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Trypanosoma cruzi: The effects of dehydroepiandrosterone (DHEA) treatment during experimental infection

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Abstract

The aim of this study was to evaluate the efficacy of the immunomodulator dehydroepiandrosterone (DHEA) in the treatment of *Trypanosoma cruzi* infection and the possible biochemistry alterations in male and female Wistar rats. DHEA also known as the steroid of multiple actions has attracted distinct medical areas. Prior studies show that DHEA enhances immune responses against a wide range of viral, bacterial and parasitic pathogens. Furthermore, administration of DHEA seems to protect animals against obesity and diabetes. Male animals subcutaneous treated with 40 mg/kg body weight/day of DHEA displayed a significant reduction in blood parasites during parasitaemia peak, when compared to untreated animals ($P < 0.001$). For female group parasitaemia was also reduced although values are not statistically significant ($P > 0.05$). Sexual dimorphism was also observed, since females displayed lesser parasitaemia levels compared to males group treated ($P > 0.05$) and untreated ($P < 0.001$). Enhanced leucocytes number was observed in control females when compared to control males ($P < 0.05$). DHEA treatment did not triggered any significant alterations in leucocytes levels ($P > 0.05$). DHEA administration induced an enhanced number of macrophages in infected male ($P < 0.01$). DHEA administration causes a decrease in glucose ($P < 0.001$). Cholesterol and tryglicerides levels did not display results statistically significant ($P > 0.05$) during the treatment. These results suggest that DHEA treatment enhances the immune response as evidenced here by reduced levels of parasites. Up-regulation of the immune system by exogenous DHEA may be useful in the treatment of American tripanosomiasis.

Keywords: Dehydroepiandrosterone; *Trypanosoma cruzi*; Glucose; Peritoneal macrophages; Parasitemia; Leucocytes

1. Introduction

Chagas' disease is endemic in Latin America, affecting 16–18 million people, with more than 100 million exposed to the risk of infection (WHO, 1991).

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American trypanosomiasis is a protozoan infection caused by *Trypanosoma cruzi* and is one of the most important public health problems in Latin America.

Gender and the corresponding sex steroids have shown several effects on immune response in a wide range of different species including humans, rodents and birds (Schuurs and Verheul, 1990). A bulk of evidence shows that sexual dimorphism plays an important role in the modulation of the immune response when hosts are exposed to distinct etiological agents. This means that a bi-directional relationship between endocrine and the immune system exists, in order to maintain homeostasis (Syrt and Sugarman, 1991; Prado et al., 1998, 1999). Women are more efficient in clearing peripheral parasitaemia these facts are probably linked to sexual dimorphism and steroid hormones (Brabin and Brabin, 1992).

Estrogens exert a positive action on B cell proliferation, leading to enhanced immunoglobulin production. For this reason, women evade the pathological actions of a wide range of etiological agents more rapidly. Some of them produce severe illnesses in women such as *Toxoplasma gondii* and *Trichomonas vaginalis* (Roberts et al., 2001).

DHEA is one of the steroid hormones produced by the adrenal cortex. DHEA sulphatase (DHEA-S) plays an important role in converting most all DHEA in DHEA sulphate (DHEAS), the latter form being one of the most common substances found in the circulation (Parker, 1995). Just before birth and again at puberty, DHEA starts to be produced in elevated concentrations, reaching its peak at around 20–30 years of age, followed by a progressive decline (Baulieu, 1996). DHEAS is also implicated in age-related changes in the immune system (Loria et al., 1988) and has been associated with disease susceptibility (Shealy, 1995). Currently, DHEA is one of numerous immunomodulators undergoing clinical evaluation as a potential treatment of human immunodeficiency virus infection (Christeff et al., 1999; Lee et al., 1999). DHEA has been shown to protect mice from a variety of normally lethal infections. This includes protection against infection with bacteria (Ben-Nathan et al., 1999), and with parasites like *Cryptosporidium parvum* (Rasmussen et al., 1993, 1995), *Plasmodium falciparum* (Kurtis et al., 2001; Leenstra et al., 2003) and *Schistosoma mansoni* (Fallon et al., 1998; Morales-Montor et al., 2001).

DHEAS is a potent immune-activator modulating both T and B cell functions (Yang et al., 1998) and is responsible for augmenting antibody titers (Degelau et al., 1997). DHEAS also acts as a powerful down-modulator of the pro-inflammatory cytokines tumor necrosis factor-α, interleukin-6, and interleukin-1 (Danenberg et al., 1992; James et al., 1997), thus attenuating their deleterious consequences.

A variety of biological activities of DHEA have been reported and include a decrease of total body weight (Aoki et al., 2004), an anti-diabetic effect with reduction of blood glucose tolerance (Coleman et al., 1982), and inhibition of lipid synthesis (Ben-David et al., 1967; Sonka et al., 1968; Kritchevsky et al., 1983). High DHEA or DHEAS levels have been suggested to be protective for cardiovascular disease (Khaw, 1996). DHEA supplementation is reported to lower levels of low-density cholesterol in humans (Nestler et al., 1992).

To evaluate the response of male and female Wistar rats infected with the Y strain of *T. cruzi* treated with dehydroepiandrosterone we focus our analyses on its influences on parasitaemia, leucocytes, peritoneal macrophages, body weight and biochemical parameters such glucose, cholesterol and trygliceride levels.

2. Materials and methods

2.1. Animals and diet

Male ($n = 45$) and female ($n = 45$) Wistar rats weighing 90–100 g were used. Animals were divided in groups: Male: Non-Infected Males-Without-DHEA treatment (MWDNI), Non-Infected Males-DHEA treated (MDNI), Infected Males-Without-DHEA treatment (MWDI), Infected Males-DHEA treated (MDI). Female: Non-Infected Females-Without-DHEA treatment (FWDNI), Non-Infected Females-DHEA treated (FDNI), Infected Females-Without-DHEA treatment (FWDI), Infected Females-DHEA treated (FDI). Rats were separated in number of 5 in plastic cages and commercial rodent diet and water were available ad libitum. Twelve hours before the experiment, animals were placed under dietary restriction and were given access to water only so as to minimize feeding-related variations in the biochemical parameters we measured.