Steroids, sex and the cerebellar cortex: implications for human disease

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Abstract

Neurosteroids play an important role in the development of the cerebellum. In particular, estradiol and progesterone appear capable of inducing increases in dendritic spine density during development, and there is evidence that both are synthesized \textit{de novo} in the cerebellum during critical developmental periods. In normal neonates and adults, there are few differences in the cerebellum between the sexes and most studies indicate that hormone and receptor levels also do not differ significantly during development. However, the sexes do differ significantly in risk of neuropsychological diseases associated with cerebellar pathology, and in animal models there are noticeable sex differences in the response to insult and genetic mutation. In both humans and animals, males tend to fare worse. Boys are more at risk for autism and Attention Deficit Hyperactivity Disorder than girls, and schizophrenia manifests at an earlier age in men. In rats males fare worse than females after perinatal exposure to polychlorinated biphenyls, and male mice heterozygous for the \textit{staggerer} and \textit{reeler} mutation show a more severe phenotype. Although very recent evidence suggests that differences in neurosteroid levels between the sexes in diseased animals may play a role in generating different disease phenotypes, the reason this hormonal difference occurs in diseased but not normal animals is currently unknown.

Key words: Neurosteroids, cerebellum, neuropsychological diseases, gender

Introduction

The cerebellum is importantly involved in sensory perception and discrimination in addition to its well known role in motor coordination (1). The visual, auditory, and somatosensory cortices project to the cerebellum via the pontine nuclei, and association cortices project to it via the superior colliculus. It has been proposed that the cerebellum may be responsible for sensory modulation and the integration of multisensory information. Additionally, the cerebellum’s bidirectional connection with the limbic lobe, amygdala, septal nuclei, thalamus and hypothalamus all point to a role for the cerebellum in emotional processing, also suggested by the blunting of emotional affect observed following lesions to the cerebellar vermis (2). The cortico-thalamic-cerebellar-cortical circuit may coordinate the ‘fluid execution of cortical activity’, suggesting a role in more cognitive tasks (3). Moreover, functional magnetic resonance imaging (fMRI) studies have demonstrated cerebellar activity during attentional tasks in humans, and that cerebellar activation during such tasks differs between healthy controls and autistic patients (4). Animal studies have revealed deficits in working memory in animals with cerebellar lesion (5). Taken together, these findings demonstrate that it is no longer accurate to think of the cerebellum as simply a motor control center, and make less surprising the frequent finding that cerebellar pathology is often associated with complex neuropsychological diseases.

The cerebellum: A sexually dimorphic area?

Structurally, the cerebellum has traditionally been considered to be a fairly monomorphic structure with few reliable sex differences. Some magnetic resonance imaging (MRI) studies have found that in humans the cerebellum is larger in adult men than women even when controlling for height; in the hemispheres and anterior vermis the effect size of gender is large and in the posterior vermis it is moderate (6). In children and adolescents MRI reveals an 8% difference in cerebellar volume, with the cerebella of males being larger even when controlling for height and weight (7). In juvenile rats, we have found a trend towards increased volume in lobule seven of the posterior vermis in males versus females (Figure 1). However, in other
cases MRI (8) and examination of fixed human tissue (9) have failed to find volumetric differences in the cerebella of women and men, and men and women have an equal number of Purkinje cells (10). Some differences in glial structure may exist. In hamsters, glial fibrillary acidic protein (GFAP) staining is more intense in males, whereas vimentin staining in the Bergman glia is more intense in

Figure 1. (A) Volume of vermian lobule seven in females and males, males exhibited a statistical trend toward slightly greater volume (t-test, $p<0.06, n=5$). (B) Photomicrograph of a coronal section the cerebellar vermis at low magnification, with lobule seven circled in red.