The Effects of Steroid Hormones in HIV-Related Neurotoxicity: A Mini Review

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This review examines the interaction of steroid hormones, glucocorticoids and estrogen, and gp120, a possible causal agent of acquired immune deficiency syndrome–related dementia complex. The first part of the review examines the data and mechanisms by which gp120 may cause neurotoxicity and by which these steroid hormones effect cell death in general. The second part of the review summarizes recent experiments that show how these steroid hormones can modulate the toxic effects of gp120 and glucocorticoids exacerbating toxicity, and estrogen decreasing it. We then examine the limited in vivo and clinical data relating acquired immune deficiency syndrome–related dementia complex and steroid hormones and speculate on the possible clinical significance of these findings with respect to acquired immune deficiency syndrome–related dementia complex.

Key Words: gp120, HIV, glucocorticoids, estrogen, AIDS-related dementia (ADC), review

Introduction

Among patients with acquired immune deficiency syndrome (AIDS), AIDS-related dementia complex (ADC) is a neurologic disorder that develops in the later stages of AIDS in a small but significant number of patients (Bacellar et al 1994; Budka 1991; Price et al 1988). It has been characterized by a variety of neurologic and neuropsychologic impairments, including loss of memory, confusion, motor deficits, delayed development, and a wide range of behavioral abnormalities. There are indications of neuropathologic changes and cell loss in cortical and subcortical regions that may account for these behavioral manifestations (Epstein and Gelbard 1999; Gendelman et al 1994; Glass and Johnson 1996; Masliah et al 1992; Michaels et al 1988; Price et al 1988). In some cases, it has proven difficult to directly correlate the extent of neuron loss with the severity of symptoms in ADC, suggesting that dysfunction of neurons, rather than overt neuron death, also may be an aspect of ADC (Adle-Biassette et al 1999; Bell 1998; Everall et al 1999).

HIV does not appear to infect and kill neurons directly (Michaels et al 1988). Although glia (the other principal cell type of the central nervous system [CNS]) can be infected, the extent is insufficient to account for the cell damage observed. The virus may enter the CNS in association with macrophages or by disrupting the blood brain barrier, however (Annunziata et al 1998; Haase 1986; Persidsky et al 1997b; Sharer 1992). Therefore, the virus can be present in the brain within microglia and macrophages (the disease-fighting proinflammatory cells of the CNS), from whence it may cause neuron death and dysfunction (Giulian et al 1990; Lipton 1994; Ohagen et al 1999; Pulliam et al 1993; Tan and Guiloff 1998).

In the first part of this review, we briefly summarize current knowledge about the mechanisms underlying the adverse effects of HIV on neurons, focusing on the actions of gp120. This is a prelude to the core of this review, which considers the modulatory effects of two steroid hormones on the actions of gp120.

gp120

There are relatively few effective treatments for dementia and prevention by impeding the initial neuron death or dysfunction is perhaps the most promising treatment for ADC. Because the intact virus does not infect and destroy cells in the brain directly, the causal agents of neurotoxicity were hypothesized to be factors that originated from HIV, such as gp120, the major envelope glycopolyptptide of HIV that acts as the binding protein for viral entry. It is formed from the cleavage of gp160, leaving a gp41 fragment and can be readily shed to become a soluble protein (Gelderblom et al 1987; Pahwa et al 1985; Schneider et al 1986). The neurotoxicity of gp120 was first demonstrated (Brenneman et al 1988) in mice retinal and hippocampal tissue and then confirmed in human cortical tissue (Pulliam et al 1991), and rodent spinal cord, hippocampus, cortex, cerebellum, and retinal ganglion with LD50’s in the picomolar range (Aggoun-Zouaoui et al 1996; Bagetta et al 1996b; Barks et al 1997; Corasaniti
TNF-α is the first mechanism involved in the release of cytokines, such as TNF-α, and members of the interleukin family by macrophages and microglia as part of an inflammatory response that alerts the immune system to a foreign body. Research has shown that there is a correlation between severity of dementia and the amount of gp41 in the brain after autopsy of HIV patients (Adamson et al. 1999). Therefore, we hope soon to have definitive answers on the relationship between HIV coat proteins and ADC.

With the demonstration of gp120 neurotoxicity in the brains of animals, there has been an understanding of several mechanisms by which gp120 can cause neuron death. The first mechanism involves the release of cytokines, such as TNF-α, and members of the interleukin family that alert the immune system to a foreign body. Researchers have reasonably documented that gp120 releases such cytokines in the periphery with increasing evidence for similar effects within the CNS (Adamson et al. 1996; Ilyin and Plata-Salaman 1997; Koka et al. 1995; Kong et al. 1996; Wiley et al. 1994; Yeung et al. 1998). Paradoxically, within the CNS these compounds can kill the neurons they were released to protect (Bjugstad et al. 1998; Ensoli et al. 1999; Jeohn et al. 1998; Van der Meide and Schellekens 1996; Yeung et al. 1998). As part of the signaling mechanism of the cytokines, cytosolic calcium concentrations can be increased, with potentially neurotoxic consequences (see below). At present it remains unclear the extent to which gp120 effects on cytokine and interleukin release in the CNS contribute to neurotoxicity.

A second route of damage may involve a potent excitatory neurotransmitter system involving the N-methyl-D-aspartate (NMDA) receptor (Diop et al. 1994; Lipton 1994; Lipton et al. 1991; Pittaluga et al. 1996; Sweetnam et al. 1993). Excitatory amino acids (EAA), such as glutamate, as well as its agonists kainic acid and NMDA can be neurotoxic. Glutamate, in addition to its use in its traditional role for metabolism and protein synthesis within the cell is used in the CNS for synaptic transmission. Under normal circumstances, glutamate may be involved in several synaptic functions that result in an influx of calcium into the cell, most notably the synaptic plasticity, which is thought to underlie learning. Overstimulation of the synapse by EAs results in excess calcium entering the cell, however, initiating a cascade of oxygen radical production, lipid peroxidation, and promiscuous stimulation of proteases and nuclease; all of these factors can ultimately culminate in neuron death (reviewed in Choi 1992). Several aspects of the EAA cascade are manifested by gp120 neurotoxicity: it can increase cytosolic calcium in cells (Ciardo and Meldolesi 1993; Codazzi et al. 1995; Diop et al. 1994; Dreyer et al. 1990; Lannuzel et al. 1995; Lo et al. 1992; Nath et al. 1995), its neurotoxicity is inhibited by NMDA receptor antagonists (Barks et al. 1997; Lipton et al. 1991; Pittaluga et al. 1996; Toggas et al. 1996) and it increases oxygen radicals levels and lipid peroxidation (Corasaniti et al. 1998b; Foga et al. 1997). Because gp120 itself does not act directly on NMDA receptors, it has been hypothesized that gp120 causes the release from macrophages and glia of an as yet unidentified NMDA receptor agonist, causing EAA neurotoxicity. This unknown substance has been speculated to be quinolinic acid (Kerr et al. 1997), arachidonic acid (Dreyer and Lipton 1995; Genis et al. 1992; Schroder et al. 1998), nitric oxide (Adamson et al. 1996; Bagetta et al. 1997; Mollace et al. 1994) or perhaps even glutamate because gp120 appears to increase release and block its reuptake (Dreyer and Lipton 1995; Vesce et al. 1997).

There may also be some directly endangering effects of gp120 on neurons. The glycoprotein can mimic the amino acid glycine (which has a neuromodulatory function at NMDA receptors), enhancing its activity (Pattarini et al. 1998b; Pittaluga et al. 1996). In addition, gp120 may also act on neuronal chemokine receptors, initiating a calcium cascade leading to neuron death, as previously described (Blanco et al. 1999; Hesse et al. 1998; Hesse et al. 1999; Kaul and Lipton 1999; Madani et al. 1998; Meucci et al. 1998).

The mechanisms of toxicity already described primarily effect neurons. The other major cell type in the CNS, glia, may be a significant factor in gp120 neurotoxicity as well.
Glia perform primarily a supporting role for neurons such as uptake of toxic substances, regulation of extracellular pH, acting as a sink for potassium, releasing neuroactive substances necessary for repair, supplying nutrition and responding to injury. Glia also appear susceptible to gp120 toxicity, possibly via the chemokine receptor (Benos et al 1994; Bernardo et al 1994; Ciardo and Meldolesi 1993; Codazzi et al 1995, 1996; Kurt 1998; Pulliam et al 1993; Shrikant et al 1996). Given the key supporting role of glia, their loss or dysfunction could result in increased neuron death.

Other routes by which gp120 alters cell activities are increased expression of nitric oxide synthase (Bagetta et al 1997) decreased release of the neurotransmitter noradrenaline (Pittaluga et al 1996), decreased expression of nerve growth factor (Bagetta et al 1996a), and decreased glucose utilization (Kimes et al 1991), any of which could compromise neuronal function or viability.

Based on the gp120’s putative mechanism of action, a number of categories of agents have been proposed to prevent gp120 neurotoxicity, such as NMDA and chemokine receptor blockers, antioxidants, calcium binding compounds, and neuroprotective peptides and cytokines (Dibern et al 1997; Diop et al 1995, 1996; Foga et al 1997; Meucci and Miller 1996; Miller and Meucci 1999; Uchida et al 1996). The first clinical trials aimed at relieving ADC symptoms without using antiviral medication also have been reported (Navia et al 1998). The calcium channel blocker nimodipine was given with encouraging results to AIDS patients who were exhibiting signs of ADC and neuropathy. For more detailed account of possible mechanisms and treatments for gp120 neurotoxicity and ADC the reader is referred to a recent review (Lipton 1998).

Along with the knowledge of the basic mechanisms by which gp120 causes neurotoxicity, and perhaps ADC, has come an appreciation of extrinsic factors that can modulate the neurotoxicity of gp120. We now review the relatively recent findings regarding two of these modulators, both of which may have some clinical significance. The two hormones to be considered are glucocorticoids (GCs), which appear to exacerbate neurotoxicity, and estrogen, which may be neuroprotective.

**Glucocorticoids and Neurotoxicity**

Glucocorticoids are steroid hormones secreted by the adrenal glands primarily in response to physical and psychologic stress. The GCs include natural hormones, such as cortisol (hydrocortisone) in humans and other primates and corticosterone (CORT) in rats, as well as synthetic analogues such as dexamethasone, prednisone, and triamcinolone. The release and regulation of naturally occurring steroids are controlled by the hypothalamic–pituitary–adrenal axis (HPA). In the short term and primarily in the peripheral systems, GCs can be beneficial to surviving a major physical stressor. They mobilize energy (primarily to muscle), help increase cardiovascular tone, and enhance cognition, all functions necessary for an organism to cope with a stressful crisis. To conserve energy for these tasks, unessential activities such growth, digestion, reproduction, and immunity are turned off. If the stressful situation is prolonged, however, as with many human psychologic stressors, GCs can have adverse effects throughout the body, including hypertension, reproductive impairment, ulceration, increased infectious disease risk, and cognitive impairment (Munck et al 1984). We will first briefly examine how GCs can affect neuron survival in general within the CNS before considering how they exacerbate gp120-induced neurotoxicity.

Although GCs can endanger a number of brain regions, the hippocampus, a brain region rich in corticosteroid receptors (Jacobson et al 1993; Joels and de Kloet 1994), is most susceptible to GCs exacerbation of neurotoxicity. This region, which plays a key role in learning and memory, is vulnerable to a number of neurotoxic conditions that are exacerbated by GCs, including toxins such as glutamate, kainic acid, the antimetabolite 3NP, cyanide, ischemia, and hypoglycemia, and oxygen radical generators (reviewed in Chang et al 1998; Sapolsky 1996). Under conditions in which GCs themselves are not toxic, they appear to prime the system so that exposure to another insult results in increased neuronal death.

Although other factors may be involved, the ability of GCs to decrease glucose transport into neurons (Carter-Su and Okamoto 1985; Doyle et al 1993; Freo et al 1992; Horner et al 1990) is a likely mechanism for exacerbation of neurotoxicity. Within hours, GCs sequester glucose transporters from the membrane, and within days they downregulate levels of glucose transporter. Limited amounts of glucose transporter result in limited glucose for the neuron and limited production of adenosine triphosphate (ATP); however, when faced with an excitotoxic insult, the cells require more energy to fuel the high-affinity removal of EAAs from the synapse, to pump out the excess calcium from the cytosol, to quench oxygen radicals that have been generated, and to repair oxidative damage. If cellular energy reserves have been curtailed by GCs, the neurons are less able to cope with all the potential destruction of an insult, and death is more likely (Sapolsky 1996). To support this model, researchers have demonstrated that GCs increase glutamate accumulation in the synapse (Lowy et al 1995; Stein-Behrens et al 1992, 1994; Virgin et al 1991), worsen calcium accumulation in the neurons, (Elliott et al 1993), and increase oxygen radical formation after insult (McIntosh and Sapolsky 2000; 48:881–893).
1996). Moreover, energy supplementation blunts these effects and results in decreased neuron death (Sapolsky 1996).

Glucocorticoids can also inhibit glucose transport in glia (Horner et al. 1990). In their supportive role, glia also require energy, especially during an insult. If the glia are compromised, they cannot provide adequate maintenance for the neurons, resulting in a greater likelihood of death of the latter.

Given GCs ability to exacerbate neurotoxicity insults that act via the same EAA and calcium excess pathways as gp120, we will now examine the literature showing that GCs can also increase gp120 neurotoxicity.

Glucocorticoids and gp120 Neurotoxicity

The exacerbation of gp120 neurotoxicity by GCs has been demonstrated in primary hippocampal, cortical, and striatal cultures of rat (Brooke et al. 1997; Iyer et al. 1998). Figure 1A is a summary of these data showing that in all three tissues there is a synergistic neurotoxicity between gp120 and the GCs corticosterone (CORT). Increased toxicity was shown to occur at 100 nmol/L to 1 μmol/L concentration of CORT (at what are considered to be high physiologic levels). At cortisol levels of 10 and 1 nmol/L in the normal to low range of GC levels, however, there was no exacerbation of gp120 neurotoxicity by GCs (Brooke et al. 1997). In fact, gp120 alone is not always toxic, but there is consistently a loss of neurons with gp120 in the presence of CORT. Perhaps greater clinical significance, the synthetic GCs prednisone (Figure 1A) and dexamethasone also enhance gp120 neurotoxicity (Brooke et al. 1997).

A gp120-induced rise in cytosolic calcium, whether via the NMDA or chemokine receptor, may in part explain its neurotoxicity. Increased calcium mobilization with gp120 is exacerbated in the presence of CORT in cortical, striatal, and hippocampal cultures (summarized in Figure 1B; Brooke et al. 1997; Iyer et al. 1998). Moreover, GCs also worsen gp120-induced calcium mobilization in hippocampal and cortical slices, particularly in the CA1 and CA3 cell fields of the hippocampus (Yusin et al. 2000).

A downstream effect of increased calcium mobilization is oxygen radical production and lipid peroxidation, and GCs worsen this gp120 effect as well, both in hippocampal (Figure 2) and cortical cultures (Howard et al. 1999). Nonetheless, these studies indicate that there is not a simple GCs exacerbation of gp120 effects on oxygen radical accumulation and subsequent lipid peroxidation. It would appear that GCs and gp120 have different but perhaps accumulating effects on various aspects of this neurotoxic pathway. The reader is referred to Howard and colleagues (Howard et al. 1999) paper for more detailed descriptions.

As previously mentioned, the exacerbating properties of GCs may be caused by a disruption of energy stores, and this also appears to be true for gp120 neurotoxicity. It has been confirmed that there is a correlation between energy availability and the enhanced neuron death from gp120 in the presence of CORT. The synergistic effects of gp120 and CORT on neurotoxicity and calcium mobilization could be reversed with glucose supplementation (Brooke et al. 1998). The rationale for excess energy requirements...
is summarized in Figure 3, in which CORT is shown to significantly worsen the disruptive effects of gp120 on ATP levels and mitochondrial potential (Brooke et al 1998).

We have also observed that CORT exacerbates the gp120 disruption of metabolism in hippocampal slices (Figure 4). Using a microphysiometer (which indirectly measures metabolic rate in real time in tissue), we ascertained metabolic rates in slices from normal, adrenalectomized, CORT-treated, or prednisone-treated rats. After challenge with gp120, slices from CORT-treated and prednisone-treated rats had significantly decreased metabolic rates in the CA1 region and dentate nucleus of the hippocampus and in the cortex, compared with slices from intact and adrenalectomized rats (Yusin et al 2000).

These in vitro studies suggest that GCs augment the neurotoxicity of gp120. If gp120 is a factor in the development of the neuropathology of HIV infection, then GCs may be a factor in its manifestation. Other studies have been done in vivo to support work relating GCs to HIV-related neuropathology.

Gendelman and colleagues have developed a model of ADC by injecting severe combined immunodeficient (SCID) mice with HIV-infected monocytes, producing an HIV-encephalitis with neuropathologic features reminiscent of that seen in HIV patients with dementia (Avgereopoulos et al 1998; Persidsky and Gendelman 1997; Persidsky et al 1995, 1997a; Tyor et al 1993). The original hypothesis was that these neuropathologic changes were due to the release of inflammatory compounds in response to the encephalitis, so the researchers attempted to reverse the neurotoxicity with dexamethasone treatment. Synthetic
GCs such as dexamethasone and prednisone are used extensively as antiinflammatory drugs because they prevent the formation and action of cytokines. Contrary to expectations, neuron loss was greatly enhanced by dexamethasone, leading the authors to conclude that the results suggested the need for caution in administering glucocorticoids for treatment of HIV encephalitis in humans and consider nonsteroidal antiinflammatory agents (Gendelman et al 1998; Limoges et al 1997).

Another report (Bressler et al 1993), although not showing increased neurotoxicity, did demonstrate that GCs enhance the production of TNF-α in the brain, a possible route of toxicity of gp120. Because of these findings those authors likewise cautioned about the use of GCs with AIDS patients.

In the sole relevant human study, Oberfield et al (1994) examined HIV-infected children who had high levels of cortisol, a condition that sometimes accompanies HIV infection, and found that hypercortisolemia was predictive of neurologic abnormalities (Oberfield et al 1994). Because of the clinical implications, they suggested further studies to confirm these results. Therefore, from the data presented, GCs exacerbation of the neurotoxic effects of gp120 is sufficient to warrant concern.

Glucocorticoids and HIV

It has been demonstrated that gp120 raises GCs levels by interfering with the HPA axis in rodents (Raber et al 1996). It appears that HIV also effects the HPA axis in humans because about 40% of AIDS patients (Coodley et al 1994; Corley 1995; Lortholary et al 1996) have increased endogenous cortisol concentrations and 20% show insufficient adrenal function and lowered cortisol levels (Norbiato et al 1994; Piedrola et al 1996). If GCs do indeed worsen gp120 neurotoxicity, then there is the potential for a negative neurotoxic cascade in those patients with hypercortisolemia; however, studies to determine the clinical significance of these altered levels of cortisol with respect to cognitive abilities have not been done. Only one study could be mentioned here that perhaps is relevant (Gorman et al 1991). There was a small but significant correlation between cortisol level in HIV patients and increased levels of depression and anxiety that was not evident in non-HIV patients with similar levels. Depression could have a further deleterious, neurotoxic effect in HIV patients. Because GCs appear to be a factor in increased gp120 neurotoxicity in vivo studies, it is perhaps reasonable to at least consider that GCs may be a factor in ADC.

Nonetheless, the use of the synthetic GCs, such as prednisone, in the treatment of complications associated with AIDS also would result in increased GC levels. There are many instances of AIDS-related diseases in which the use of GCs is recommended, including such conditions as HIV-induced high-grade non-Hodgkin’s lymphoma, wasting syndrome, nephropathy, optic neuropathy, and idio-
pathic colonic inflammation (Gopal et al 1997; Jager 1994; Kimmel et al 1998; Lu et al 1995; Machet et al 1996; Watterson et al 1997). The most significant use of GCs is in the treatment of pneumocystis carinii pneumonia, the most common opportunistic infection associated with AIDS. High doses of prednisone (60–160 mg/day; Bozzette et al 1990; Gagnon et al 1990; Miller et al 1996; Pareja et al 1998; Smith et al 1996; Urakami et al 1997) are common. There have even been reports of using 300 to 1000 mg/day of prednisone and hydrocortisone (Frey and Speck 1992; Montaner et al 1989) for at least 7 days with repeat treatment lasting up to 26 weeks. Experimental administration of far lower doses of GCs to healthy human volunteers causes significant cognitive impairments (Newcomer et al 1991, 1994, 1998; Wolkowitz et al 1990, 1997). Because it has been shown that GCs interact with gp120 to disrupt cell function and increase neuron death in vitro, there is a possibility that similar phenomena may be occurring in vivo.

If, with continued research in this field, the gp120 neurotoxicity data discussed in the early part of this review can be unequivocally shown to cause some of the neuronal damage associated with ADC, then it should also be recognized that GCs might adversely affect the nervous system in individuals with HIV-infection. This conclusion is still somewhat hypothetical because the connection between gp120 and ADC is not absolutely confirmed, but we feel that there are sufficient data to warrant further study and concern. In contrast, the other recent literature to be reviewed suggests that estrogen may prove to be beneficial because it appears to have neuroprotective properties against gp120 neurotoxicity.

**Estrogen and Neurotoxicity**

Estrogen appears to promote neuron survival and function. Its neuroprotective attributes include protection against glutamate (Goodman and Mattson 1996; Singer et al 1996), β-amyloid toxicity (Green et al 1996), glucose, and serum deprivation (Bishop and Simpkins 1994; Faivre-Bauman et al 1981; Green et al 1997), regulation of calcium homeostasis (Mermelstein et al 1996; Nakajima et al 1995), decreasing the production of oxygen radicals (Behl et al 1997; Keaney et al 1994; Lacort et al 1995; Mooradian 1993), and increasing release of neutrophins and promotion of dendritic growth (Brinton et al 1997; Chowen et al 1992; McEwen and Woolley 1994). The exact mechanism of estrogen action is still being determined, but neuroprotection appears to involve both traditional (genomic) and nontraditional mechanisms (McEwen 1999). Genomic mechanisms involve steroids binding to intracellular receptors, which are then translocated to the DNA where they can serve as positive or negative transcriptional regulators. This process is relatively slow, requiring a number of minutes to hours. Evidence for nonreceptor (nontraditional) mechanisms include incremental increases in protection from estrogen well beyond the K₄ of the estrogen receptor and the fact estrogen effects occur too rapidly to be genomically mediated. Mechanisms of nontraditional estrogen activity are primarily antioxidant properties and perhaps some of the effects on calcium flux and facilitation of neurite growth.

Clinically, the neuroprotective abilities of estrogen appear to be important in decreasing the severity of Alzheimer’s disease and other CNS degenerative diseases. Hormone replacement therapy in Alzheimer’s disease is associated with less severe symptoms of dementia (higher test scores on neuropsychologic exams, even if the treatment is started after the disease has been diagnosed (Fillit et al 1986; Henderson et al 1994; Honjo et al 1989; Robinson et al 1994; Tang et al 1996). A more extensive discussion of estrogen action and neuroprotection can be reviewed in a recent publication (McEwen and Alves 1999). Nonetheless, it also must be understood that estrogen’s beneficial effects are controversial because a recent study has contradicted previous findings showing no significant benefit in Alzheimer’s patients with estrogen treatment (Mulnard et al 2000).

**Estrogen and gp120**

The protective effects of estrogen also extend to decreasing gp120-induced neurotoxicity and calcium mobilization (Figure 5; Brooke et al 1997). Preliminary data regarding the interaction of gp120 and estrogen on cell lipid peroxidation would indicate that perhaps the estrogen protection in this case is via its antioxidant properties.

There are no animal studies in which estrogen protection against gp120 has been examined. Likewise there is little literature regarding to estrogen and AIDS. One clinical study (Clark and Bessinger 1997) reported that among postmenopausal women with AIDS, estrogen replacement therapy was associated with a decreased risk of dementia (although there are multiple confounds in this study, and the data must be interpreted cautiously). The authors suggested that hormone replacement therapy be considered for HIV-infected postmenopausal women. These results closely parallel the results, as previously described, in which estrogen decreases severity of Alzheimer’s symptoms.

**Conclusions and Future Direction**

We have summarized in this article significant data obtained from rats and mice both in vivo and in vitro showing that GCs can worsen the deleterious effects of...
gp120, a possible causative agent of ADC. Although human and clinical implications of this data are not known, we would hope that those working with HIV patients would press for further studies to determine if the implications of this data are a possible factor in the development of AIDS-related dementia. Although the immediate CNS effect of large doses of GC may not be evident, the long-term neurologic effect on these patients could be detrimental.

Certainly more study is needed to confirm these results with other forms of gp120, with the transgenic mice that overexpress gp120 and ultimately in primates. It would also be informative if some human studies followed that would show whether or not high cortisol levels or the use of artificial GCs effect the onset and course of ADC.

On the other hand, estrogen’s apparent neuroprotective abilities are encouraging. It would also be useful if in vivo studies could be carried out with estrogen. Only if the animal results continue to be positive should human studies looking at the possibilities of protecting or reversing ADC with estrogen treatment be explored.

With new treatments, AIDS patients are living longer, and they no doubt hope to maintain normal cognitive function. Therefore, the potential for neurologic difficulties arising as a result of treatment with GCs and the potential benefits of estrogen should be taken into consideration.

References


gp120 causes ultrastructural changes typical of apoptosis in the rat cerebral cortex. *Neuroreport* 7:1722–1724.


Meucci O, Miller RJ (1996): gp120-induced neurotoxicity in...


apoptosis by calmodulin-dependent intracellular Ca\(^{2+}\) elevation in CD4\(^+\) cells expressing gp160 of HIV. *Virology* 224:18–24.


