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Genetic, hormonal, and metabolomic influences on social behavior and sex preference of XXY mice

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Abstract

XXY men (Klinefelter syndrome) are testosterone deficient, socially isolated, exhibit impaired gender identity, and may experience more homosexual behaviors. Here, we characterize social behaviors in a validated XXY mouse model to understand mechanisms. Sociability and gender preference were assessed by three-chambered choice tasks before and after castration and after testosterone replacement. Metabolomic activities of brain and blood were quantified through fractional synthesis rates of palmitate and ribose (GC-MS). XXY mice exhibit greater sociability than XY littermates, particularly for male mice. The differences in sociability disappear after matching androgen exposure. Intact XXY, compared with XY, mice prefer male mice odors when the alternatives are ovariectomized female mice odors, but they prefer estrous over male mice odors, suggesting that preference for male mice may be due to social, not sexual, cues. Castration followed by testosterone treatment essentially remove these preferences. Fractional synthesis rates of palmitate are higher in the hypothalamus, amygdala, and hippocampus of XXY compared with XY mice but not with ribose in these brain regions or palmitate in blood. Androgen ablation in XY mice increases fractional synthesis rates of fatty acids in the brain to levels indistinguishable from those in XXY mice. We conclude that intact XXY mice exhibit increased sociability, differences in gender preference for mice and their odors are due to social rather than sexual cues and, these differences are mostly related to androgen deficiency rather than genetics. Specific metabolic changes in brain lipids, which are also regulated by androgens, are observed in brain regions that are involved in these behaviors.

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