Psychoneuroendocrinology 77 (2017) 90–94

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Short Communication

Heterogeneity in HPA axis dysregulation and serotonergic vulnerability to depression

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ARTICLE INFO

Article history:
Received 1 July 2016
Received in revised form
15 November 2016
Accepted 15 November 2016

Keywords:
Cortisol
Depression
Elderly
Hypothalamic-pituitary-adrenal axis
Serotonin transporter-linked promoter region
Stress

ABSTRACT

Variability in the serotonin transporter (*5-HTTLPR*) gene can influence the risk of depression associated with adversity, as well as cortisol stress reactivity, although not consistently. No study has examined the impact of both a stressful environment and corticotropic-axis dysfunction on depression, as a function of *5-HTTLPR*. This population-based study included 334 subjects aged 65 and older. Depression was measured at both diagnostic (major depression according to DSM-IV) and symptomatic (subthreshold depression) levels of caseness, in addition to *5-HTTLPR* and *rs25531* genotyping and diurnal cortisol measures. For participants with the *SS* genotype, higher morning cortisol levels were associated with a 4-fold increased risk of depression. Among *LL* participants, both evening cortisol levels and recent stressful events increased depression risk, although only the latter remained significant after multivariable adjustment. Conversely, *SL* individuals appeared somewhat resilient to depression in terms of cortisol and recent stress. These findings indicate that *5-HTTLPR* genetic variability appears to influence the association between stress-related factors and late-life depression, although the gene-environment interactions failed to reach statistical significance levels. Participants homozygous for the short allele appeared to have a cortisol-related neuroendocrine vulnerability to depression, while long allele homozygotes were more reactive to stressful events in terms of depression risk.

1. Introduction

In the past, clinicians have made the distinction between 'endogenous' and 'reactive' depression in accordance with the empirical observation that depressive episodes may be triggered in some patients by environmental stressors, but not in others, where it was attributable to genetic vulnerability. The most recent meta-analysis confirmed a robust link between the short (*S*) form of the serotonin transporter gene (*5-HTTLPR*), experiencing stress, and resulting depression (Sharpley et al., 2014). Around 35% of these studies however, failed to show any significant association or found opposite results, with carriers of the long (*L*) form being at a higher risk of depression following life stress. The studies reporting opposing findings did not appear to be flawed by reduced power or methodological weaknesses, and the results were independent of study design, depression measure and type of stressful event (Sharpley et al., 2014). Age has been frequently evoked as a potential source of inconsistent findings for depression (Uher and McGuffin, 2008) and post-traumatic stress disorder (Navarro-Mateu et al., 2013). Further, unlike in younger populations where the S allele is a risk factor, the *LL* genotype appears a risk factor for mental and physical distress in elderly people highly exposed to chronic disorders and severe stressors (Grabe et al., 2011). This may explain why there is no generally accepted gene-dose model. Another important source of heterogeneity pointed by Sharpley et al. and potential limitation of previous studies is the method used to assess stress, *i.e.* whether extrinsic stress was self-reported or objectively recognized (Sharpley et al., 2014). They also raised the possibility of different neurobiological underpinnings and path-

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http://dx.doi.org/10.1016/j.psyneuen.2016.11.016

ways for depression but, so far, intrinsic biological stress measures have not been examined.

The hypothalamic-pituitary-adrenal (HPA) axis is one of the principal stress signaling pathways, and results in releases of cortisol (Kudielka et al., 2012). Cortisol secretion is not only a good indicator of HPA responsivity and differential biological response to short-term versus long-term effect of stress (Miller et al., 2007; Morris et al., 2012) but it also constitutes one important neurobiological characteristic of depression (Stetler and Miller, 2011). Heightened diurnal cortisol levels have been frequently reported in depressed individuals (Belvederi Murri et al., 2014), and remain high after recovery from major depression (Beluche et al., 2009), suggesting it may constitute a trait marker for vulnerability to depression. Conversely, exposure to traumatic events has been associated with lower evening cortisol (Chaudieu et al., 2008; Morris et al., 2012). There is also a link between serotonergic signaling and HPA axis functioning (Vazquez et al., 2012), and the *5-HTTLPR* gene has been shown to influence cortisol reactivity in young adults exposed to acute psychosocial stress, whereas the unique study in elderly reported an inverse association (Miller et al., 2013). So far, no study has examined the impact of both an adverse environment and corticotropic axis dysfunctioning, which could represent different aspects of stress with distinct biological effects (Grabe et al., 2011) and consequences for depression risk. Whether this could differ as a function of *5-HTTLPR* genotype, yielding contradictory findings has also not been investigated.

This study evaluated whether both recent stressful events and cortisol levels are associated with late-life depression and if this differs according to *5-HTTLPR* genotype, while taking into account sociodemographic and stress-related factors, as well as past major depression.

2. Subjects and methods

Eligible participants, who were at least 65 years of age and non-institutionalized, were recruited by random selection from the electoral rolls between 1999 and 2001 (Ritchie et al., 2009). The standardized interview in the Esprit study included information on socio-demographic characteristics, physical health, and medical history of the participants. This study was based on a random sample of 344 non-demented participants who underwent depression assessment, responded to all questions concerning their experience of recent stressful events, had complete diurnal cortisol samples, and agreed to provide blood samples for *5-HTTLPR* genotyping. Repeated diurnal salivary cortisol samples and measures were taken, as published previously (**see Supplemental Methods** for details). Genotyping of *5-HTTLPR* and the A/G polymorphism (*rs25531*) within the promoter region were performed as described previously (Ritchie et al., 2009), which was validated with independent genotyping of matched buccal DNA samples. Major depression and anxiety disorder were diagnosed according to DSM-IV criteria using the Mini International Neuropsychiatric Interview (MINI, French version 5.00), a standardized psychiatric examination validated in the general population (Sheehan et al., 1998). Case-level late-life depression was defined as a MINI diagnosis of current major depression or high levels of depressive symptomatology (score ≥16) on the Center for Epidemiologic Studies-Depression Scale (Radloff, 1977). Exposure to stressful events during the past year was assessed using the validated Gospel Oak questionnaire (Harwood et al., 1998). The national ethics committee approved the study and all participants provided written informed consent.

The association between the *5-HTTLPR* allelic frequency and depression was examined by logistic regression analysis, using the conventional biallelic and the triallelic model further considering the *rs25531* polymorphism within the promoter. Previous association studies have suggested dominant, codominant, and recessive models of the *5-HTTLPR S* (or *S'*) allele without a clear consensus (Uher and McGuffin, 2008). To overcome this problem, we compared both possible allele groups separately by aggregating samples according to an *S* (or *S'*) recessive model (having two alleles), and an *S* (or *S'*) dominant model (having at least one allele). We also examined whether there was a statistical significant interaction between genotype (*5-HTTLPR*) and stress-related variables on the risk of depression. In keeping with the original aim of our study, we then stratified analysis by *5-HTTLPR*, and generated multivariable models to determine the association between stress-related variables (morning and evening cortisol levels, recent stressful events), and depression. SAS (v9.4, SAS Institute, NC, USA) was used for the statistical analyses with a significance level of $p < 0.05$.

3. Results

Participant characteristics are summarized in Table 1 and 4.5% currently used antidepressants. The mean (SD) age of first onset depression was 48.3 (16.6) years and 43% of the participants with past depression had recurrent episodes. There were no significant differences in socio-demographic or clinical characteristics across genotype groups. In logistic regression models adjusted for age and sex, experiencing a recent stressful event and a history of major depression were both associated with a >2-fold increased risk of clinical depression in the whole sample, but cortisol levels were not associated with depression risk (Table 2A). There was some evidence that *5-HTTLPR* (+/− *rs25531*) genotype modified the association between stress-related factors and depression risk, in particular for recent stressful events, although the multiplicative interaction term failed to reach statistical significance ($p < 0.10$ in both the dominant and recessive models) (**Tables S1 and S2**).

After stratification by genotype, the associations of recent stressful events and depression with depression more than doubled in strength for *L* homozygous individuals, but were clearly not significant for individuals homozygous for the *S* allele (Table 2B). A distinct pattern was found when examining cortisol levels. Higher morning cortisol levels were associated with a 4-fold increased risk of depression in the *SS* individuals only. Conversely, a negative association between evening cortisol and depression risk was found specifically for *LL* participants. In multivariable models combining the significant stress-related risk factors, evening cortisol levels were no longer significantly associated with depression in *LL* participants, after accounting for recent stress (evening cortisol: OR = 0.57, 95% CI = 0.29-1.11, $p = 0.10$; recent stressful events: OR = 5.16, 95% CI = 1.35-19.78, $p = 0.017$). These findings remained similar after inclusion of past major depression **(Table S3A**) and were not modified when taking into account recurrent episodes or current antidepressant use. Additional variables shown in Table 1 were not significantly associated with depression (all $p \geq 0.15$). The associations remained consistent when examining the triallelic model, and in addition recent stressful events were associated with depression among *S'L'* heterozygotes (**Table S3B**).

4. Discussion

To our knowledge, this is the first study to investigate the impact of stress on depression, using both extrinsic (self-report of stressful events) and intrinsic (cortisol secretion) stress indicators. Our findings show differential stress-related susceptibility to late-life depression, with some indication that this might also vary depending on *5-HTTLPR* genotype, although the GxE interaction term failed to reach the 5% significance level. In stratified analysis, the risk of depression was significantly associated with higher morning cortisol levels specifically in the *SS* participants and this