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Review

Cortisol levels and suicidal behavior: A meta-analysis

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ABSTRACT

Suicide is a major cause of death worldwide, responsible for 1.5% of all mortality. The causes of suicidal behavior are not fully understood. Dysregulated hypothalamic–pituitary–adrenal (HPA) axis activity, as measured by cortisol levels, is one potential risk factor. This meta-analytic review aimed (i) to estimate the strength and variability of the association between naturally fluctuating cortisol levels and suicidal behavior and (ii) to identify moderators of this relationship. A systematic literature search identified 27 studies ($N = 2226$; 779 suicide attempters and 1447 non-attempters) that met the study eligibility criteria from a total of 417 unique records initially examined. Estimates of effect sizes (r) obtained from these studies were analysed using Comprehensive Meta-Analysis. In these analyses, we compared participants identified as having a past history of suicide attempt(s) to those with no such history. Study quality, mean age of sample and percentage of male participants were examined as potential moderators. Overall, there was no significant effect of suicide group on cortisol. However, significant associations between cortisol and suicide attempts were observed as a function of age. In studies where the mean age of the sample was below 40 years the association was positive (i.e., higher cortisol was associated with suicide attempts; $r = .234$, $p < .001$), and where the mean age was 40 or above the association was negative (i.e., lower cortisol was associated with suicide attempts; $r = -.129$, $p < .001$). These findings confirm that HPA axis activity, as indicated by age-dependent variations in cortisol levels, is associated with suicidal behavior. The challenge for theory and clinical practice is to explain the complete reversal of the association with age and to identify its clinical implications.

Contents

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1. Introduction

Suicide is a major cause of death worldwide, responsible for 1.5% of all mortality. The causes of suicidal behavior are not fully understood; however, this behavior clearly results from a complex interplay between many different factors. Numerous models have been proposed that differ in their emphasis on the role of psychological, social, psychiatric and neurobiological factors in predicting risk of suicide and identifying targets for intervention to improve suicide prevention (Mann et al., 1999; O'Connor, 2011; O'Connor & Nock, 2014; van Heeringen and Mann, 2014; van Orden et al., 2010). However, central to many models is a stress-diathesis component which states that suicidal behavior is a result of an interaction between acutely stressful events and a susceptibility to suicidal behavior (a diathesis). Evidence is accumulating from post-mortem, neuroimaging and in-vivo studies that a trait diathesis is not only manifested in impairments of the serotonergic and noradrenergic neurotransmitter systems, in structural brain abnormalities and via epigenetic pathways but also in dysregulation of hypothalamic–pituitary–adrenal (HPA) axis stress response activity (Mann, 2013; Turecki et al., 2012; van Heeringen et al., 2011; van Heeringen and Mann, 2014). Moreover, it has been suggested that biomarkers of a trait-diathesis following serious stressful and traumatic psychosocial events, independent of psychiatric comorbidities, may be useful predictors of suicide risk (van Heeringen and Mann, 2014). One such potential biomarker is the glucocorticoid, cortisol.

When we experience stress, the HPA axis is activated and releases cortisol from the adrenal glands. Once released, cortisol has several important functions such as increasing access to energy stores, increasing protein and fat mobilization, as well as regulating the magnitude and duration of inflammatory responses (Sapolsky et al., 2000). Cortisol has also been found to be associated with impairments in cognitive control, decision-making and emotional processing linked to suicidal behavior (Giletta et al., 2015; Turecki et al., 2012). As such, cortisol is the primary effector hormone of the HPA axis stress response system and has received extensive empirical investigation. As with other aspects of the endocrine system, the HPA axis is regulated by a negative feedback system, whereby the hypothalamus and the pituitary gland have receptors that detect changes in cortisol levels. For example, cortisol secretion will be inhibited when circulating levels rise or it will be stimulated when levels fall. However, if the HPA axis is repeatedly activated, this will trigger increased cortisol output, thereby exposing bodily tissues to excessive concentrations of the hormone (McEwen, 1998; McEwen, 2000; Miller et al., 2007). Over time, such repetitive activation may lead to tissue damage and contribute to future ill health by placing excessive pressure on various bodily systems including the HPA axis (known as allostatic load; McEwen, 1998). Nonetheless, the precise effects of psychological stress on HPA axis regulation in relation to the diurnal cortisol profile and how this relates to suicidal behavior remains unclear.

The majority of previous research on cortisol and suicidal behavior relations has focused on assessing HPA axis functioning through pharmacological manipulation of the stress system (Mann and Currier, 2007; Pompili et al., 2010). The Dexamethasone Suppression Test (DST; Carroll et al., 1968) has been commonly employed to assess HPA axis dysregulation by measuring cortisol inhibition after the administration of the synthetic glucocorticoid dexamethasone. Failure to suppress cortisol is evidence for HPA-axis hyperactivity and has consistently been found to predict completed suicide in patients with mood disorder for example (Coryell and Schlesser, 1981; Coryell et al., 2006; Jokinen and Nordstrom, 2008, 2009; Jokinen et al., 2009; Norman et al., 1990). However, while DST research has contributed enormously to knowledge regarding HPA axis dysregulation and suicide vulnerability, findings remain inconsistent and contradictory (McGirr et al., 2011). Pharmacological manipulation has also been criticised as it may not adequately mimic the size of the endogenous HPA response to naturally occurring stressors (Burke et al., 2005). In addition, more recent studies have begun to explore other aspects of the cortisol response, such as the diurnal cortisol rhythm (including morning and afternoon/evening cortisol levels) and cortisol reactivity to stressors (for example, see McGirr et al., 2010).

Studies that have explored the relationship between naturally fluctuating cortisol and suicidal behavior have yielded inconsistent findings. For example, Westrin et al. (1999) found elevated cortisol levels in patients who had recently attempted suicide compared to healthy controls, while Lindqvist et al. (2008a,b) found that cortisol levels were significantly lower in suicide attempters compared to controls. A number of methodological factors may account for these mixed findings including the timing of the cortisol sampling (morning vs afternoon/evening) and study quality (both of which are examined in the current meta-analysis). However, age is another important variable that has been found to be associated with cortisol levels and suicidal behavior (Hawton et al., 2012; Hawton and van Heeringen, 2009). For example, cortisol levels have been shown to increase as part of normal aging (possibly mediated by diminished negative feedback inhibition), but normal-to-low levels of cortisol have also been observed in older Holocaust survivors with posttraumatic stress disorder (PTSD) and in patient groups with different stress-related disorders such as fibromyalgia (Ferrari et al., 2000; Fries et al., 2005; Yehuda et al., 2005). Taken together, these data suggest that the relationship between age and cortisol levels is far from straightforward and it is likely moderated by stress-related factors. In terms of suicidal behavior, age has been found to be differentially associated with suicide. In most regions in the world, suicide rates are highest in individuals aged 70 years and older (World Health Organization, 2014). However, in some countries, the highest levels of suicide are among the young (15–29 year olds) and in more wealthy countries, men are three times as likely to die by suicide. However, it is worth noting that age has also been found to be inversely associated with suicide attempt, such that greater levels of suicide attempt have been observed in younger people (e.g., Nock et al., 2008). Therefore, for these reasons, the mean age of the sample and percentage of males in each sample will be also explored as potential moderators of the relationship between cortisol and suicide attempter status (Hawton et al., 2012; Hawton and van Heeringen, 2009). Therefore, the goal of this review was to synthesize findings from all existing research that has compared