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Altered circadian patterns of salivary cortisol in low-functioning children and adolescents with autism

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Repeated stress;
Sensitization to stressors;
Flattened cortisol patterns;
Trait anxiety

Summary
Background: Reports of higher stress responsivity, altered sleep-wake cycle and a melatonin deficit in autism have stimulated interest in the cortisol circadian rhythm in individuals with autism.
Methods: The study was conducted on 55 low-functioning children and adolescents with autism (11.3 ± 4.1 years-old) and 32 typically developing controls (11.7 ± 4.9 years-old) matched for age, sex and puberty. Behavioral assessment was performed using the Autism Diagnostic Observation Schedule (ADOS). Salivary samples for measurement of cortisol were collected during a 24-h period (at least 0800 h-Day1, 1600 h, 0800 h-Day2 for 46 individuals with autism and 27 controls, and 0800 h-Day1, 1100 h, 1600 h, 2400 h, 0800 h-Day2 for 13 individuals with autism and 20 controls). Overnight (2000 h—0800 h) urinary cortisol excretion was also measured.
Results: The autism group displayed significantly higher levels of salivary cortisol at all time-points, flatter daytime and nighttime slopes, higher 0800 h cortisol levels on Day2 compared to Day1, and greater variances of salivary and urinary cortisol. There was a significant relationship between salivary cortisol levels and impairments in social interaction and verbal language. Overnight urinary cortisol excretion was similar in the autism and control groups.
Conclusion: Anticipation of the stressful collection procedure appears to contribute to the higher 0800 h-Day2 versus 0800 h-Day1 salivary cortisol levels in autism. This sensitization to stressors might be as, or even more, important clinically than exposure to novelty in autism. The similar group means for overnight urinary cortisol excretion indicate that basal HPA axis functioning is unaltered in low-functioning autism. The elevated salivary cortisol levels observed in autism over the 24-h period in a repeated stressful condition, flattened diurnal cortisol patterns and the apparent effect of anticipation are consistent with prior findings in high trait anxiety.

1. Introduction

Cortisol, the primary hormonal endoproduct of the hypothalamic-pituitary-adrenal (HPA) axis, is a crucial component of the response to environmental stressors followed by the restoration of basal activity via HPA axis feedback inhibition mechanisms. Chronic elevation of cortisol, including hypercortisolemia and elevated nadir has been implicated in the pathogenesis of psychiatric disorders such as depression (for a review, see Keller et al., 2006).

Cortisol circadian rhythm has been well documented in typically developing children and its pattern is usually well established by 6 months of age (Onishi et al., 1983; Price et al., 1983). The lowest cortisol levels are observed between 2000 h and 0200 h and levels increase thereafter up to the highest levels observed shortly after awakening regardless of age, followed typically by a decrease throughout day in absence of external stimuli (Weitzman et al., 1971; Touitou et al., 1981; Pruessner et al., 1997). Cortisol is considered as an important marker of the circadian time structure as the pattern of its secretion is highly reproducible from day to day (Selmaoui and Touitou, 2003). Cortisol circadian rhythms depend upon exogenous factors such as light (Levine et al., 1994) and season (Touitou et al., 1983; Matchock et al., 2007; Persson et al., 2008), and might be also influenced by social factors (Aschoff et al., 1971; Moore-Ede et al., 1982). Cortisol circadian rhythms, like any circadian rhythm (such as melatonin circadian rhythm, sleep-wake cycle, body temperature rhythm) allow optimal and anticipatory temporal organization of biological functions in relation to periodic changes of the environment (Schibler, 2009; Challet, 2010; Pevet and Challet, 2011).

Much of the impetus to study cortisol in autism has come from the apparent heightened anxiety and disordered arousal often observed in individuals with autism (Van Steensel et al., 2011 for a meta-analysis of anxiety disorders in Autistic Disorder; Ozsivadjian et al., 2012; Simon and Corbett, 2013). Reports of higher stress responsivity (for a review, see Tordjman et al., 1997), alterations in circadian sleep-wake rhythm (Glickman, 2010; Leu et al., 2011; Kotagal and Broomall, 2012) and altered melatonin secretion (Melke et al., 2008; Mulder et al., 2010; Tordjman et al., 2005, 2012, 2013) have further stimulated interest in the study of cortisol circadian rhythm. The reports of studies on cortisol circadian rhythm in Autistic Disorder are listed in Table 1

Although some of the studies have found abnormalities in cortisol circadian rhythm (see Table 1: Yamazaki et al., 1975; Hill et al., 1977; Hoshino et al., 1987; Aihara and Hashimoto, 1989; Kaneko et al., 1993), the results were not entirely consistent (typical cortisol circadian rhythm was, for example, observed by Richdale and Prior, 1992; Corbett et al., 2006; Marinović-Curin et al., 2008). Discrepancies in the results might be related to the level of cognitive functioning, study methods (plasma cortisol measures vs. urinary or salivary cortisol measures) and sample sizes. Thus, most of the studies were hampered by relatively small sample sizes due in particular to methodological challenges of repeated blood measures in individuals with Autistic Disorder. With the development of salivary cortisol