

Commentary: Cortisol Levels and Conduct Disorder in Adolescent Mothers

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The study by Azar et al. (2004) in this issue investigates the function of the hypothalamic-pituitary-adrenal (HPA) axis in adolescent antisocial girls. This question is important because disturbance of HPA functioning has been found in populations of violent adult males and antisocial adolescent males, suggesting that it may be a marker of a physiological disorder associated with antisocial behavior. The investigators examined 228 pregnant or postpartum teenage girls, categorizing them as having conduct disorder (CD) or not having conduct disorder (NCD). HPA axis function was assessed with saliva cortisol samples obtained in the mid-morning when the girls were 4 and 9 months postpartum. The hypothesis was that girls with CD would have lower cortisol levels than girls without CD. The investigators did not find any significant difference in cortisol levels between the two groups, an important but puzzling finding. Azar et al. suggested that this result may demonstrate a lack of clear HPA axis involvement in antisocial mothers.

Azar and Colleagues' Finding and Previous Research

As Azar et al. noted, their result is at variance with the findings from previous studies of HPA axis function in antisocial girls (Pajer et al., 2001a, b; Susman et al., 1999) and the majority of findings in antisocial males (McBurnett et al., 1991, 1996, 2000; Moss et al., 1995; van Goozen et al., 1998; Vanyukov et al., 1993;

Virkkunen, 1985; Woodman et al., 1978). They offered three possible explanations. First, they stated that they may have found no difference in cortisol levels because their antisocial and non-antisocial groups were better matched than those in previous studies on the basis of socioeconomic status (SES), exposure to adverse events, and psychiatric comorbidity. This, they believe, would imply that a low morning cortisol level is not a biological correlate specific to antisociality in females, but rather is a correlate for low SES, exposure to adverse life events, other psychiatric disorders, or all three. The other two possible explanations for their failure to find a difference in HPA functioning between their antisocial and non-antisocial girls may depend on (1) the methodology used to measure HPA functioning or (2) on the population of girls that was sampled. We will comment on each of these three explanations.

Matching on Socioeconomic Status, Adverse Life Events, and Other Psychiatric Disorders

Azar et al. believe that their CD and NCD groups were better matched than those in previous studies on several factors that could be alternative explanations for the differences in HPA functioning seen in previous research. However, whether their CD and NCD groups were actually more closely matched is uncertain. Their participants were mostly of low SES, and because they were adolescent mothers many had doubtless experienced adverse life events. The authors did control statistically for depression and substance abuse in the data analysis, but they apparently did not use any matching procedure to equate their CD and NCD groups, nor did they report statistical controls for possible differences in SES or adverse life events between CD and NCD girls. We therefore are not persuaded that the fact that Azar and colleagues' subjects were adolescent mothers implies that the CD and

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NCD groups were necessarily comparable on these factors.

Pajer and colleagues' (2001a) CD and NCD groups were matched or statistically controlled on race, SES, and substance use. Some of these CD girls had comorbid psychiatric disorders, the most common being oppositional defiant disorder (43%) and substance abuse or dependence (36%). None of the NCD girls had any psychiatric disorder. However, statistical controls for comorbid disorders, including posttraumatic stress disorder, did not account for the CD versus NCD difference in cortisol levels in the Pajer et al. study.

In summary, Azar et al. raise a crucial question about what factors explain observed differences in HPA function associated with adolescent female CD. However, we do not believe that either the Azar et al. study or ours involved matching of CD and NCD girls that was sufficiently rigorous to fully clarify the relative importance of CD and these other factors.

Methodology of HPA Axis Assessment

Cortisol has a pronounced diurnal rhythm. In all of the previous studies on antisocial girls, cortisol was measured as close as possible to the expected time of peak secretion (8–9 A.M.) (Pajer et al., 2001a, b; Susman et al., 1999). Susman et al. also measured corticotrophin releasing hormone (CRH) during the morning peak. The findings from these studies were consistent: antisocial behavior was associated with lower HPA axis activity at this time, although in the study by Susman et al. (1999), CRH levels were correlated negatively with the number of antisocial symptoms, whereas overall total plasma cortisol levels were not. It is likely that this was because those girls were pregnant (see below). Azar et al. did not measure cortisol levels during the expected peak, but later in the morning, a time in the diurnal cycle when levels are declining. There is high interindividual variability in saliva cortisol and, of course, intraindividual variability during this time phase, because the levels are declining. This variability may make it more difficult to find differences between groups.

There is no "right" time when cortisol should be measured, because the entire cycle is of interest. Moreover, the differences in cortisol secretion between CD and NCD girls may be more complex than a shift up or down of the diurnal curve: it may be that the shapes of these curves differ in important ways. If so, the

absence of differences at midmorning (as Azar et al. found) would not be inconsistent with an attenuation of the early-morning peak.

Another difference between the Azar et al. study and some of the previous work on antisocial girls is that Azar et al. used salivary cortisol, while Pajer et al. (2001a) and Susman et al. (1999) used plasma cortisol. Total plasma cortisol includes protein-bound (cortisol binding globulin [CBG] and albumin) and free cortisol, while salivary cortisol, being an ultrafiltrate of plasma, includes only free cortisol. Anything that affects the concentration of CBG (e.g., pregnancy dramatically increases it, with great interindividual variability) or albumin (e.g., malnutrition decreases it) will increase or decrease total cortisol levels (Demey-Ponsart et al., 1982; Dhillon et al., 2002; Vining et al., 1983). Pregnancy-induced CBG levels may be why there was no significant correlation between plasma cortisol levels and antisocial behavior in the pregnant girls studied by Susman et al. This negative finding was at odds with their data demonstrating a significant negative correlation between CRH levels and the number of antisocial symptoms, a finding that supports a theory of hypoactive HPA axis function in antisocial females.

A consequence of measuring plasma cortisol in the Pajer et al. study was that it was impossible to determine whether the CD girls had lower cortisol levels than the NCD girls because one of the groups had altered CBG levels. To test this, we conducted another investigation of girls exhibiting antisocial behavior and used peak morning salivary cortisol instead (Pajer et al., 2001b). The two were significantly negatively correlated, thus confirming our earlier findings and ruling out that these results were due to differing CBG levels.

Sample Selection

There are two aspects of sample selection and assessment methods in the study by Azar et al. that may have differed significantly from those of Pajer et al. (2001a) and may have affected the results. First, Azar et al. studied adolescent mothers, and second, Pajer et al. may have sampled girls with more severe CD.

Sampling from adolescent mothers yields a subgroup of the population of antisocial girls: those who get pregnant and choose to deliver and keep the baby. Because the subjects in the Azar et al. study were chosen after 8 to 13 months of pregnancy and childrearing,

it is possible that many of them were no longer engaging in antisocial behaviors on a regular basis. Indeed, many adolescents exhibit antisocial behavior but desist as they become older; those who persist in deviant behaviors are more likely to have risk factors for persistent adult antisocial behavior, including biological abnormalities (Moffitt, 1993; Newman, 1997).

For this reason, Pajer and colleagues' antisocial group comprised girls who, although living in the community at the time of intake, had a high rate of prior arrests, detainments, or group home treatments. They were selected on the basis of meeting lifetime criteria for conduct disorder on the Diagnostic Interview Schedule for Children (DISC) (Shaffer et al., 1996), and continuing to meet those criteria for at least 12 months prior to intake. In addition, although aggressive CD was not an inclusion factor, 80% of the CD girls were aggressive. Thus, it is not clear whether Azar and coworkers' participants exhibited the same degree of persistent, aggressive behavior as these CD girls. If our group was more severely conduct-disordered than that of Azar et al., this might explain why we found a difference and they did not.

Directions for Future Research

In summary, the study by Azar et al. has contributed additional important information on HPA axis function in antisocial girls. Their data suggest that the morning decline in cortisol is not disturbed in antisocial girls, and their discussion of these findings raises important scientific questions that should be pursued by researchers on antisocial behavior. Comparison of their study with previous studies understandably reveals limitations among all and points to several goals for future research. First, studies should measure HPA functioning periodically throughout 24 hours rather than at a single time, so that the circadian cycle of cortisol secretion can be delineated. In addition, the reactivity of the HPA axis to psychological and physical stress at different clock times should also be examined and endocrinologic challenges should be used to further characterize the pathophysiology. Second, investigators must carefully consider the effects of sample selection procedures in recruiting participants. Similar procedures are fundamental to making comparisons among studies.

Finally, and most importantly, researchers must consider multiple explanations for differences in HPA axis

functioning associated with antisocial behavior, including socioeconomic factors, personal histories of adverse life events, and comorbid psychiatric conditions. We conclude by offering some suggestions about what future research may show with respect to this last issue. Low SES has been actually been associated with higher levels of cortisol (Adler et al., 2000; Lupien et al., 2001), as has exposure to adverse events such as abuse or neglect (Cicchetti and Rogosch, 2001; Gunnar et al., 2001; Heim et al., 1997, 2000; Kaufman et al., 2000; Pike et al., 1997). Higher cortisol levels were also found in the one study of children that investigated the effect of exposure to multiple types of adversity, such as poverty, family turmoil, and community violence (Evans and English, 2002). Similarly, depression and substance abuse have also been associated with elevated cortisol levels (Gianoulakis et al., 2003; Risher-Flowers et al., 1988; Rivier, 1999; Rubin et al., 1987), although in depressed children and adolescents, normal or low cortisol levels have also been reported (Birmaher et al., 1996; Dorn et al., 1996). However, a study that tested the effect of internalizing disorder symptoms on saliva cortisol levels in antisocial boys reported that the presence of internalizing symptoms moderated the relationship between low cortisol and antisocial behavior such that the boys without any comorbid symptoms had the lowest cortisol levels (McBurnett et al., 1991). Similarly. In the study by Pajer et al. (2001a), the CD girls without any comorbid disorders had significantly lower cortisol levels than the antisocial girls who did have comorbid problems (primarily internalizing disorder symptoms and substance abuse). This latter subgroup was still significantly lower than the NCD group.

Based on all these data, we are skeptical of the conclusion that low morning cortisol levels in the antisocial population can be completely explained by low SES, exposure to adverse life events, or comorbid depression and substance abuse. However, it is possible that adverse life events and psychiatric comorbidity may affect HPA axis function in antisocial girls through the development of posttraumatic stress disorder. Many girls with CD suffer from this disorder, and it has frequently been associated with low morning cortisol levels (Lemieux and Coe, 1995; Pitman et al., 1999; Yehuda, 1998). The study by Pajer et al. (2001a) had only two CD girls who had posttraumatic stress disorder (although 36% of the CD and 12% of the NCD girls had been exposed to traumatizing events),

but these girls had the lowest cortisol levels in the entire sample. This question remains an open one, and we look forward to future contributions by Azar et al. in this area of study.

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