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Content

Summary

Depression and other mental disorders are the leading cause of disability worldwide and their burden has increased considerably over past decades. However, advances in psychopharmacology of psychiatric disorders are not in measure with this negative trend. As a result, a large body of research in psychiatry and neurosciences tries to further develop our understanding of pathophysiological mechanisms underlying mood disorders and other mental illnesses in order to improve the efficacy of current treatments and to identify new therapeutic agents. According to current evidence, stress-related pathways and inflammation processes are directly involved in the development of depressive disorder and several other psychiatric conditions. The study of the effects and consequences of stress exposure requires an interdisciplinary approach, taking into account specific aspects of the "inputs", such as chronic stress and traumatic experiences, and related psychological processes, with the crucial role of dissociation.

Following these theoretical findings, the empirical research performed in two cohorts of inpatients with depressive disorder focused on immune and endocrine responses to stress and their relationship to psychopathological symptoms, specifically trauma-related symptoms, psychic and somatoform dissociation and depressive symptoms.

The main finding of the empirical research shows, that tumor necrosis factor alpha (TNF-α), that has been intensively studied as one of the major candidates in the cytokine model of depression, is related to both psychic and somatoform dissociative symptoms and trama-related symptoms. This finding suggests that TNF-α regulation and dissociation could be interrelated in the complex response to stress.

Other main results of this study indicate that prolactin is associated with psychic dissociative symptoms, supporting the findings of

previous research, pointing to the relationship between prolactin regulation and passive coping behaviour. Finally, cortisol has been found to be related to somatoform dissociation, suggesting that low level of cortisol could be associated with active defensive or antiarousal intrapsychic processes, such as avoidance, withdrawal and denial.

Although no clinical conclusions can be taken at this point, the findings encourage further efforts to describe more in details the interplay between TNF-α, prolactin and cortisol regulations, chronic stress and dissociative processes in the development and clinical manifestation of depression.

Shrnutí

Deprese a některá další psychiatrická onemocnění představují ve světovém měřítku jednu z hlavních příčin pracovní neschopnosti, jejichž vliv navíc v průběhu několika desetiletí významnou měrou narůstá a to navzdory významným pokrokům v psychofarmakologii. V důsledku toho je výzkum v psychiatrii a v neurovědách značnou měrou zaměřen na hlubší porozumění patofyziologických mechanismů deprese a dalších psychických poruch s cílem zlepšit účinnost léčby. Podle stávajících poznatků stres a imunitní procesy hrají významnou roli v patofyziologii afektivních poruch a některých dalších psychických onemocnění. Tento interdisciplinární výzkum vlivů a následků stresu zahrnuje celou řadu aspektů jako například chronický stres nebo traumatické zkušenosti v nichž významnou úlohu má proces disociace.

V návaznosti na tyto poznatky byl v této studii realizován empirický výzkum zahrnující dva vzorky pacientů s depresivní poruchou, který byl zaměřen na vztahy imunitních a endokrinních odpovědí na stres v souvislosti s psychopatologickými symptomy a to především se zaměřením na symptomy vztahující se k traumatickému stresu, psychickým a somatoformním disociativním symptomům a také k symptomům deprese jako takové. Hlavní výsledky tohoto empirického výzkumu ukazují na to, že tumor necrosis factor alpha (TNF-α), který je jedním z hlavních faktorů v patogenezi depresivní poruchy podle tzv. cytokinového modelu deprese, vykazuje velmi významný vztah k symptomům psychické a somatoformní disociace a také k symptomům vztahujícím se k traumatickému stresu. Tento poznatek ukazuje na významnou roli TNF-α ve vztahu k disociativním procesům.

Další z hlavních výsledků této studie ukazuje na významný vztah psychických disociativních symptomů a prolaktinu v souladu s dosavadními poznatky, které poukazují na souvislosti mezi zvýšenou

hladinou prolaktinu a pasivní odpovědí na stres. Další výsledky této studie také ukazují, že somatoformní disociace, která je také formou pasivní odpovědi na stres, vykazuje souvislost se snížením hladiny kortizolu.
Ačkoliv z těchto získaných poznatků nelze zatím vyvozovat klinicky aplikovatelné závěry, výsledky této studie dokládají nové poznatky, které ukazují na významnou úlohu TNF-α, prolaktinu a kortizolu v patogenezi deprese a disociativních procesů.

1. Introduction

According to the Global Burden of Disease Study 2010, mental disorders are the leading cause of disability worldwide (Murray et al. 2012), with depression playing the major role (Whiteford et al. 2013). In fact, mental disorders tend to be chronic, are associated with increased rate of comorbid medical conditions compared to the general population (Buckley et al. 2009; De Hert et al. 2009; Krishnan 2005) and impair patients' life quality more than other chronic illnesses (Bonicatto et al. 2001; Kuehner & Buerger 2005; Tarrier et al. 2007). Yet, many of the treated patients continue to experience residual symptoms or remain resistant to treatment (Crown et al. 2002; Haro & Salvador-Carulla 2006; Rosenblat et al. 2014), and advances in psychopharmacology do not seem to meet the expectations (Kinch et al. 2014).
As a result, a large body of neuroscience research focuses to further our understanding of the pathophysiological pathways underlying mental illnesses in order to improve the efficacy of current treatments and identify new therapeutic agents. Stress research represents one of the important areas, because stress has been consistently involved in the pathophysiology of depression, schizophrenia and other mental

disorders (Gold et al. 2015; Juster et al. 2011). Underlying mechanisms are complex, including specific stress-related neurodevelopmental and neurological changes, behavioral alterations and various physiological dysregulations with a particular role of inflammation processes (Bizik et al. 2013; Rosenblat et al. 2014). Nevertheless, these mechanisms refering to objective biological outcomes represent only one piece in the multidimensional construct of stress, which involves reciprocal interactions between inputs (such as environmental stressors and subjective psychological distress), and outputs (objective biological stress responses) (Levine 2005; Levine & Ursin 1991). Accordingly, studies of the effects and consequences of stress exposure require an interdisciplinary approach, taking into account specific aspects of the "inputs", such as chronic stress exposure and traumatic stress (Teicher et al. 2003), together with related psychological processes, with the crucial role of dissociation (Bob 2003).

2. Hypotheses and aims of the study

2.1. Advances in psychoneuroimmunological research suggest that the activation of pro-inflammatory mechanisms plays an important role in the pathophysiology of depression (Blume et al. 2011; Raison et al. 2006; Rosenblat et al. 2014; Schiepers et al. 2005; Wichers & Maes 2002). Pro-inflammatory cytokines are substantially involved in this process and it has been proposed that, at least for a sub-group of depressed patients, they may represent a causal factor (Himmerich et al. 2008).

Tumor necrosis factor alpha (TNF-α) is one of the most frequently studied pro-inflammatory cytokines in this context (Himmerich et al. 2008). It has been associated with the depressive disorder in a number of cross-sectional studies (Dowlati et al. 2010; Howren et al. 2009; Zorrilla et al. 2001), as well as one longitudinal study (van Zuiden et al.

2011). Moreover, TNF-α has been related to different aspects of the depressive symptomatology (Hauser et al. 2002; Kraus et al. 2003), specific emotional and cognitive disturbances (Reichenberg et al. 2001) and response to acute stress (García-Bueno et al. 2008; Weinstein et al. 2010). To our knowledge, association to specific trauma-related phenomena in depressed population, namely trauma-related and dissociative symptoms, has not been explored yet.
Based on these data, it was postulated that serum TNF-α levels, measured in depressed inpatients, would be related to both the depressive symptomatology, and trauma-related and dissociative symptomatology.

2.2. Hypothalamic-pituitary-adrenal axis (HPA axis) activity has a profound effect on neuroendocrine balance, neuroimmuno-modulation and disturbances of memory during stress reaction (Bob et al. 2008; Bob et al. 2007a; Esch & Stefano 2005; Jasova et al. 2007; Kellner & Yehuda 1999; Mason et al. 2001; Newport & Nemeroff 2000; Payne et al. 2006; Plotsky et al. 1998; Stefano & Esch 2007; Teicher et al. 2003; van West & Maes 2007). Traumatic events may have a long-lasting effect on HPA axis functioning (Lupien et al. 2009; Newport & Nemeroff 2000; Teicher et al. 2003; van West & Maes 2007). Considering that traumatic stress is typically associated with dissociation, HPA axis reactivity in relationship to the dissociative symptoms is of interest, as documented by previous studies in patients with disociative disorders and borderline personality disorder (Bob et al. 2007b; Carvalho Fernando et al. 2012; Giesbrecht et al. 2007; Simeon et al. 2001; Simeon et al. 2007a; Simeon et al. 2007b).
Nevertheless, data from depressed population are missing. Accordingly, the aim of the study was to examine stress-related disturbances of HPA axis functioning indexed by basal cortisol and prolactin, and to assess their relationship to psychic and somatoform

dissociative symptoms, trauma-related symptoms, and depressive symptoms in patients with depressive disorder.

3. Material and Methods

3.1. In order to examine the hypothesis, assessment of plasma TNF-α level was performed, using immunoradiometric essay (IRMA) analysis of venous blood samples drawn in rest condition between 7:30 and 8:00. In addition, psychometric measures of trauma-related symptoms (using Trauma symptom checklist - TSC-40), depressive symptoms (using Beck depression inventory - BDI-II), and psychic and somatoform dissociative symptoms (using Dissociative experiences scale – DES, and Somatoform dissociation questionnaire - SDQ-20) were performed in a sample of 66 consecutive inpatients with unipolar depression.

3.2. With the aim to examine the second hypothesis, assessment of plasma prolactin level and plasma cortisol level were performed, using chemiluminescent immunoessay (CLIA) analysis of venous blood samples drawn in rest condition between 7:00 and 8:00. Additionally, psychometric measures of trauma-related symptoms (assessed by TSC-40), depressive symptoms (assessed by BDI-II) and psychic and somatoform dissociative symptoms (assessed by DES and SDQ-20, respectively) were performed in a sample of 40 consecutive inpatients with unipolar depression.

4. Results

4.1. The results indicate that TNF-α is significantly correlated to DES (Spearman $R=-0.42$, $p<0.01$), SDQ-20 (Spearman $R=-0.38$, $p<0.01$) and TSC-40 (Spearman $R=-0.41$, $p<0.01$), but not to BDI-II. These correlations show that TNF-α levels exhibit a significant relationship to

psychic and somatoform dissociation and the symptoms related to traumatic stress. Other statistically significant correlations were also found between psychometric measures of depression, traumatic stress and dissociation.

4.2. The results confirm a relationship between HPA-axis activity and psychosocial stressors leading to dissociative symptoms in depressed patients. Data show that prolactin and cortisol levels as indices of HPA axis functioning manifest a significant relationship to dissociative symptoms. The main finding is represented by a highly significant correlation obtained by simple regression between psychic dissociative symptoms assessed by DES and serum prolactin levels ($R=0.55$, $p<0.001$). Significant correlation was also found between somatoform dissociative symptoms assessed by SDQ-20 and serum cortisol levels ($R=-0.38$, $p<0.01$). Significant relationships indicate also Pearson product-moment correlations for psychometric measures of dissociation, symptoms of traumatic stress and depressive symptoms.

5. Discussion

5.1. To our knowledge, this was the first study examining the association between TNF-α and trauma-related and dissociative symptomatology, which makes the interpretation more delicate. The relationship between TNF-α and dissociative symptoms is in accordance with studies reporting that TNF-α increases the HPA activity in depression (Himmerich et al. 2008) and that there is a negative correlation between cortisol levels and somatoform dissociation in depressed patients (Bob et al. 2008). Additionally, the negative correlation between TNF-α and trauma-related symptoms is in line with Batolomucci's research, that describes an inhibitory effect of

chronic psychosocial stress on TNF-α (Bartolomucci et al. 2003). In contrast to previous research (Dowlati et al. 2010), no significant association between TNF-α levels and depressive symptoms was found. Nevertheless, as TNF-α assessment was not performed in healthy controls and the self-report scale BDI-II was used to assess the severity of depressive symptoms, this result is interpreted as inconclusive.

It needs to be mentioned, that while the patients recruitment led to a quite naturalist clinical cohort, the characteristics of the studied group (inpatients, heterogeneous antidepressant treatment) limit the findings. In particular, the effect of different antidepressant treatment on TNF-α may vary considerably (Brustolim et al. 2006; Janssen et al. 2010; Kraus et al. 2002).

5.2. In line with the previous studies (Bob et al. 2007b; Carvalho Fernando et al. 2012; Giesbrecht et al. 2007; Simeon et al. 2001; Simeon et al. 2007a; Simeon et al. 2007b), the results point to a relationship between HPA-axis reactivity and dissociative symptoms.

The correlation between serum prolactin levels and DES is in agreement with the findings of other cross-sectional and longitudinal studies, showing prolactin variations in response to different psychosocial stressors (Sonino et al. 2004; Theorell 1992; Uhart et al. 2006). Specifically, stressful experiences resulting in passive coping behavior are associated with increased prolactin levels, whereas stress situations associated with active coping are associated with unchanged or lowered levels (Theorell 1992). The results regarding the correlation between prolactin and DES found in this study further supports other findings suggesting that there is a close relationship between prolactin and dissociation as a typical form of passive coping behavior related to withdrawal and disengagement related to chronic stress conditions.

The correlation between serum cortisol levels and SDQ-20 is in accordance with the results of other studies showing that chronic stress

exposure resulting in the activation of defense mechanisms is associated with decreased cortisol levels (Mason et al. 2001; Van Der Hart et al. 2005).

Limitations of the study are mainly imposed by cortisol assessment, as the potential confounding factors related to sampling methodology (Levine et al. 2007), gender and age (Van Cauter et al. 1996), and menstrual cycle (Gordon & Girdler 2014) were not included in the analyses.

6. Conclusions

The findings of this study indicate an interplay of TNF-α regulations and chronic stress and dissociative processes in the development and clinical manifestation of depression. Moreover, they show a relationship between prolactin and cortisol levels, and specific aspects of dissociation in depressed patients. These aspects of stress response may be related to passive coping strategies and other defense mechanisms in depression.

List of original publications

1. publications in extenso in relationship to the subject of dissertation

a) with IF

Bizik G., Bob P., Raboch J., Pavlat J., Uhrova J., Benakova H., Zima T., Dissociative symptoms reflect levels of TNF alpha in patients with

unipolar depression. Neuropsychiatric disease and treatment. 2014; 10, 675-679. IF = 1,809

Bizik G., Juster R. P., Picard M.,Nijjar R., Tourjman V., McEwen B. S.,Lupien S. J., Allostatic load as a tool for monitoring physiological dysregulations and comorbidities in patients afflicted by severe mental illnesses, Harvard Review Of Psychiatry. 2013; 21(6), 296-313. IF = 3,046

Juster R P, Bizik G, Picard M, Arsenault-Lappierre G, Sindi S, Trepanier L, Marin M F, Wan N, Sekerovic Z, Lord C, Fiocco A J, Plusquellec P, McEwen B S, Lupien S., A transdisciplinary perspective of chronic stress in relation to psychopathology. Development and Psychopathology. 2011; 23, 725-776. IF = 4,4

Bob P, Fedor-Freybergh P, Jasova D, Bizik G, Susta M, Pavlat J, Zima T, Benakova H, Raboch J. Dissociative symptoms and neuroendocrine dysregulation in depression. Med Sci Monit. 2008; 14(10), 499-504. IF = 1,699

Bob P, Freybergh PF, Jasova D, Susta M, Pavlat J, Zima T, Benakova H, Bizik G, Svetlak M, Vevera J, Miklosko J, Hajek K, Raboch J. Depression, cortisol and somatoform dissociative symptoms, Neuro Endocrinol Lett. 2008; 29(2), 235-239. IF = 1,621

b) without IF

Bizik G., Bob P., Raboch J., Svetlak M., Simek J., Pec O., Benakova H., Uhrova J., Zima T., Dissociation and immune dysregulation: a preliminary report, Activitas Nervosa Superior. 2011; 53, 141-145.

Total cumulative IF = 12,575

2. publications in extenso without relationship to the subject of dissertation

a) with IF

Bob P, Jasova D, Bizik G, Raboch J. Epileptiform activity in alcohol dependent patients and possibilities of its indirect measurement. PLoS One. 2011; 6(4), art. no. e18678. IF = 4,411

b) without IF

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