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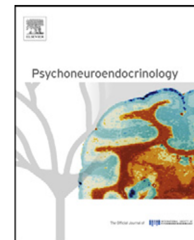

Comparison of salivary cortisol as measured by different immunoassays and tandem mass spectrometry

Robert Miller [a,*], Franziska Plessow [a], Manfred Rauh [b], Michael Gröschl [b], Clemens Kirschbaum [a]

[a] Department of Psychology, Technische Universität Dresden, Germany
[b] Department of Pediatrics, Universität Erlangen-Nürnberg, Germany

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Summary Assessing the amount of bioavailable cortisol in saliva with immunoassays and thus sampling an endocrine marker of hypothalamus—pituitary—adrenal axis activity is of major interest in both research and clinical practice. However, absolute cortisol concentrations obtained with different immunoassays (IAs) are barely comparable precluding direct comparison between studies or individuals whenever cortisol analyses were not based on the same IA. The present technical report aims to solve this problem by evaluating the validity of, as well as agreement between the most commonly used immunoassays in psychoneuroendocrinological research (i.e., IBL, DRG, Salimetrics, DSL, and DELFIA) and a reference method (LC—MS/MS) in a sample of 195 saliva specimen covering the whole range of cortisol concentrations in adults. A structural equation modelling framework is applied to decompose systematic assay variance and estimate cortisol reference values, which are adjusted for measurement error and interference of salivary cortisone. Our findings reveal nonlinear relations between IAs and LC—MS/MS, which are discussed in terms of IA cross-reactivity with saliva matrix components. Finally guidelines for converting cortisol concentrations being obtained by these immunoassays into comparable reference values are proposed by providing conversion functions, a conversion table, and an online conversion tool.
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1. Introduction

Due to its non-invasiveness, precision, and cost efficiency the measurement of steroid levels from saliva has become a valuable tool in psychoneuroendocrinological research over the past two decades. While other steroid hormones are also measured with increasing frequency, cortisol still represents

* Corresponding author at: Technische Universität Dresden, Department of Psychology, Andreas-Schubert-Bau, Zellescher Weg 19, 01069 Dresden, Germany. Tel.: +49 351 463 33708; fax: +49 351 463 37274.
E-mail address: miller@biopsych.tu-dresden.de (R. Miller).

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the prime hormone assessed in saliva samples collected in basic stress research, epidemiological, as well as clinical studies (Kirschbaum and Hellhammer, 1989, 2007).

The vast majority of salivary cortisol determinations are performed using immunoassays (IA). These IAs rely on chemical binding of analytes to antibodies, which show varying specificity for molecules to be detected and quantified. Although these antibodies are specifically raised to bind analytes selectively, structurally related substances in the same specimen compete with the analyte for available binding sites. For the determination of salivary cortisol, a major source of such interference is cortisone, which is abundant in saliva due to cortisol oxidation via 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in the parotid glands (Smith et al., 1996). Cortisone cross-reactivity is especially important, considering that its concentration amounts to, due to its prolonged half-life, on average 280% as compared to cortisol (Perogamvros et al., 2011), implying that its impact is supposed to be more pronounced with increasing temporal distance from the preceding secretory cortisol burst. This would eventually result in rising cortisone-to-cortisol ratios, with decaying cortisol concentrations.

Additionally, antibody design varies across different IAs, resulting in differential analyte and matrix affinity (cf. Davies, 2005). Thus, measuring identical samples with different IAs can result in absolute analyte concentrations that differ by a factor of three or more between separate IAs (Kirschbaum and Hellhammer, 1989; Raff et al., 2002). The same seems to apply to blood plasma specimen (Roberts and Roberts, 2004; Cohen et al., 2006). Furthermore it has been demonstrated, that most IAs' results overestimate absolute cortisol levels in saliva when compared with data obtained by mass spectrometry as reference method (Jönsson et al., 2003). Although absolute steroid levels may not be of prime importance for most studies conducted for research purposes only, it would be advantageous if salivary cortisol levels could be compared with each other across different studies, and assay technologies.

Based on this, the present report serves two main purposes. First, we aim to evaluate salivary cortisol results obtained by IAs most frequently used in psychoneuroendocrinological research for the last four years, and compare them to results obtained with liquid chromatography tandem mass spectrometry (LC—MS/MS). Our second aim is to investigate the influence of cortisone cross-reactivity on salivary cortisol as determined by the respective IAs. Apart from these major points, we further intend to provide preliminary conversion guidelines, which shall enable the comparison of salivary cortisol data from different studies, but should be utilized with caution considering that IA manufacturers occasionally change IA antibodies and/or other components across time. Nonetheless, they may render helpful to, for example, perform meta-analyses of raw mean differences (cf. Bond et al., 2003) or interpret absolute cortisol values. The latter is particularly important within the clinical practice, as transgression of threshold criteria for steroid levels has been frequently employed as an indicator for adrenocortical functioning (e.g., Trilck et al., 2005).

2. Methods

2.1. Sample

195 saliva specimen, which had been obtained using Salivettes® (Sarstedt, Nümbrecht, Germany; see Gröschl et al., 2008), were randomly drawn from a larger pool of saliva samples. The pool comprised specimen being mostly collected from healthy (i.e., free of glucocorticoid or other medication) subjects during psychosocial stress studies. A minority of specimen from pharmacological challenge studies was selected in order to cover cortisol levels in the upper measurement range. Therefore absolute cortisol levels were expected to comprise circadian and ultradian variability within the natural, non-pathological cortisol spectrum, as well as to a smaller extent pharmacologically altered levels.

2.2. Preanalytical precautions

Specimens were aliquoted and stored at −20 °C for up to six months before they were sent to reference laboratories in Erlangen and Trier (Germany). Although salivary cortisol remains stable for at least four days at room temperature (Gröschl et al., 2008), aliquot shipment was conducted in cooled boxes to prevent cortisol degradation. Repeated thawing and freezing of specimen and storage at −20 °C for up to 12 months is reported to have no sustainable effect on salivary cortisol concentrations (Garde and Hansen, 2005).

2.3. Biochemical analyses by IAs

Upon arrival at the respective destination, aliquots were analysed with either four commercial IAs (IBL, DRG, Salimetrics, and DSL; see Table 1), or with one in-house method

Table 1 Characteristics of the immunoassays (IAs) distributed by the respective manufacturers in 2008 and 2012.

Label	Type	Sales	Origin	IA cross-reactivities in 2008			IA cross-reactivities in 2012		
				Cortisone	17α-OHP	DEX	Cortisone	17α-OHP	DEX
IBL	CLIA	IBL International	Hamburg, Germany	3.2	0.5	<0.1	4.5	2.0	<0.1
DRG	EIA	DRG Instruments	Marburg, Germany	3.0	0.5	<0.1	3.0	0.5	<0.1
Salimetrics	EIA	Salimetrics	State College, PA, USA	0.3	0.6	1.3	0.1	<0.1	19.2
DSL	EIA	Diagn. System Lab.	Webster, TX, USA	7.0	0.9	0.9	—	—	—
DELFIA	EIA	In-house	Trier, Germany	0.6	NA	0.4	0.6	NA	0.4

Note: Distribution of the DSL kit has meanwhile been ceased after acquisition of Diagnostic System Laboratories by Beckman Coulter. Another available high sensitivity DRG kit features a higher cross-reactivity with cortisone (6.9%). CLIA, chemiluminescence IA; EIA, enzyme IA; 17α-OHP, 17α-hydroxyprogresterone; DEX, dexamethasone; NA, not available/not determined by manufacturer.

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