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How to use and interpret hormone ratios

Silja Sollberger, Ulrike Ehlert*

Department of Psychology, Clinical Psychology and Psychotherapy, University of Zurich, Zurich, Switzerland

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ABSTRACT

Hormone ratios have become increasingly popular throughout the neuroendocrine literature since they offer a straightforward way to simultaneously analyze the effects of two interdependent hormones. However, the analysis of ratios is associated with statistical and interpretational concerns which have not been sufficiently considered in the context of endocrine research. The aim of this article, therefore, is to demonstrate and discuss these issues, and to suggest suitable ways to address them. In a first step, we use exemplary testosterone and cortisol data to illustrate that one major concern of ratios lies in their distribution and inherent asymmetry. As a consequence, results of parametric statistical analyses are affected by the ultimately arbitrary decision of which way around the ratio is computed (i.e., A/B or B/A). We suggest the use of non-parametric methods as well as the log-transformation of hormone ratios as appropriate methods to deal with these statistical problems. However, in a second step, we also discuss the complicated interpretation of ratios, and propose moderation analysis as an alternative and oftentimes more insightful approach to ratio analysis. In conclusion, we suggest that researchers carefully consider which statistical approach is best suited to investigate reciprocal hormone effects. With regard to the hormone ratio method, further research is needed to specify what exactly this index reflects on the biological level and in which cases it is a meaningful variable to analyze.

1. Introduction

In recent years, there has been a growing awareness that endocrine systems such as the hypothalamic-pituitary-gonadal (HPG) and the hypothalamic-pituitary-adrenal (HPA) axes do not operate independently of each other but interact in complex ways. Consequently, the single hormone approach has been more and more abandoned in favor of methods which allow for the simultaneous consideration of hormones assumed to co-regulate (e.g., inhibit or potentiate) each other. One highly popular way of achieving this goal is to compute the ratio of two hormones by simply dividing the concentration of one hormone, e.g. testosterone (T), by the concentration of a second hormone, e.g. cortisol (C). Based on the assumption that the balance between two interdependent hormones determines their eventual effects on brain and other tissues (Maninger et al., 2009), this index has been commonly interpreted as an indicator of the balance between two endocrine systems.

However, this appealing method of compounding two hormones into a single value is associated with statistical implications which, to the best of our knowledge, have not been appropriately considered and discussed in the endocrine literature. Moreover, the interpretation of hormone ratios is complicated and in many cases not sufficiently supported from a theoretical point of view. By contrast, the statistical properties of ratios, their interpretation, and associated problems have been controversially discussed for several decades in other disciplines such as finance and accounting (e.g., Bedingfield et al., 1985; Deakin, 1976; Frecka and Hopwood, 1983; Kane and Meade, 1998), biology (e.g., Atchley et al., 1976), medicine (e.g., Gullberg, 1991; Keene, 1995; Senn, 1989), and geology (e.g., Chayes, 1949; Weltje, 2012). These established insights will be considered and incorporated throughout the course of this article.

The aim of the present paper, therefore, is to demonstrate and discuss the statistical and interpretational concerns of ratios in the context of endocrine research. As a starting point, we will give a brief overview of previous studies that employed various forms of hormone ratios in their analyses. In a second step, we will demonstrate the statistical properties of hormone ratios on exemplary T and C data. One central aspect we will consider is the fact that there inherently are two possibilities to calculate the ratio, depending on which of the two hormones is assigned to the numerator and

* Corresponding author at: University of Zurich, Department of Psychology, Clinical Psychology and Psychotherapy, Binzmühlestrasse 14/26, CH-8050 Zurich, Switzerland. Fax: +41 44 635 7359.
E-mail addresses: s.sollberger@psychologie.uzh.ch (S. Sollberger), u.ehlert@psychologie.uzh.ch (U. Ehlert).

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denominator of the quotient (e.g., T/C versus C/T). From a biological perspective, there is no reason to expect one form of the ratio to be more valid than the other. We therefore examine the distributions of both the T/C and C/T ratios, the relationship between the two and their respective associations with an exemplary third variable (i.e., body height). In the course of this, we demonstrate characteristic problems of the ratio method and propose suitable ways to deal with these concerns. Subsequently, we address the important and often complex question of how ratios should be interpreted, discuss the general advantages and limitations of the ratio method and describe promising alternative approaches for the analysis of interdependent endocrine effects.

Taken together, we hope to provide a stepping stone to a critical discussion on how and when hormone ratios should be calculated, analyzed and interpreted, and thus to contribute to the development of methods suitable for the analysis of interdependent endocrine variables.

2. Hormone ratio findings and assessment methods

In the following, we give a non-exhaustive overview of frequently used hormone ratios, with an emphasis on how they are commonly interpreted. The details of the presented studies are summarized in Table 1. In the last paragraph of this chapter, we additionally review the methods that have been used to calculate these ratios.

2.1. Testosterone and cortisol

We first focus on the T/C ratio, which has been proposed as an indicator of the general (im) balance between the mutually inhibiting HPG and HPA axes (Glenn et al., 2011; Terburg et al., 2009). This balance has been suggested to be a marker for aggressive behavior, based on findings that T and C have opposing effects on subcortical areas and resulting behaviors (Terburg et al., 2009; van Honk and Schutter, 2006). More precisely, it has been argued that T increases reward-seeking and approach behavior, whereas C promotes punishment sensitivity and withdrawal behavior. Consequently, a combination of high T and low C levels has been assumed to make individuals more likely to confront threat and more prone to engage in aggressive behavior. In accordance with this hypothesis, the T/C ratio has been found to be associated with psychopathy scores (Glenn et al., 2011), marital violence (Romero-Martínez et al., 2013), as well as neural activity in response to social threat (Hermans et al., 2008) and anger provocation (Denson et al., 2013b). In an independent line of research, the T/C ratio has been proposed as an indicator of catabolic/anabolic balance during physical training because T has mainly anabolic effects while C has mainly catabolic effects (Adlercreutz et al., 1986; Häkkinen et al., 1989). A great number of studies have since examined how the T/C ratio relates to training load and physical performance in the context of various sports (e.g., Choi et al., 2013; Gomes et al., 2013; Silva et al., 2013; Wahl et al., 2013). Furthermore, ratios of testosterone and cortisol, i.e., T/C or C/T, have also been investigated in the context of health and disease. While the T/C ratio has been found to be associated with general health status (Wang et al., 2013) and heart rate variability (Huovinen et al., 2009), its reciprocal value C/T has been reported to be related to obesity (Chan et al., 2014) and heart diseases (Pereg et al., 2013; Smith et al., 2005). Taken together, ratios of T and C have been investigated in association with different behavioral and health-related variables. In general, a higher T/C ratio was related to higher health and fitness but also to increased antisocial behavior. Interestingly, most studies used T/C ratios while only few studies focused on the C/T ratios. This choice was generally not reflected upon and appeared to be mainly influenced by convention.

2.2. DHEA(S) and cortisol

A second example is the ratio of C and dehydroepiandrosterone (DHEA) or its sulfated metabolite DHEA-S. Like T, DHEA has anabolic effects and the C/DHEA(S) ratio has therefore—similar to the T/C ratio—been proposed as an indicator of catabolic/anabolic balance (Maninger et al., 2009; Wolkowitz et al., 2001). Generally, a higher C/DHEA(S) ratio, reflecting a lower anabolic balance, has been suggested to be indicative of increased chronic stress and poorer psychiatric and health status (Wolkowitz et al., 2001). Accordingly, ratios of C and DHEA(S) have been studied in association with depression (Markopoulou et al., 2009; Young et al., 2002), stress (Moriguchi Jeckel et al., 2010; Warnock et al., 2010), posttraumatic stress disorder (Yehuda et al., 2006) and panic disorder (Fava et al., 1989) as well as in the context of Alzheimer's disease (Armanini et al., 2003), acute ischemic stroke (Blum et al., 2013), amyotrophic lateral sclerosis (Gargiulo-Monachelli et al., 2014), multiple sclerosis (Kümpfel et al., 1999), and HIV infection (Christeff et al., 1997). Notably, in the case of C and DHEA(S), C is more commonly used in the numerator of the ratio (see Table 1).

2.3. Further hormone ratios

Apart from the two described examples, a number of other hormone ratios have been investigated. For instance, the salivary alpha amylase (sAA) over C ratio has recently been suggested as a marker for the dysregulation of the two major stress systems HPA and sympathetic nervous system (Ali and Pruessner, 2012). Further hormone ratios include the ratios of norepinephrine and C (Spitzer et al., 2005; Wang et al., 1997), C and cortisone (Dötsch et al., 2001), C and adrenocorticotropic hormone (Rubinow et al., 2005), morning and evening C (Dorn et al., 2009; Susman et al., 2007), T and estradiol (Caufriez et al., 2013; He et al., 2007), T and progesterone (Gargiulo-Monachelli et al., 2014), estradiol and progesterone (He et al., 2007), norepinephrine and epinephrine (Ostroff et al., 1985), luteinizing hormone and follicle-stimulating hormone (Banaszewska et al., 2003), as well as triiodothyronine and thyroxine (Wang et al., 1997).

2.4. Methods of hormone ratio analysis

In the existing literature, researchers have predominantly calculated hormone ratios at a single time point, often with the intention of assessing how relatively stable baseline concentrations of two hormones relate to a behavioral or health-related outcome measure. Thus, the ratio is typically calculated by simply dividing the raw value of one hormone by the raw value of a second hormone. However, endocrine parameters may fluctuate considerably within individuals across short periods of time on the basis of circadian rhythms or contextual factors. Psychoneuroendocrine studies therefore often measure hormones repeatedly, for instance to examine how they vary over the course of an intervention. Nevertheless, the ratio method has so far only rarely been applied in the context of repeated endocrine assessments.

Notable exceptions are studies that explicitly examined how hormone ratios are affected by interventions, such as physical training (Gomes et al., 2013; Silva et al., 2013; Wahl et al., 2013), competition (Choi et al., 2013), acute stress (Romero-Martínez et al., 2013), or hormone supplementation (Caufriez et al., 2013). In this type of study, the ratio of interest is repeatedly computed to analyze time-dependent increases and decreases in its magnitude. Considering that different hormones often show different response dynamics, changes in the ratio thus reflect intervention-related