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Glucocorticoids and central nervous system inflammation

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Glucocorticoids (GCs) are well known for their anti-inflammatory and immunosuppressive properties in the periphery and are therefore widely and successfully used in the treatment of autoimmune diseases, chronic inflammation, or transplant rejection. This led to the assumption that GCs are uniformly anti-inflammatory in the periphery and the central nervous system (CNS). As a consequence, GCs are also used in the treatment of CNS inflammation. There is abundant evidence that an inflammatory reaction is mounted within the CNS following trauma, stroke, infection, and seizure, which can augment the brain damage. However an increasing number of studies indicate that the concept of GCs being universally immunosuppressive might be oversimplified. This article provides a review of the current literature, showing that under certain circumstances GCs might fail to have anti-inflammatory effects and sometimes even enhance inflammation. *Journal of NeuroVirology* (2002) **8,** 513–528.

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Stress and glucocorticoids

Stress is the "nonspecific response of the body to any demand." This rather general definition of stress was given over 60 years ago by famous stress-pioneer H. Selye (Selye, 1936), who introduced the study of stress (Selye, 1978) as a scientific topic dealing with the physiological changes occurring in the structural and chemical composition of the body in response to a stressor (a neologism at the time, also created by Selye). A stressor is defined as a physical and/or psychological stimulus that induces these changes. Because most of the vast scientific literature shows the negative and dangerous effects of stress for the body, one could easily get the impression that the physiological systems activated by stress are generally bad and damaging in nature. Instead, stress should be seen as one of the most important and complex adaptive bodily reactions. Stress by itself represents a threat to the body's homeostasis, but adaptation to stress confers a survival advantage. Successful adaptation, however, requires not only the ability to respond to a stressor but also to control that response appropriately.

A key mechanism in the response to acute ("fight or flight" reaction) and chronic (accumulation of minor or major day to day reactions) stressors is the activation of the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1). First, the hypothalamus is stimulated to secrete the corticotrophin-releasing hormone (CRH), which after passage of the hypothalamic-pituitary portal system, leads to pituitary adrenocorticotrophic hormone (ACTH) secretion into the peripheral circulation (Trainer *et al*, 1995). ACTH in turn triggers adrenal glucocorticoid (GC) release and production. Once GCs are secreted, approximately 90% are bound to GC-binding globulins and albumin, whereas unbound or free GCs are responsible for GC effects. The primate GC is cortisol, although most rodents secrete corticosterone from the adrenals; the plasma half-life of cortisol is 70 to 90 min (Tyrrell *et al*, 1994). The HPA axis is highly sensitive to everyday challenges in animals and humans (McEwen,

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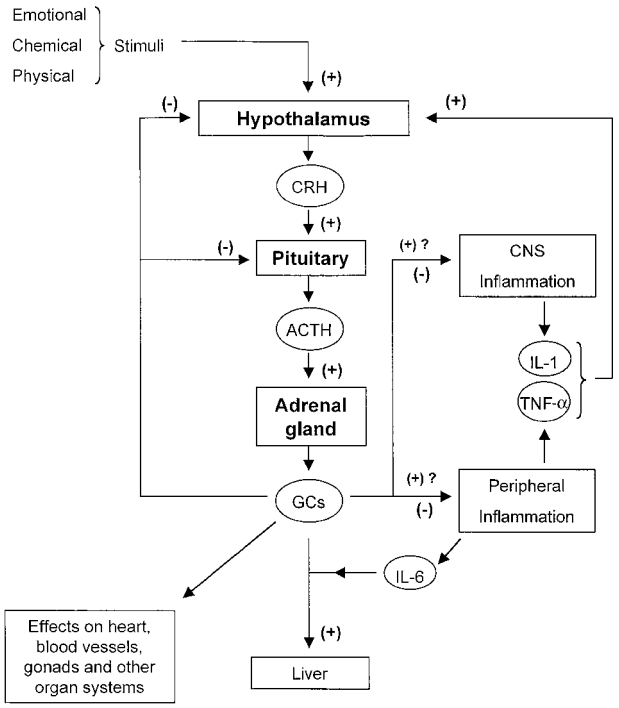

Figure 1 The HPA axis and inflammation. Various stressors can activate the HPA axis. The hypothalamus is stimulated to secrete CRH, which leads to ACTH secretion into the peripheral circulation. ACTH in turn triggers adrenal GC release and production. The CRH system is inhibited by GCs in a negative feedback loop. TNF-α and IL-1 are produced from inflammatory sites and are potent activators of the HPA axis. IL-6 acts synergistically with GCs to stimulate the hepatic secretion of acute phase proteins. Although GCs are widely known for their anti-inflammatory actions, "(−)," more recently also proinflammatory effects have repeatedly been reported, "(+) ?" HPA = hypothalamic-pituitary-adrenal; CRH = corticotrophin-releasing hormone; ACTH = adrenocorticotrophic hormone; GCs = glucocorticoids; IL = interleukin; TNF = tumor necrosis factor; (+) = enhancing; (−) = suppressing.

2000; Ottaviani and Franceschi, 1996). GCs, as the main effectors of the HPA axis, are released into the bloodstream and induce systemically a variety of physiological changes in different organs/organ systems of the body. For example, energy is mobilized from storage sites and energy delivery is increased in parts of the nervous system, muscles, and stressed body sites. In synergy with catecholamines, GCs increase the cardiovascular tone. Furthermore, energetically expensive and, at the very moment, nonessential processes like growth, reproduction, food uptake, and parts of the immune system are suppressed (Munck *et al*, 1984, 1994; McEwen *et al*, 1986; Sapolsky *et al*, 2000). An impaired stress response can have deleterious consequences: Patients with Addison's disease suffer from adrenal dysfunction, which results in failure to respond to even minor stressors (addisonian crisis) and can lead to coma or death if the patients are not treated with GCs. It has also been proposed that a disruption of the HPA axis in animals could explain increased susceptibility to autoimmune diseases (Sternberg *et al*, 1989; Calogero *et al*, 1992).

Although these GC-induced changes serve to promote homeostasis and are essential for survival, it has been found that under certain circumstances, exposure to an excess (acute and chronical) of GCs can also have serious negative side effects on various target tissues of the body. Elevated GC levels is a common feature of chronic stress, and is seen, for example, in caregivers of dementia patients, who show impaired cell-mediated immunity and thus an increased vulnerability to infection (Vedhara *et al*, 1999; Bauer *et al*, 2000). The concept of a "eucorticoid state" (Munck *et al*, 1984; Burchard, 2001) recognizes that neither too little (absent/impaired cortical function) nor too much GC (pharmacological dosing/hyperfunction) is beneficial.

How are GCs able to induce these rapid systemic physiological changes? First, within minutes after activation of the HPA axis, GCs are being released from the adrenal glands; second, GCs are hydrophobic molecules, which enables them to enter any cell through the hydrophobic cell membrane; and third, the intracellular cytosolic GC receptors have a widespread distribution throughout tissues. GC effects are mediated by either the high-affinity mineralcorticoid receptor (MR) or the low-affinity glucocorticoid receptor (GR) (De Kloet *et al*, 1998; Birnstiel *et al*, 1995). Binding of GCs to these receptors leads to the dissociation of a heat-shock protein from the receptor, followed by receptor dimerization, which then triggers the nuclear translocation of the ligand–receptor dimer complex. In the nucleus, the complex binds to specific DNA sequences called glucocorticoid responsive elements (GREs) and induces/facilitates transcription of the respective genes (De Bosscher *et al*, 2000; Boumpas *et al*, 1993). However, some effects may not require receptor dimerization but may occur primarily through protein-protein interactions (Kellendonk *et al*, 1999). The expression of an estimated 1% of genes may be regulated by GCs, which may be either up- or down-regulated. Given this large number of genes influenced by GCs, it is hardly surprising that the effects of different steroid interactions are rather complex and therefore the therapeutic use of GCs has to be carefully evaluated by consideration of beneficial versus potentially harmful effects. Regarding (neuro)inflammation, it is important to note that besides the psychological and physiological stimuli mentioned before, proinflammatory cytokines such as interleukin (IL)-1 proved to be potent stimulators of the HPA axis (Figure 1; Besedovsky *et al*, 1986; Berkenbosch *et al*, 1987; Sapolsky *et al*, 1987).

Because of the complex nature of the theme, this review has to integrate findings from the disciplines of neurobiology, neurendocrinology, and (neuro)immunology. By giving a broad overview of GCs, the stress response, and adaptive and maladaptive effects, we have introduced some basic concepts of endocrinology that are essential to understanding

the even more complex mechanisms when the endocrine, nervous, and immune systems interact during central nervous system (CNS) inflammation. Before dealing with this most complicated topic, where all three physiological systems act simultaneously and influence each other, it is useful to first focus on adverse GC effects in the CNS and then on interactions between the nervous and the immune systems. After that, we consider GC effects in inflammation, thereby emphasizing possible differences between the well-characterized GC effects on peripheral inflammation and the so far much less studied GC effects on CNS inflammation. It will become clear that this review is not just merely summarizing and updating well-known anti-inflammatory GC effects, but is also showing a quite unexpected and very different side of GCs in CNS inflammation.

Adverse glucocorticoid effects in the central nervous system

In the brain, GCs feed back negatively onto the hypothalamus (Figure 1), thereby inhibiting their own overproduction and maintaining homeostasis (Jacobson and Sapolsky, 1991; Lilly and Gann, 1992). Although most cells in the brain predominantly express GRs, principal cells of the limbic system often contain MRs as well as GRs (Joels, 2001). The hippocampus, for example, a brain part vital for learning and memory, has one of the highest GC receptor concentrations in the brain (McEwen *et al*, 1986; Sapolsky, 1994), and is therefore particularly sensitive to GC effects. Acute stress seems to facilitate the formation of memories of events associated with strong emotions (McGaugh, 2000; Meaney, 1988). Sustained exposure to GCs, however, seems to contribute to impairment of cognitive function and promote atrophy of brain structures such as the dendrites of pyramidal neurons in the CA3 region of the hippocampus (McEwen *et al*, 1995; Magarinos *et al*, 1999; Sapolsky, 1992). Magnetic resonance imaging studies in humans have shown that GC-related disorders such as Cushing's disease or posttraumatic stress disorder are assocociated with atrophy of the whole hippocampus (Sapolsky, 1996; McEwen and Magarinos, 1997). However, it is not known whether the loss of total volume is due to the atrophy of the dendrites on a cellular level. GCs have also been found to inhibit neurogenesis in the dentate gyrus of the hippocampus (Gould *et al*, 1997, 1998). There have been reports that stress lasting many months or years can kill hippocampal neurons directly (Landfield *et al*, 1981; Sapolsky *et al*, 1985); it remains unclear whether this is a physiological or pharmacological effect.

A few days of stress/GC exposure does not kill the neurons but has been shown to impair the capacity of neurons to survive during a neurological insult, such as ischemia, trauma, seizure, exposure to gp 120, oxygen radicals, or beta-amyloid, and eventually exacerbates the resulting neuropathological damage (Sapolsky and Pulsinelli, 1985; Sapolsky, 1985; Koide *et al*, 1986; Miller and Davis, 1991; Stein-Behrens *et al*, 1992). In these neurological disorders, the injury and death of neurons is caused at least in part by overstimulation of receptors for excitatory neurotransmitters such as glutamate (Whetsell, 1996; Beal, 1992; Lipton and Rosenberg, 1994). A massive increase of extracellular glutamate results in prolonged depolarization of neurons, inducing further glutamate release and in turn increase in intracellular Ca^{2+}-levels, which then activates Ca^{2+}-dependent enzymes (e.g., proteases degrading the cytoskeleton), and eventually leading to neuronal cell death. This pathophysiological mechanism is called excitotoxicity (Olney, 1978) and involves a complex series of events over time (Figure 2). GCs have been found to exacerbate the extent of neurological necrotic cell death. A variety of different primary physiological GC effects on neurons have been identified that could contribute to the overall "endangering" effect: (1) Interfering with neuronal

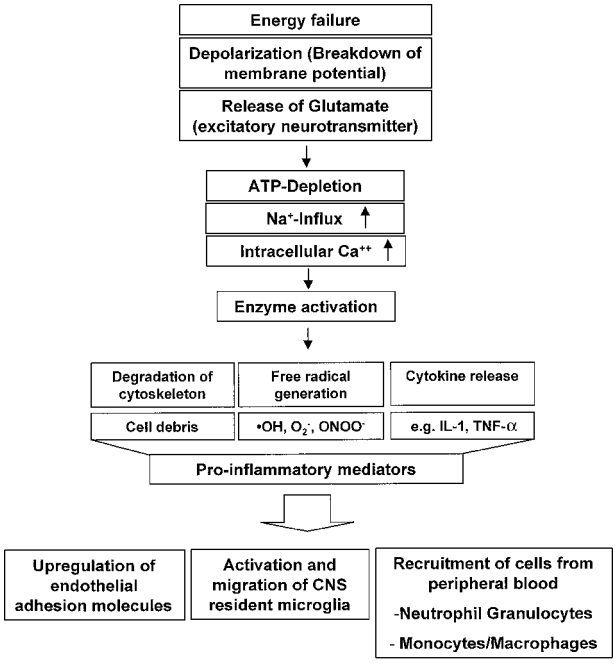

Figure 2 Excitotoxic brain injury and inflammation. Energy failure leads to the depolarization of neurons, causing a massive release of excitatory neurotransmitter (e.g., glutamate). The increased extracellular glutamate results in continuous excitation of neurons, inducing further glutamate release, ATP depletion, and a dramatic increase in intracellular Ca^{2+} levels, which then activates Ca^{2+}-dependent enzymes (e.g., proteases, lipases, peroxidases), and eventually leading to neuron death. Free radicals are generated, which damage membranes; injured neurons and glial cells secrete certain cytokines such as IL-1 or TNF-α. Several of these molecules produced during brain injury (cytokines, free radicals) also act as potent inflammatory mediators, which activate microglia and lead to the infiltration of blood-borne inflammatory cells into the brain parenchyma. Na, sodium; Ca, calcium; IL, interleukin; TNF, tumor necrosis factor.

energy metabolism (e.g., down-regulation of glucose uptake); (2) suppression of neuroprotective mechanisms (e.g., down-regulation of radical-scavenging enzymes such superoxide dismutase); and (3) exacerbation of excitotoxicity via increased synaptic glutamate concentrations and increased cytosolic calcium mobilization. Although some of these effects are secondary to the disruptive effects of GCs on neuronal energetics, some are direct and energy independent (Kerr *et al*, 1989; Joels and de Kloet, 1989; Bhargava *et al*, 2000).

In excitotoxic brain injury, a large part of neurons seem to die by necrosis. In contrast to apoptotic cell death, necrotic cells swell and burst, releasing proinflammatory mediators. As shown in Figure 2, neuronal tissue injury (e.g., caused by direct trauma, ischemia/excitotoxicity, or viral infections) also induces a well-defined inflammatory reaction in the CNS.

CNS and inflammation

The brain has long been regarded immunologically privileged because of the blood-brain barrier (Dermietzel, 1975; Risau and Wolburg, 1990), the lack of professional antigen-presenting cells, the very low expression of major histocompatibility complex (MHC) I and MHC II molecules (Wekerle *et al*, 1986), and the prolonged survival of tissue transplants. In fact, studies over the last 10 years proved that the immunoprivileged status of the CNS is not due to the absence of the imune system in the CNS but reflected an active process, which includes a dynamic interaction between the objectives of the imune response and the specialized needs of the CNS with its highly specialized and sensitive neurons (Ferguson and Griffith, 1997; Dalakas, 1995; Becher, 1998). This means that immune surveillance and immune function are minimal under healthy conditions but are inducible whenever required. It is important to differentiate between two major parts of the immune system: On the one hand, there is the adaptive immune system, which involves T/B lymphocytes, responsible for specific antigen recognition and long-lasting protection after vaccination. This adaptive system can also be responsible for deleterious autoimmune diseases such as multiple sclerosis or bystander damage during viral or bacterial infections. On the other hand, there is the innate, nonspecific immune system, where the main players are the short-lived but fast-acting neutrophil granulocytes and longer lived macrophages. These cells migrate upon activation into the injured tissue and provide host defense by phagocytosis and release of cytotoxins. After that, these cells play also a major role in tissue remodeling and wound healing. However, an inadequate or to prolonged immune reaction might be an important factor in neurodegenerative diseases or stroke. Although being part of the innate immune system, macrophages also interact with the adaptive system by presenting antigen to T lymphocytes.

Accumulating evidence during the last decade has shown that many neurological insults and neurodegenerative disorders are also accompanied by a marked acute inflammatory reaction. This inflammation is characterized by infiltration of blood-borne granulocytes and monocytes/macrophages into the respective brain parenchyma as well as activation of CNS resident microglial cells, astrocyte swelling, and the expression of cytokines, adhesion molecules, and other inflammatory mediators (Perry and Gordon, 1991; Dirnagl *et al*, 1999; Feuerstein *et al*, 1998; Beal, 1995; Lee *et al*, 1999). The expression of proinflammatory transcription factors such as nuclear factor kappa B (NF-κB) and hypoxia-inducible factor 1 has been found to be triggered by the Ca^{2+}-related activation of intracellular second messenger systems, the increase in oxygen free radicals, products of membrane peroxidation, and deprivation of oxygen and nutrients (O'Neill and Kaltschmidt, 1997; Ruscher *et al*, 1998). Consequently, the injured brain cells produce proinflammatory cytokines like IL-1α, IL-1β, or tumor necrosis factor alpha (TNF-α) (Rothwell *et al*, 1996). Adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) are up-regulated on endothelial cells of the CNS microvasculature and interact with surface receptors (e.g., lymphocyte function-associated antigen [LFA-1]) on neutrophils in the bloodstream. The neutrophils adhere to the endothelium, migrate through the vascular wall and into the tissue (diapedesis). Macrophages are usually the second wave of tissue-infiltrating cells after the neutrophils (Iadecola, 1997). Recruitment of these peripheral immune cells, as well as migration of microglia, are regulated by chemokines such as monocyte chemoattractant protein (MCP-1), which are expressed by astrocytes (Ransohoff and Tani, 1998), or the neuron-derived chemokine fractalkine (Chapman *et al*, 2000). There is considerable evidence that the inflammation is contributing significantly to the developing brain damage by such mechanisms as releasing neurotoxic substances, such as cytokines or free radicals (Beal, 1995; Barone and Feuerstein, 1999; McGeer and McGeer, 1999; Sanderson *et al*, 1999; Vila *et al*, 2000). In experimental models of stroke, inflammation seems to contribute to cerebral ischemic injury (Becker, 2001). The importance of inflammatory reaction in the pathogenesis of brain injury has been reviewed previously (Feuerstein *et al*, 1998; Stoll *et al*, 1998; del Zoppo *et al*, 2001). The role of inflammation in brain injury, however, is a controversial subject in neurology because a growing number of recent studies suggest that the impact of inflammatory mediators may actually be beneficial in the recovery from brain damage (Feuerstein and Wang, 2001; Schwartz and Moalem, 2001; Kerschensteiner *et al*, 1999; Rapalino *et al*, 1998). The imune response

at the right time and extent certainly could serve an important function in tissue reconstruction and remodeling, just as it does in the process of wound-healing in the periphery. This is reflected in the controversial literature about the role of proinflammatory cytokines in stroke or seizures, being either neurotoxic or neuroprotective (Yoles *et al*, 2001). For example, mice overexpressing IL-6 and TNF-α in glia develop both seizures and neurodegeneration (Campbell *et al*, 1993; Akassoglou *et al*, 1997), on the other hand, mice lacking TNF-α receptors sustain larger infarcts than wild-type mice (Bruce *et al*, 1996; Cheng *et al*, 1994; Gary *et al*, 1998). A clinical trial using a monoclonal antibody to ICAM-1 (Enlimomab Study) aiming at shutting down the inflammatory response after brain injury has failed to deliver any beneficial effect in stroke patients (DeGraba and Pettigrew, 2000; De Keyser *et al*, 1999). Recent data (Iadecola and Alexander, 2001), however, indicate that immune activation induced by the heterologous protein as well as insufficient preclinical data may have played an important role in the failure of this trial. In summary, even though the understanding of role of inflammation might have to be modidfied under certain circumstances, there is still overwhelming evidence that proinflammatory mediators do play an important part at certain stages of brain injury and contribute to the developing damage.

The innate immune sytem, with its ability to promote a fast, acute inflamation at target sites, seems also to play an important role in the pathogenesis of Alzheimer's disease and other neurodegenerative disorders (McGeer and McGeer, 1994, 1995, 1999). Large numbers of reactive microglia have been identified in CNS lesions. Microglia represent the phagocytic system of the brain, very similar to the blood-borne macrophages, and release upon stimulation potentially neurotoxic products such as excess glutamate or free radicals (respiratory burst) (Banati *et al*, 1993; Kreutzberg, 1996; Neumann, 2001). Neuronal populations in close proximity to activated microglia are exposed to proinflammatory molecules such as IL-1α (Walker *et al*, 1995), TNF-α (Hetier *et al*, 1991), and superoxide anions (Colton *et al*, 1996). The important role of inflamation was confirmed by studies investigating kainic acid–induced cell death (Akiyama *et al*, 1994), animal models of acute cerebral ischemia (DeGraba, 1998; Nogawa *et al*, 1997; Feuerstein *et al*, 1998), stroke (Beamer *et al*, 1998; Becker, 1998), and acquired immunodeficiency syndrome (AIDS)-related dementia (Adamson *et al*, 1996; Griffin *et al*, 1994). Therefore inflammation has been attributed to wide aspects of secondary injury phenomena, such as lipid peroxidation, free radical production, and edema formation. According to these findings, anti-inflammatory drugs should have a beneficial effect in the context of a neurological insult; suppression or inhibition of the immune response should ameliorate the neuronal tissue damage. As discussed later in this review, GCs did not prove to be very successful in the treatment of a variety of neurological insults.

Glucocorticoids and inflammation: Challenging the dogma

Glucocorticoids have been used widely for the treatment of diseases associated with activation of the immune system since their original application in the late 1940s (Hench *et al*, 1949). This work was awarded the Nobel Prize for medicine and provided the foundation for the dogma that GCs are uniformly immunosuppressive. The use of GCs in the treatment of various clinical disorders such as autoimmune diseases, chronic inflammation, or transplant rejection has been proven successful. The therapeutic value of GCs is attributed to their potent anti-inflammatory and immunomodulatory effects (Table 1, anti-inflammatory effects) on T-cell activation, adhesion molecule expression, cell migration, and cytokine production (Cato and Wade, 1996). GC-mediated reduction of leukocyte infiltrate, for example, occurs via the down-regulation of adhesion molecules, such as ICAM-1, endothelial-leukocyte adhesion molecules (ELAM-1), and vascular cellular adhesion molecule (VCAM-1) (Cronstein *et al*, 1992). In addition, monocyte and neutrophil recruitment during acute inflammation has been found to be under the negative modulatory control of the GC-induced lipocortin-1 (Getting *et al*, 1997). This clearly shows that GCs have anti-inflammatory effects in the periphery.

GCs have also been used to treat inflammatory diseases within the CNS, such as edema arising from brain tumors (Barnes and Adcock, 1993; Galicich *et al*, 1961), viral encephalitis, bacterial meningitis (Coyle, 1999), or to improve recovery from acute exacerbation in multiple sclerosis patients (Fillipini, 2000). Patients with malignant brain tumors are often treated with GCs to reduce vasogenic brain edema. In about 50% of cases, all clinical signs disappear (Vecht, 1998); however, GC treatment seems to provide a survival advantage to both normal and tumor cell types (Newton *et al*, 2001). Even low doses of dexamethasone were found to inhibit significantly the infiltration of brain tumors by lymphocytes and microglia (Badie *et al*, 2000), thus suppressing the cellular immunity against the tumor. The findings in these cases, showing that GCs also had anti-inflammatory effects in the CNS, gave rise to the assumption that GCs should be uniformly anti-inflammatory in all kinds of different CNS injuries, including hypoxia-ischemia and seizure. Accordingly, GCs should ameliorate damage during these neurological insults by suppressing the acute inflammation; but instead, as mentioned before, GCs have been found to increase neuron loss. Given the assumed anti-inflammatory properties of GCs in these neurological insults, the most likely explanation for these seemingly contradictory findings would be that the harmful GC effects on neuronal survival ability simply outweigh the

Table 1 Glucocorticoid effects on inflammation

Anti-inflammatory[a]	*Proinflammatory*[b]
Lymphocytes (adaptive)	
Decreased cytokine-induced proliferation	Enhanced immunglobulin synthesis
Decreased cytotoxicity	
Decreased cytokine production (IL-1, IL-2)	
Induction of apoptosis (Lymphopenia)	
Neutrophil granulocytes (innate)	
Decreased extravasation	Peripheral neutrophilia (mobilization of the "bone marrow reserve")
Decreased adhesion molecule expression	Delayed apoptosis
Decreased phagocytosis	
Decreased free radical generation	
Decreased chemotaxis	
Macrophages/monocytes (innate, adaptive)	
Decreased extravasation	Induction of macrophage migration inhibitory factor (MIF) expression
Inhibition of differentiation	
Decreased phagocytosis	
Decreased MHC I and II expression	
Decreased antigen presentation	
Miscellanous	
Decreased adhesion molecule expression (e.g., ICAM-1, VCAM-1)	Potentiation of acute phase reaction (liver)
Decreased pro-inflammatory cytokine production (e.g., IL-1α/β, TNF-α, IL-6, IL-2)	Increased pro-inflammatory cytokine receptor expression (e.g., IL-1 receptor)
Inhibition of cyclooxygenase-2 synthesis (COX-2)	Improved woundhealing Stimulation of 5-lipoxygenase expression

[a]References by first authors: Marx, 1995; Kern, 1988; Goulding, 1998; Perretti, 1994; Chrousos, 1995; Zuckerman, 1989; Barber, 1993; Burchard, 2001; Mukaida, 1991; Bailey, 1988.
[b]References by first authors: Burton, 1995; Cox, 1997; Wiegers, 1998; Wilckens, 1997; Chrousos, 1995; Davis, 1991; Donnelly, 1997; Liles, 1995; Calandra, 1995.

protective anti-inflammatory effects. There is, however, another possible explanation. During the past decade, numerous studies have shown that GCs can also have stimulatory or permissive effects on immune function (see Table 1, proinflammatory effects), suggesting that the current concept of uniformly anti-inflammatory GC effects is an oversimplification of GC physiology and needs to be extended.

GCs have been shown to act synergistically with exogenously added cytokines in the periphery. In hepatic cell cultures (Baumann and Gauldie, 1995) as well as in rats (Nishio *et al*, 1993), GCs strongly potentiate the IL-1 and IL-6–induced expression of acute phase proteins. Synergistic effects between GCs and IL-1 and IL-6 have also been observed in human B cells, potently inducing the production of IgG and IgM (Emilie *et al*, 1988). Other biological responses to a variety of cytokines such as IL-2 (Fernandez-Ruiz *et al*, 1989), Interferon (INF)-γ (Bergsteindottir *et al*, 1992) and granulocyte colony-stimulating factor (G-CSF) are also enhanced in the presence of GCs.

A few studies have even shown that GCs promote the production and release of several cytokines, such as IL-6 and TNF-α (Liao *et al*, 1995; Alcorn *et al*, 1992). Despite the proven ability of GCs to suppress proinflammatory cytokine expression, there are a large number of studies showing that the expression of many cytokine receptors are potently upregulated by GCs. To date, it has been shown that membrane-bound receptors for IL-1, IL-2, IL-4, IL-6, IFN-γ, G-CSF, and TNF-α are induced by GCs on several cell types (Wiegers and Reul, 1998). Up-regulation of membrane-bound receptors and associated signal transduction components enhances the effects, whereas up-regulation of soluble receptors ("decoy receptors") can attenuate the effects of the respective cytokine; soluble receptor up-regulation by GCs has only been shown for IL-1 and TNF-α (Wilckens and De Rijk, 1997; De Rijk, 1994). Furthermore, the common signal transducer gp130 has been found to be augmented by GCs (Pietzko *et al*, 1993; Schooltink *et al*, 1992); this subunit is shared by several cytokine receptors such as the IL-6, IL-11, leukemia inhibitory factor (LIF) receptors. Thus, GCs are able to potentiate the action of several cytokines by increasing the expression of a single, common subunit. In studies on patients with sepsis/septic shock, the synthetic GC methylprednisolone elevated proinflammatory cytokine serum levels, and not only failed to have any beneficial effect, but even increased mortality rate in some patient groups (Bone *et al*, 1987).

Recent studies indicate yet another ability of physiological GC levels to be proinflammatory, namely by inducing synthesis of macrophage migration inhibitory factor (MIF) (Donnelly and Bucala, 1997; Leech *et al*, 1999; Bucala, 1996). MIF was one of the first cytokines to be identified and was named because of its ability to prevent the random migration of macrophages in culture (David, 1966). Research since then revealed a broad range of proinflammatory actions of MIF such as induction of macrophage

TNF-α synthesis, up-regulation of phagocytosis, induction of nitric oxide synthase activity, and playing an important role as a cofactor in T-cell activation (Donnelly and Bucala, 1997; Juettner *et al*, 1998). Thus, amid the textbook picture of GCs being anti-inflammatory in the periphery, there are numerous instances where they are anything but. Recent work suggests some instances of proinflammatory GC effects in the CNS as well.

A profound proinflammatory effect of GCs on the innate immune system, which also plays a major part in CNS inflammation, is the mobilization of the so called "bone marrow reserve" of granulocytes, which results in a pronounced peripheral neutrophilia (Goulding *et al*, 1998). Several studies even observed that stress-induced increases in GC concentrations enhanced the adaptive immune response by redistributing leukocytes to local areas of injury or infection (Dhabhar *et al*, 1996; Dhabhar and McEwen, 1996, 1997). Several investigators found a GC-induced selective suppression of cellular adaptive immunity (T cells) and enhancing of humoral (B cells, antibodies) immunity (see Elenkov *et al*, 1999, for review).

In a recent study, dexamethasone treatment failed to down-regulate the cytokines IL-1α and TNF-α after chemically induced hippocampal injury in mice (Bruccoleri *et al*, 1999). GCs are of no therapeutic benefits in stroke patients (Millikan *et al*, 1987); nonsteroidal anti-inflammatory drugs exert a stronger protective effect in Alzheimer's disease (Asanuma *et al*, 2001; Breitner, 1996), and several studies argue even against their use in the treatment of poststroke edema (Fishman, 1982; Tominaga *et al*, 1988). Furthermore, GC treatment failed to have beneficial effects in a recent clinical trial with Alzheimer's patients (Aisen *et al*, 2000) and was also not recommended for treatment of Guillain-Barré syndrome (Hughes, 2001), a disease involving inflammation of peripheral nerves. Administration of dexamethasone (Kiwerski, 1993; Hall and Braughler, 1982) and methylprednisolone (Bracken *et al*, 1990, 1997), however, have resulted in beneficial effects in cases of spinal cord trauma. However, because these data are now strongly criticized (Nesathurai, 1998) because of the study design and the inability of several other groups to reproduce the results, the observed beneficial GC effect remains at least questionable. Furthermore, a number of studies indicate that either GCs failed to have anti-inflammatory actions in the CNS under certain circumstances or their potentially beneficial anti-inflammatory effects were outweighed by their damaging effects on neurons. Even more surprisingly, some studies even demonstrated proinflammatory GC effects in the CNS: 5-lipoxygenase (5-LO), the enzyme crucial for the biosynthesis of inflammatory leukotrienes, is present in neurons and 5-LO expression has been found to be increased in the rat brain after GC treatment (Uz *et al*, 1999) and during aging (Uz *et al*, 1998). Because aging is also associated with increased GC levels, it is certainly interesting to look at the effects of aging on the immune system. Despite a general immunosenescence (decrease of immunological parameters such as phagocytosis, cell trafficking, etc.), some increased immune functions like IL-4, IL-6, and TNF-α production could be observed (Straub *et al*, 2000). All these examples clearly demonstrate that GCs not only suppress immune function but have also the potential to enhance certain parts of the immune system.

We could also confirm this in a recent study from our group (Dinkel and Sapolsky, 2003). In order to reconcile the anti-inflammatory and potentially beneficial GC effects with their ability to worsen the outcome after a neurological insult, we addressed the question how this acute inflammatory reaction is affected by different levels of GCs. We investigated the GC effect on lesion size, cellular inflammatory infiltrate, and mRNA cytokine pattern after excitotoxic brain injury in the rat hippocampus. Kainic acid was injected into the hippocampus of adrenalectomized/basal GC–supplemented, intact, and corticosterone pretreated rats. First, we could confirm that elevated GCs accelerated and exacerbated the kainate-induced neuronal damage. In all three groups, activated microglia as well as blood-borne granulocytes and macrophages were detected after kainate injection. Compared to basal GC levels, acute high GC levels reduced these inflammatory cells at early timepoints, but cell numbers were increased later on, suggesting a delaying and proinflammatory effect of GCs. Even more surprisingly, chronically elevated GC levels resulted in rapid infiltration and a further increase of cellular infiltrate compared to the other two groups. In contrast to their immunosuppressive effects in the periphery (reduction of cellular inflammatory infiltrate), GCs seemed to have a proinflammatory effect (increase of total inflammatory cell numbers) in this model of CNS inflammation. In the periphery, GCs reduce inflammatory infiltration by suppressing ICAM-1, an adhesion molecule expressed on endothelial cells, which is necessary for extravasation of granulocytes and macrophages from the bloodstream into the inflamed tissue (Cato and Wade, 1996; Perretti and Flower, 1994). In the context of a neurological insult, GCs could alter blood-brain barrier permeability to facilitate recruitment of blood-borne cells into the CNS. This would dramatically increase the number of infiltrating cells, considering reports that GCs delay apoptosis in neutrophils and cause peripheral neutrophilia (see Table 1; proinflammatory effects).

CNS cytokine expression is normally low (Vitkovic, 2000). As part of the inflammatory reaction in various neurological insults, an increased expression of proinflammatory cytokines (e.g. IL-1α, TNF-α) has been detected (Dirnagl, 1999; Iadecola and Alexander, 2001; de Bock *et al*, 1996). We found elevated mRNA levels of the proinflammatory

cytokines IL-1α, IL-1β, IL-6, and TNF-α in all three groups after kainate injection. According to the timepoints of detection, these cytokine mRNAs seemed to have been produced by neurons and glial cells, thus providing a certain cytokine microenvironment that also affects the later infiltrating inflammatory cells. Consistent with known peripheral anti-inflammatory GC effects (Table 1), acute high GC levels inhibited IL-1α, IL-1β, TNF-α, but not IL-6, mRNA synthesis compared to basal GC levels. In contrast, chronically high GC levels caused an increase of all these four proinflammatory cytokine messages compared to basal GC levels, thus revealing yet another unexpected proinflammatory effect of GCs in CNS inflammation. Commensurate with this, GCs are of no particular benefits in stroke patients (Millikan *et al*, 1987) and their use to control poststroke edema is even associated with worsening the aspects of neurological outcome (Fishman, 1982; Tominaga *et al*, 1988). Our study showed that in the context of excitotoxic brain injury, GCs, depending on the dosage, may exert not only suppressive, but also permissive, and even strong enhancing effects on acute inflammation. These effects could further explain how GCs are worsening the outcome of neurological insults.

Glucocorticoids and viral infections

Given the number of neurotropic viruses (Table 2), it may be interesting to address the effect of GCs on the outcome of viral infection of the brain. A

Table 2 Neurotropic viruses (Peterson *et al*, 1997): the expression of cytokines during infection, physiological symptoms, and the presence or absence of a glucocorticoid response element (GRE) in the viral genome

	Cytokines			*Physiological symptom(s) and pathology*	*GRE*[e]
	IL-1α/β	*IL-6*	*TNF-α*		
Herpes viruses					
Herpes simplex virus I (Neuronal)	↑ β (1) CNS	↑ (2)	↑(3)	Encephalitis/persistent latent infection	+ (4)
Cytomegalovirus	↑α (5)	↑(5)	↑(5)	Encephalitis	± (6)[c]
Epstein-Barr Virus	↑α/β (7)	↑(8)	↑(8)	Encephalitis	+ (9)
Human herpesvirus 6	0 β (10)	—	—	Encephalitis/encephalopathy	±[d]
B virus[a]	—	—	—	Encephalitis	±[d]
Enteroviruses					
Polioviruses (Neuronal)	↑(11)	↓(12)[e]	↓(14) ↑(11)[f]	Poliomyelitis/paralysis	—
Coxsackieviruses	↑(11)	↑(13)	↑(11)	Myocarditis/meningitis	—
Echoviruses	↑β (15) CNS	—	↑(15) CNS	Meningitis	—
Retroviruses					
HIV	↑β (16) CNS	↑ (17, 18) CNS	↑ (16, 19) CNS	Dementia	+ (20)
Human T lymphotrophic virus type I	↑α (21)	↑(22)	↑(23) CNS	Chronic demyelination	—
Rabies virus (Neuronal)	↑β (24) CNS	↑(24, 25) CNS	↑(25) CNS	Encephalopathy	—
Mumps virus	↑β (26, 27) CNS	↑(28) CNS	↑(27), 0 (26) CNS	Encephalitis	—
Lymphocytic choriomeningitis virus	↑(29) CNS	—	↑(30)	Meningitis	—
Measles virus	↑(27, 31, 32, 33)	↑(32, 33)	↑(31, 32, 33)	Encephalitis, SSPE[b]	—
Rubella virus	—	↑(27)	—	Encephalitis	—
JC virus	—	—	—	Demyelination	—
Borna disease virus (Neuronal)	0 β (34) CNS	—	0 (34) CNS	Behavioral abnormalities	—

[a]Cercopithecine herpesvirus (B virus).
[b]Subacute sclerosing panencephalitis.
[c]Reactivation in the presence of glucocorticoid.
[d]Presence of GRE unknown but probable.
[e]IL-6 secretion inhibited in infected cells.
[f]TNF receptor transport to cell membrane inhibited in infected cells.
Arrows indicate an increase or decrease in cytokine level, CNS indicates that expression of a particular cytokine was determined within and during infection of the central nervous system. (Neuronal) indicates primary site of infection and/or primary ecological niche of the respective virus versus opportunistic infection of the brain parenchyma.
References by first authors: (1) Ben-Hur, 2001. (2) Noisakran, 1998. (3) Gosselin, 1992. (4) Hardwicke, 1997. (5) Ruzek, 1997. (6) Tanaka, 1984. (7) Foss, 1994. (8) Andersson, 1996. (9) Kupfer, 1990. (10) Inagi, 1996. (11) Vreugdenhil, 2000. (12) Dodd, 2001. (13) Heim, 2000. (14) Neznanov, 2001. (15) Nishikawa, 2000. (16) Ilyin, 1997. (17) Koedel, 1999. (18) Zidovetzki, 1998. (19) Nuovo, 1996. (20) Ghosh, 1992. (21) Mori, 1996. (22) Yamamura, 1998. (23) Fox, 1996. (24) Marquette, 1996. (25) Camelo, 2000. (26) Takikita, 2001. (27) Cavallo, 1992. (28) Joblonowska, 1999. (29) Hildeman, 2000. (30) Nguyen, 1999. (31) Leopardi, 1992. (32) Yamabe, 1994. (33) Schneider-Schaulies, 1993. (34) Sauder, 2001.

number of studies (for a detailed review, see Pearce *et al*, 2001) have shown an up-regulation of proinflammatory cytokines (Table 2) and in turn cytokine-mediated increased GC release during viral infections. The available data examining the stimulation of the HPA axis by cytokines indicate that depending on the virus and the respective cytokine pattern, several immune-endocrine pathways can be invoked. Endogenous GCs are capable of modulating the immune response by supporting protective immunity as well as suppressing detrimental effects of antiviral immunity such as septic shock. In mice, adrenalectomy before infection with cytomegalovirus (CMV) results in lethality but GC replacement prevents virus-induced lethality (Ruzek *et al*, 1999). In humans, chronically elevated GC levels, caused by chronic stress situations, are associated with enhanced susceptibility to viral infection (Glaser and Kiecolt-Glaser, 1998).

Because several viral genomes contain GREs (Table 2), GCs might also influence early phases of viral infection by stimulating viral replication via these GREs. Recent findings even indicate that human immunodeficiency virus (HIV)-1–associated protein Vpr is able to act as transcriptional activator and contains a nuclear receptor–binding motif that binds directly to GR (Kino and Chrousos, 2001). Therefore, Vpr may stimulate viral proliferation (facilitation of viral gene transcription) and suppress the host immune system by inducing GC hypersensitivity (GR binding).

In a recently developed animal model for herpes encephalitis, it was found that treating the animals with dexamethasone decreased viral load. But in the presence of acyclovir, a small, nonsignificant increase in viral load was observed, and acyclovir in combination with dexamethasone did not decrease viral spread over acyclovir by itself (Thompson *et al*, 2000). The role of circulating GCs in the pathogenesis of HSV-1 encephalitis was also examined. Circulating GCs were removed or blocked by adrenalectomy, hypophysectomy, or receptor blocking. In the absence of circulating GCs, fever and behavioral changes (motor hyperactivity and agression) associated with herpes encephalitis were not observed, although overall mortality was unchanged. With GC replacement therapy, the clinical responses to HSV-1 encephalitis was again observed. IL-10 levels were also measured and shown to increase with infection only in the presence of GCs (Ben-Hur *et al*, 2001). Overall, in the case of HSV-1, the use of GCs to abrogate the course of infection is unclear. Dexamethasone administration resulted in a worsened neurpathological outcome in a model human HIV-1 encephalitis in SCID mice (Limoges *et al*, 1997). In another study, pneumovirus-infected mice responded to hydrocortisone treatment with enhanced viral replication and accelerated mortality (Domachowske *et al*, 2001). These results indicate that exogenous administration of GCs may be of limited benefit or even be harmful for treatment of certain viral infections.

Conclusion

The major finding reported in this review is that GCs are not always anti-inflammatory and can even be proinflammatory in peripheral as well as in CNS inflammation. Although there are not enough studies yet to begin to delineate rules that explain why and under what circumstances GCs have anti- or proinflammatory effects, based on small numbers of data, there is, however, at least room to speculate as to what parameters determine the respective GC effects.

Synthetic versus endogenous GCs

Much of the current understanding of the mechanisms of GC action stems from observations made with synthetic/exogenous GCs and their effect on peripheral immune activation. These pharmacological agents, such as prednisolone or dexamethasone, have been proven to be several times more potent immunosuppressants than endogenous GCs, such as the primate cortisol and the rodent corticosterone (Nelson, 1995; Wilckens and De Rijk, 1997; Craig and Stitzel, 1994); in addition, therapeutic doses are usually much higher than physiological levels of GCs. The physiological role of GCs in relation to immune reactions on the basis of *in vitro* as well as *in vivo* data cannot be solely based on the use of synthetic ligands without comparison with the endogenous GCs; this is especially the case because synthetic GCs are exclusively GR agonists and do not bind to MRs. For example, GCs are bound in the hippocampus by the high-affinity MR, which is almost entirely occupied under basal conditions. In contrast, the hippocampus also contains the low-affinity GR, which is not heavily occupied until stress levels of GCs are achieved. Therefore, it is certainly questionable whether the actions of endogenous GCs on inflammation could be predicted from those observations.

Microenvironment and type of injury

Furthermore, considering the extraordinary microenvironment of the CNS, one should also be very cautious in assuming that GC effects seen in peripheral inflammation also apply to CNS inflammation. Our study (Dinkel and Sapolsky, 2001), for example, investigated effects of GCs on the innate immune system and neurons/glial cells in the context of acute CNS inflammation. GCs might down-regulate cytokine production of certain immune cells, but just cause the opposite effect in neurons or glial cells. The effects of GCs are determined by highly specific regulatory mechanisms, which may also display tissue specificity. Given the growing appreciation of the complexity and heterogeneity of various forms of brain injury, GC use as treatment may find a rational place in management only of a subset of neurological insults.

Chronic versus acute exposure

Another important factor to consider is whether GCs are elevated acutely or chronically. Chronic exposure to GCs might induce changes on certain cell types (e.g., receptor up- or down-regulation) that result in completely different cellular responses to tissue injury and inflammatory mediators.

There is convincing evidence for the effectiveness of GCs in the acute phase of optic neuritis and multiple sclerosis attacks (Brusaferri and Candelise, 2000), but there is no beneficial GC effect on the progression of the disabilities. The initial effects of high-dose therapy occur rapidly, but are lost as the diseases progress. This declining responsiveness to GCs over time and the known side-effects limit the therapeutic use of GCs in multiple sclerosis and other autoimmune diseases. Furthermore, there is no consensus about the optimal form, dose, route, or duration of corticosteroid therapy (Noseworthy *et al*, 2000).

Myasthenia gravis patients who do not respond well to anticholinesterase treatment are candidates for GC (prednisolone) therapy. Interestingly, there is a well-documented early exacerbartion of myasthenic weakness immediately after starting high-dose GC administration (Pascuzzi *et al*, 1984). In an attempt to avoid this transient exacerbation, treatment is started at a low dose, then gradually increased, and eventually (on remission) reduced (Vincent *et al*, 2001).

Clinical implications

Although high-dose GC therapy has become the standard for acute management of certain forms of spinal cord injury, its therapeutic value in traumatic brain injury has been severely questioned (Segatore, 1999). In two major studies (Lefering and Neugebauer, 1995; Cronin *et al*, 1995) reviewing available randomized control trials, it has been recommended that high-dose GC treatment of septic shock patients with severe infection should be abandoned. On the other hand, GCs remain the most effective therapy for inflammatory disorders such as asthma or rheumatoid arthritis (van der Velden, 1998; Belvisi *et al*, 2001). More clinical investigations are needed in order to understand the molecular and cellular mechanisms responsible for the inefficacy of GCs in the treatment of disorders such as septic shock or inflammation after stroke.

When studying GCs and inflammation, one has to take into consideration that effects will differ depending on GC type (e.g., synthetic, endogenous), GC concentrations, location (CNS, periphery), type of inflammation (innate, adaptive, combined), and immune cells (e.g., T cells, B cells, granulocytes) involved. In light of these complex multifactoral interactions and the increasing number of studies showing proinflammatory GC effects, it seems appropriate to reconsider the dogma of GCs being universally immunosuppressive and, accordingly, the broad use of GCs as the anti-inflammatory drug of choice in a very large number of CNS disorders.

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