Effects of Hormones and Sex Chromosomes on Stress-Influenced Regions of the Developing Pediatric Brain

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ABSTRACT: Recently discovered sexual dimorphism within developing brain structures such as the amygdala and hippocampus suggests that biological factors may account for many of the sex differences in stress reactivity. In this study, we have relied on studies of naturally occurring anomalous processes, such as congenital adrenal hyperplasia (CAH) and Klinefelter's syndrome (XXY), to observe the effects of hormones and sex chromosomes on brain structures thought to influence an individual's vulnerability to stress. Brain magnetic resonance imaging (MRI) scans were obtained both from 16 boys with classic CAH and 34 age- and sex-matched controls and from 20 XXY children and 40 age-matched controls. Smaller amygdala volumes were observed in boys with CAH than in matched controls, and in XXY patients than in matched controls. XXY patients were also found to have smaller hippocampus volumes when compared with matched controls. Acknowledging that hormone and sex chromosome effects upon the developing human brain are widespread and complex, it is difficult to conclude, with any certainty, the etiology of the differences found in this study. Future studies that examine longitudinal data and/or other diagnostic groups, however, may help to better elucidate specific hormone and sex chromosome effects upon stress-related structures in the brain.

KEYWORDS: hormones; sex chromosomes; stress; pediatric brain

INTRODUCTION

Males and females have often been shown to react differently to the same environment, but how much of that difference is attributable to environmental versus biological factors is a matter of debate. Recently discovered sexual dimorphism within developing brain structures such as the amygdala and hippocampus (both structures known to have many androgen and glucocorticoid receptors) suggests that

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Ann. N.Y. Acad. Sci. 1032: 231–233 (2004).
doi: 10.1196/annals.1314.027

biological factors may account for many of the sex differences in stress reactivity.[1] From a purely biological perspective, sex differences in the brain are likely due to the effects of sex chromosomes and/or hormones. We have relied on studies of naturally occurring anomalous processes, such as congenital adrenal hyperplasia (CAH)[2] and Klinefelter's Syndrome (XXY), to observe the effects of hormones and sex chromosomes on brain structures thought to influence an individual's vulnerability to stress.

MATERIAL AND METHODS

Subjects. Brain magnetic resonance imaging (MRI) scans were obtained both from 16 boys with classic CAH (mean age 10.5 ± 2.9 years) and 34 age- and sex-matched controls and from 20 XXY children (mean age 15.1 ± 4.6 years) and 40 age-matched controls.

Scan Acquisition. All subjects were scanned on the same GE 1.5 Tesla Signa scanner using the same three-dimensional spoiled gradient recalled echo in the steady state (3D SPGR) imaging protocol (axial slice thickness 1.5 mm, time to echo 5 ms, repetition time 24 ms, flip angle 45 degrees, acquisition matrix 192 × 256, number of excitations 1, and field of view 24 cm). A clinical neuroradiologist evaluated all scans and no gross abnormalities were reported.

Image Analysis. Measures of the hippocampus and the amygdala (right, left, and total) were obtained by manual tracing in the coronal plane by a single experienced rater who was blind to subject characteristics. One of the authors (J.D.F.) rated all CAH subjects and matched controls, whereas another (A.C.V.) rated all XXY subjects and matched controls.

Because the boundary between the hippocampus and the amygdala is difficult to delineate (even at a histological level), the slice containing the most anterior portions of the mamillary bodies was used as the boundary to separate the two structures.[3]

RESULTS

Smaller volumes in both total amygdala ($P = 0.01$) and left amygdala ($P = 0.003$) were observed in boys with CAH compared with age- and sex-matched controls.

Smaller volumes in total amygdala ($P = 0.03$), left amygdala ($P = 0.02$), total hippocampus ($P = 0.01$), left hippocampus ($P = 0.01$), and right hippocampus ($P = 0.04$) were observed in XXY patients compared with age- and sex-matched controls.

DISCUSSION

Acknowledging that hormone and sex chromosome effects upon the developing human brain are widespread and complex, it is difficult to say with any certainty why, in this study, CAH patients had smaller amygdala volumes than did matched controls, and XXY patients had smaller amygdala and hippocampus volumes than did matched controls. It is possible that the large amount of syndrome-related environmental stress that CAH and XXY patients experience may explain these findings

in part. Future studies that examine longitudinal data and/or other diagnostic groups may help to better assess specific hormone and sex chromosome effects upon stress-related structures in the brain.

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