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Relation among HPA and HPG neuroendocrine systems, transmissible risk and neighborhood quality on development of substance use disorder: Results of a 10-year prospective study☆

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ABSTRACT

Background: Research has shown involvement of hormones of the hypothalamic pituitary adrenal (HPA) axis and hypothalamic pituitary gonadal (HPG) axis in the regulation of behaviors that contribute to SUD risk and its intergenerational transmission. Neighborhood environment has also been shown to relate to hormones of these two neuroendocrine systems and behaviors associated with SUD liability. Accordingly, it was hypothesized that (1) parental SUD severity and neighborhood quality correlate with activity of the HPG axis (testosterone level) and HPA axis (cortisol stability), and (2) transmissible risk during childhood mediates these hormone variables on development of SUD measured in adulthood.
Methods: Transmissible risk for SUD measured by the transmissible liability index (TLI; Vanyukov et al., 2009) along with saliva cortisol and plasma testosterone were prospectively measured in boys at ages 10–12 and 16. Neighborhood quality was measured using a composite score encompassing indicators of residential instability and economic disadvantage. SUD was assessed at age 22.
Results: Neither hormone variable cross-sectionally correlated with transmissible risk measured at ages 10–12 and 16. However, the TLI at age 10–12 predicted testosterone level and cortisol stability at age 16. Moreover, testosterone level, correlated with cortisol stability at age 16, predicted SUD at age 22.
Conclusion: HPA and HPG axes activity do not underlie variation in TLI, however, high transmissible risk in childhood predicts neuroendocrine system activity presaging development of SUD.

1. Introduction

Up to 100% of genetic variance and 80% of phenotypic variance are congenerous to the risk for developing all categories of substance use disorder (SUD; Kendler et al., 2003; Tsuang et al., 1998; Vanyukov et al., 2003b). Whereas SUD risk is phenotypically and genetically correlated with disinhibitory and externalizing behavior in childhood (Elkins et al., 2007; Fu et al., 2002; Grove et al., 1990; Krueger et al., 2002; Iacono et al., 2008), many additional psychological characteristics are also related to risk for SUD (Bechara, 2005; Elkins et al., 2006; Giancola et al., 1996; Spear, 2000) of which a subset are indicators of a continuous latent trait representing the component of SUD liability that is transmissible across generations (Vanyukov et al., 2003a,b, 2009). Termed the transmissible liability index (TLI), the score on this trait is highly heritable (Hicks et al., 2012; Vanyukov et al., 2009) and predicts all SUD categories in adults (Ridenour et al., 2011) as well as SUD outcome between childhood and adulthood (Kirisci et al., 2009). Notably, the interval between first cannabis experience and cannabis use disorder diagnosis negatively covaries with severity of transmissible risk. Not only is the TLI superior to parental SUD as a predictor of SUD in offspring (Ridenour et al., 2011) it bypasses the need for intrusive questioning in children about substance use and its adverse consequences in their parents. To date, five age-specific computer adaptive versions of the TLI have been validated for children, adolescents and young adults using the Web platform (Kirisci et al., 2012) thereby enabling quantitative measurement of this component of SUD risk in less than 10 min.

The biological mechanisms underlying variation in transmissible risk remain, however, to be elucidated. One fruitful line of research pertains to neuroendocrine mechanisms based on findings that cortisol level regulated by the HPA axis is related to behaviors

☆ Supplementary material can be found by accessing the online version of this paper. Please see Appendix A.

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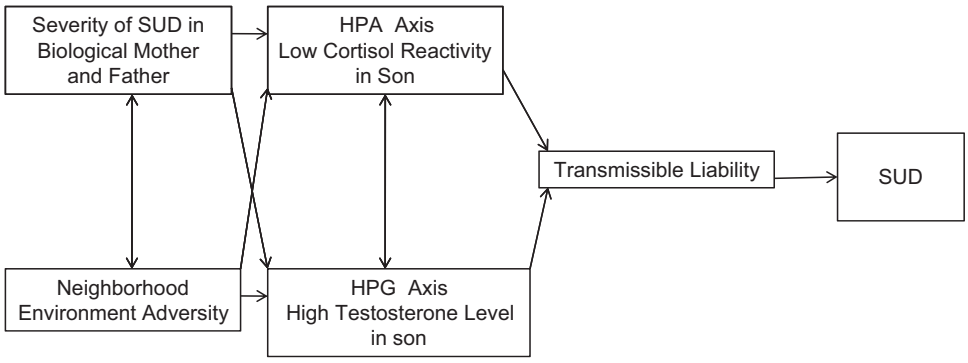

Fig. 1. Theoretical model guiding this investigation.

that are widely recognized to amplify risk for SUD. Negative results obtained in one study notwithstanding (Sondeijker et al., 2007), the evidence accrued to date points to an association between attenuated cortisol level and externalizing disorder in youths (Fairchild et al., 2008; Kobak et al., 2009; McBurnett et al., 2000; Moss et al., 1995; Shoal et al., 2003; Snock et al., 2004; Van Goozen, 2005; Virkkunen, 1985). Moreover, aggressive behavior, the most ubiquitous feature of externalizing disorder, is also associated with attenuated cortisol level in boys whose fathers have early age onset SUD (Vanyukov et al., 1993); this SUD variant has high genetic loading evinced at a young age by disinhibited and antisocial behavior (Cloninger et al., 1981). Notably, frequency of marijuana consumption during adolescence also covaries negatively with cortisol level (Huizink et al., 2006; Moss et al., 1999). In view of these results showing that externalizing behavior is a salient characteristic of transmissible risk for SUD and marijuana use is related to low cortisol level, it is hypothesized that HPA axis activity is among the mechanisms underlying variation in severity of transmissible risk.

Cortisol production, however, correlates negatively with testosterone level (Blanchard et al., 1993; Plymate et al., 1989). Research into SUD etiology has to date not taken into account this synergy between the HPA and HPG neuroendocrine systems (Viau, 2002) even though psychological characteristics frequently reported to be associated with SUD risk (e.g., impulsivity, aggressiveness, fearlessness) are similarly manifest by individuals having low cortisol and high testosterone concentration (see Terberg et al., 2009 for review). Whereas not all studies have reported an association between testosterone level and aggressivity (Constantino et al., 1993), research conducted on a subset of the present sample has shown that disruptive behavior in childhood mediates the association between testosterone level and SUD in adulthood (Reynolds et al., 2007). Furthermore, social dominance striving in concert with indifference to societal norms in mid-adolescence mediates the association between testosterone level in early adolescence and SUD in adulthood (Tarter et al., 2009). Moreover, elevated testosterone concentration has been reported in aggressive youths (Scerbo and Kolko, 1994) and men qualifying for Type 2 (antisocial) alcoholism (Dabbs et al., 1995). Indeed, it has been shown that testosterone level mediates the relation between SUD in parents and sensation seeking motivation in their adolescent sons (Kirillova et al., 2001). Importantly, parental SUD load (number of affected parents) is related to sexual maturation rate in boys that in turn predicts deviant peer affiliations, disruptive behavior disorders and subsequently SUD (Kirillova et al., 2008). Accordingly, the hypothesis is advanced that high testosterone concentration also underlies transmissible risk for SUD.

Regulation of the HPA axis (Bartels et al., 2003) and puberty onset (Silventoinen et al., 2008) are significantly heritable. Socioeconomic disadvantage is also related to HPA (Evans and English, 2002; Lupie et al., 2001) and HPG axis activity (Schaal et al., 1996; Tarter et al., 2009) as well as risk for SUD (Compton et al., 2007; Lopez-Quintero et al., 2011). Notably, genetic factors account for most variance on the TLI presaging SUD (Hicks et al., 2012; Vanyukov et al., 2009), and severe scores on this index cluster among youths domiciling in disadvantaged neighborhoods (Ridenour et al., submitted for publication). Accordingly, as shown in Fig. 1, the theoretical model guiding this investigation, it was hypothesized that parental SUD correlated with neighborhood quality predicts hypothalamic pituitary adrenal (HPA) axis and hypothalamic pituitary gonadal (HPG) axis activity in children underlying transmissible risk predisposing to SUD.

2. Methods

2.1. Participants

The sample was comprised of boys enrolled in the Center for Education and Drug Abuse Research (CEDAR), a longitudinal family/high-risk study of SUD etiology (Tarter and Vanyukov, 2001). The boys ($N = 451$) were ascertained at age 10–12 through proband fathers who either qualified for a DSM-III-R lifetime diagnosis of SUD concomitant to consumption of illegal drugs or had no axis 1 psychiatric disorder. DSM-III-R criteria were utilized because this longitudinal investigation was initiated before publication of the DSM-IV. Boys who completed the baseline study were tracked for follow-up study when they attained 16 and 22 years of age. Current SUD diagnoses were determined at age 22. The presence of any of the following characteristics disqualified potential subjects from participation: (i) WISC-III-R IQ below 80, (ii) inability to comprehend English, (iii) medical history of neurological injury requiring hospitalization, (iv) chronic life threatening medical illness, and (v) psychosis. From the baseline sample ($N = 451$), 138 participants either refused to participate or could not be located for the outcome evaluation at age 22. Thirty-seven subjects had not yet attained age 22 and thus were not included in the analyses. Accordingly, the analyses were conducted on 276 subjects (451 baseline minus 138 attrition minus 37 not old enough to participate).

Several methods were employed to accrue the sample. Public service announcements in the electronic media, random telephone calls, posters, and a market research firm were the primary methods used to identify potential participants in metropolitan Pittsburgh. Approximately 25% of the sample had fathers who recently completed treatment for SUD. It is noteworthy that this sample of youths is not atypical. Cannabis, the most frequently consumed illegal drug, had a lifetime prevalence of 34.4% in this sample at age 16 compared to 34.5% of tenth grade students in the 2011 Monitoring the Future survey (Johnston et al., 2012).

Table 1 presents the characteristics of the sample at baseline. As can be seen, grade in school, neighborhood quality, severity of transmissible liability index (TLI), severity of SUD in parents, ethnicity, and the neuroendocrine variables are not different between the retained and attrited segments of the sample. Full scale IQ is lower in the subjects who attrited ($F = 18.91$, $p < .05$); however, intelligence level of both retained and attrited subjects is in the normal range.

A test of equivalence (Rowe, 2007) of retained and attrited subjects was also conducted to evaluate attrition. To demonstrate equivalence, we computed the probability of containing the whole of the 95% confidence interval of difference between two groups within the limits of the "equivalence zone." The equivalence zone reveals how much the variable needs to change before there is a realistic possibility of practical consequences. In this study, we set limits of the equivalence zone to $\pm 1/3\ \sigma$ for the variables. The results, shown in Table 1, indicate that there is no