resistance to stress are forkhead box class O (FOXO3a) (Adler et al. 2007) and sirtuin 1 (SIRT1) (Longo and Kennedy 2006). Interestingly, they both act by inhibiting activation of NF-κB, emphasising the significance of this factor in both ageing and stress (Adler et al. 2008).

Chronic stress, ageing and the immune system

The main danger to immunity, however, occurs with synergy of ageing and *chronic* stress. In that respect, it might be that chronic stress is one of the main threats in already immune-compromised older age. As mentioned above, severe stressors with a long term effect such as a loss after death of a close family member or friend have been shown to relate to changes in the ability of aged neutrophils to produce reactive oxygen species through which they kill rapidly dividing pathogens (Khanfer et al. 2011). This detriment in neutrophil immunity was also accompanied by a higher cortisol:DHEAS ratio in the bereaved older adults relative to age-matched non-bereaved controls (Khanfer et al. 2011). Bereavement in older adults has also previously been associated with a poorer antibody response to vaccination against the influenza virus (Phillips et al. 2006). Changes in cortisol:DHEAS ratio with diminished immune function again suggest a potential mechanism

through which stress could influence the body's defence mechanism against infection. For example, older adults who had suffered the physical stress of a hip fracture and gone on to develop a bacterial infection post-surgery, showed decreased neutrophil superoxide production accompanied by a higher serum cortisol:DHEAS compared to age-matched controls (Butcher et al. 2005).

Older caregivers have most commonly been studied in this context, using the model of family dementia caregiving (Gouin et al. 2008). The severity of the stress in these circumstances comes not only from the patient's progressive deterioration in performing daily activities that pose growing problem for caregivers (Potkin 2002), but also from the loss of cognitive function, such as the ability to recognise people around them, and changes in behaviour such as hoarding, anger, and repetitive behaviour (Grossberg 2002). Both innate and adaptive immunity are affected by chronic stress experienced by older adults, and both of these components are necessary for the protection against different pathogens that can damage the body. It was shown, for example, that wound healing was slower in older dementia caregivers when compared to age, sex and income-matched controls (Kiecolt-Glaser et al. 1995). Wound healing is a complex process comprised of various phases (immediate response, inflammatory response, proliferation, migration and contraction and resolution) that activates many different cells and molecules (Shaw and Martin 2009). Cells such as neutrophils and macrophages, and high concentrations of cytokines are main players in inflammatory phase with a role to protect from invading pathogens and set the conditions for the repair process such as angiogenesis regulation (Shaw and Martin 2009). Lower production of proinflammatory cytokines involved in the wound healing process such as IL-1α, IL-8 (Glaser et al. 1999), as well as IL-1β (Kiecolt-Glaser et al. 1995) seen in caregivers compared to the controls, indicates the possibility of a direct effect of stress on cytokine production in wound healing. Natural killer cell activity between older dementia caregivers and controls showed no difference in the ability of these cells to kill K562 target tumour cells (Irwin et al. 1991), but in the presence of

cytokine stimulation (recombinant INF-γ and IL-2) this similarity between stressed individuals and controls was not preserved; NK cells from caregivers responded more weakly compared to those from the controls (Esterling et al. 1994). All this, together with the stress-induced reduction in IFN-γ production (Glaser et al. 1986), indicates cytokines as a common target during chronic stress exposure, and a potential effector through which much of the immune suppression may occur.

A further association between the chronic stress of caregiving was found for adaptive cell mediated immunity; elevated cortisol levels as well as poorer proliferation to PHA and lower IL-2 production was shown in the caregiving group (Bauer et al. 2000). As observed in younger stressed participants (Marshall et al. 1998), caregiving stress in older adults has also been shown to be associated with the Th1-to-Th2 shift in cytokine responses, with the difference that in the older stressed individuals this was driven purely by an increase in IL-10 production, with no difference in IFN-γ production by Th1 cells (Glaser et al. 2001).

Vaccination responses are affecting older adults due to immunosenescence, which makes them particularly vulnerable to frequent infections such as pneumonia and influenza, among the top five causes of high morbidity and mortality in this age group (Thompson et al. 2003). It would be expected that this aspect of immune incompetence would be further exacerbated in older adults affected by the chronic stress of caregiving. This is indeed the case; a significantly lower percentage of older caregivers of dementia patients showed a four-fold increase in antibody titre in response to vaccination against the influenza virus, a response that is clinically considered to be protective against infection (Vedhara et al. 1999). This was accompanied by higher salivary cortisol concentration in this group when compared to the controls, pointing again to the role of HPA axis in immune regulation among stressed individuals. Most microbial antigens, however, trigger both humoral, i.e. antibody response which is generated by B lymphocytes, as well as cellular responses, mainly mediated by cytotoxic $CD8^+$ T-cells (Glaser et al. 2000; Kiecolt-Glaser et

al. 1996; Siergist 2008). In addition, $CD4^+$ helper T-cell are necessary as mediators between those two. It has been shown that both the antibody response to medical vaccination against the influenza virus, as well as IL-2 production in response to antigen stimulation, was lower in caregivers comparing to the controls (Kiecolt-Glaser et al., 1996). In the case of the pneumococcal pneumonia vaccine, even though caregivers managed to exert an adequate immune response initially, shown as a rise in IgG antibody titre, it declined over time more rapidly in this group than in the group of matched controls, likely either as a consequence of decrease in number of antibody-specific B-cells, or their ability to produce IgG (Glaser et al. 2000; Vedhara et al. 1999).

A frequently used approach for assessing the severity by which caregiving stress affects the immune system of older caregivers is that of studies of latent-virus antibody titres. It is known, for example, that reactivation of latent viral infections, such as those initiated by Herpex group (HSV-1, EBV, and CMV) is typical for immunosuppressed patients such as HIV and transplant patients (Rasmussen 1991). Interestingly, older caregivers had higher IgG antibody titers against EBV VCA (virus capsid antigen) compared to the matched controls, indicating poorer control of the latent infection in this group (Kiecolt-Glaser et al. 1991b). Together with the higher antibody titre to total viral antigen of HSV-1, caregivers also had a decreased virus-specific T cell response; another component of immune system necessary for controlling the infection (Glaser and Kiecolt-Glaser 1997). Older parental caregivers have also been characterised by higher antibody titres against CMV when compared to the controls (Pariante et al. 1997).

Another concept that often occurs in the literature when discussing ageing of the immune system is inflammageing. Inflammageing indicates an imbalance between inflammatory factors necessary to fight the infection, but is damaging in excessive amounts, and anti-inflammatory components act as a counter weight. It has been suggested that ageing and longevity could, therefore, potentially be

dependent on this balance (Franceschi et al. 2007). This would mean that immunosenescence, together with inflammatory markers such as different cytokines (IL-6, IL-8 and IL-15), as well as dysregulation at the molecular level and the presence of a certain genetic environment could all be predictors of the longevity of organisms. One consequence of this might be that chronically stressed older adults, such as dementia caregivers, could have elevated inflammatory markers even when compared to non-caregiving older adults who have immunosenescence. Indeed, not only did older caregivers show higher levels of IL-6 (von Kanel et al. 2006), but its rate of increase was four times higher than in non-caregiving controls, leaving them particularly vulnerable to IL-6 related diseases such as frailty, cardiovascular diseases, osteoporosis and others (Ershler and Keller 2000).

Finally, even the effect of molecular mechanisms in ageing appears to be exacerbated by chronic stress in older adults. Caregivers of dementia patients had shorter peripheral blood mononuclear cells (PBMC), T-cell and monocyte telomere lengths, and this was not due to having a higher number of these cells with shorter telomeres (Damjanovic et al. 2007). On the other hand, they also showed an increase in basal telomerase activity, which could indicate an attempt of these cells to compensate for the loss of their telomere length (Damjanovic et al. 2007).

Conclusion

In this review we have seen that both the chronicity of stress and the ageing process prove detrimental to an organism's well being. The mechanisms of these effects are yet to be elucidated more fully. However, it is clear that many of the ways in which both ageing and stress affect the body are through shared mechanisms, with particular regard to the neuroendocrine and immune systems from the level of the tissues, cells and even intracellular components. Less is known about the additive impact of ageing and stress on the innate immune system with the exception of studies

of NK cells. A better understanding of the processes by which stress and ageing affect health will lead to a greater capacity for intervention, be it behavioural or pharmacological.

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