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Review

Levels and actions of neuroactive steroids in the nervous system under physiological and pathological conditions: Sex-specific features

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ABSTRACT

Neuroactive steroids regulate the physiology of the central and peripheral nervous system, exert neuroprotective actions and represent interesting tools for therapeutic strategies against neurodegenerative and psychiatric disorders. Sex differences in their levels are detected not only under physiological conditions but are also modified in a sex-dependent way in different pathological alterations such as Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, traumatic brain injury, spinal cord injury, stroke, diabetic encephalopathy, psychiatric disorders and peripheral neuropathy. Interestingly, many of these disorders show sex differences in their incidence, symptomatology and/or neurodegenerative outcome. The neuroprotective actions of neuroactive steroids, together with the sex specific regulation of its levels might provide the basis to design sex-specific neuroprotective therapies. Indeed, some experiments here discussed suggest the viability of this approach.

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1. Introduction

Neuroactive steroids were originally defined as natural or synthetic steroids with rapid effects on neuronal membrane excitability (Paul and Purdy, 1992). However, steroids that have rapid effects on neuronal membrane excitability may have also long term transcriptional actions on neurons and may affect the function of other cell types in the brain, including astrocytes, oligodendrocytes, microglia and endothelial cells. Therefore, the concept of neuroactive steroid has now enlarged to include all steroids that affect the function of the nervous system. Neuroactive steroids include molecules that are synthesized in the central (CNS) and peripheral nervous system (PNS) by neurons and glial cells (i.e., neurosteroids), molecules synthesized in peripheral glands, such as the testis, the ovary and the adrenal glands (i.e., steroid hormones) and synthetic molecules (Melcangi et al., 2008).

Neuroactive steroids are important physiological regulators of neural function. In addition, some neuroactive steroids exert neuroprotective actions and its levels are altered by pathological events in the nervous system, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), traumatic brain injury (TBI), spinal cord injury, stroke, diabetic encephalopathy, psychiatric disorders and peripheral neuropathy. These disorders of the nervous system show sex differences in their incidence, symptomatology and/or neurodegenerative outcome. Interestingly, the levels of neuroactive steroids show sex-differences under physiological conditions and sex also influences the changes in neuroactive steroid levels under pathological conditions. These observations, which will be reviewed here, suggest that neuroactive steroids may represent candidate molecules for a gender oriented treatment of nervous system alterations.

2. Sex difference in neural pathology

2.1. Alzheimer's disease

Epidemiological studies support a higher prevalence and incidence of AD in women (Andersen et al., 1999; Fratiglioni et al., 1997). In addition, the concentration of glutatione (GSH) (i.e., the most abundant intracellular free thiol and an important antioxidant) present in red blood cells is decreased only in male and not in female AD patients; this decrease is associated with a reduced activity of the enzyme responsible of *de novo* GSH synthesis (i.e., glutamate cysteine ligase and glutathione synthase) (Liu et al., 2005).

Regarding oxidative stress, at variance to what is observed in young males and in old females, mitochondria obtained from the brain of young females are protected against the increase in peroxide production caused by beta-amyloid (Lloret et al., 2008). It has also been reported that sex influences beta-amyloid plaque distribution in the temporal cortex (Kraszpulski et al., 2001). A similar sex difference has been detected in different amyloid precursor protein transgenic animal models (Callahan et al., 2001; Lewis et al., 2001).

Analysis of visuospatial episodic memory in AD patients also shows sex differences, with a better performance in men than in women (Beinhoff et al., 2008). Also, in a mouse triple transgenic AD model (3xTg-AD), in which animals show progressive cognitive decline (Blanchard et al., 2003), female animals perform worse than males at 6 months of age (Clinton et al., 2007).

2.2. Parkinson's disease

The incidence of PD is greater in men than in women (Benito-Leon et al., 2003; de Lau et al., 2004; Van Den Eeden et al., 2003; Wooten et al., 2004). Course and symptoms as well as pharmacological treatment show also sex differences (Fernandez et al., 2000; Haaxma et al., 2007; Homann et al., 2003; Martinelli et al., 2003; Zappia et al., 2005). For instance, women tend to be older than men at symptom onset and have more a tremor dominant form of disease, which in turn is associated with a slower disease progression (Haaxma et al., 2007). Data obtained in animal models also indicate sex differences in term of dopamine levels (i.e., male animals show higher depletion than females) and in the pattern of proinflammatory molecules (Czlonkowska et al., 2006).

2.3. Huntington's disease

Epidemiological studies of HD indicate that the age of onset is higher in women and that the course of disease is more moderate in men (Foroud et al., 1999; Pekmezovic et al., 2007; Roos et al., 1991). In an experimental model of the pathology (i.e., knock-in mouse model with 140 CAG repeat) females spend more time in the open-field grooming and more time running during the diurnal dark phase than males (Dorner et al., 2007). In another experimental model (i.e., transgenic HD rats carrying a truncated huntingtin cDNA fragment with 51 CAG repeats under the control of the native rat huntingtin promoter), males showed an impairment of motor function that was associated with the loss and atrophy of neurons expressing dopamine and cAMP-regulated phosphoprotein of 32 kDa and with a decrease in the expression of D1 dopamine