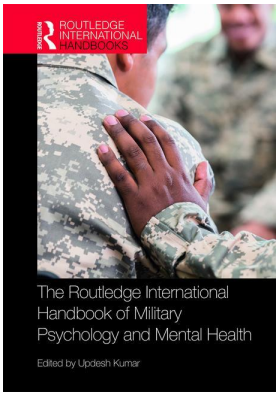

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NEUROTRANSMITTER AND NEUROTROPHIC BIOMARKERS IN COMBAT-RELATED POSTTRAUMATIC STRESS DISORDER

Gordana Nedic Erjavec, Matea Nikolac Perkovic, Dubravka Svob Strac, Lucija Tudor, and Nela Pivac

Posttraumatic stress disorder

Posttraumatic stress disorder (PTSD) is a severe mental disorder that requires direct or indirect exposure to a single traumatic event or prolonged exposure to stressful events (American Psychiatric Association, 2013). Traumatic experience might also be induced by witnessing a stressful event that happened to family members or a close friend or exposure to consequences of traumatic events in professional workers (APA, 2013; Pai, Suris & North, 2017). PTSD develops only in vulnerable individuals after traumatic exposure. Vulnerability to PTSD is still not completely understood, but is assumed to be associated with altered connectivity and disturbed functions of various CNS regions and altered immune function as well as disturbed neurotransmitter and neuroendocrine responses. The interaction between these biological/genetic factors and psychological, cognitive, emotional, environmental and psychosocial factors contributes to vulnerability to PTSD.

The biggest challenge in PTSD research is to find biomarkers of vulnerability or resilience, especially in soldiers. It is important to recognize biological characteristics associated with higher vulnerability to combat trauma in veterans (Frank, Zamorski, Lee & Colman, 2018), as vulnerability factors might impact individual responses and disturb unity in military platoons.

Characteristic symptom clusters in PTSD, according to the DSM-5 (APA, 2013; Rosebrock, Arditte Hall, Rando, Pineles & Liverant, 2018; Ito, Takebayashi, Suzuki & Horikosh, 2018) and described therein are: re-experiencing, avoidance, numbing and hyper-arousal. They should last minimally one month after traumatic exposure. However, in addition to these, individuals with PTSD frequently develop other symptoms that affect clinical picture, course of illness and treatment response. These symptoms include agitated and psychotic symptoms (Compean & Hamner, 2019) or suicidal behaviour.

Although people are exposed frequently to various traumatic events (Bisson, Cosgrove & Roberts, 2015), only a subset of individuals will develop PTSD (Kessler et al., 2017). As opposed to the prevalence of trauma, the prevalence of PTSD is less than 9% in civilians (Atwoli, Stein,

Koenen & McLaughlind, 2015), while the prevalence in combat exposed veterans ranges between 11%–30% in the United States (Dursa, Reinhard, Barth & Schneiderman, 2014; Kang, Natelson, Mahan, Lee & Murphy, 2003; Kintzle, Barr, Corletto & Castro, 2018) and 18%–40% in Croatian (Komar & Vukusic, 1999) war veterans.

Biomarkers in posttraumatic stress disorder

There are different risk factors that predispose individuals to PTSD. Finding these risk factors is the major goal in biomarker research, which is focused on finding reliable and easily available, validated and specific biomarkers related to the vulnerability to develop PTSD (Lehrner & Yehuda, 2014). Biomarkers of PTSD are related to different symptoms and behaviours which occur in PTSD and develop due to disturbances in diverse biological systems. PTSD in military veterans presents with a more severe time course, with pronounced hyper-arousal and intrusive symptoms (Guina, Nahhas, Sutton & Farnsworth, 2018).

Biomarkers are measurable and quantifiable biological parameters that should be used as key tools to provide crucial information on the complex molecular mechanisms of the disorder. They can be classified as diagnostic biomarkers, disease prognosis biomarkers and biomarkers for monitoring the clinical or therapeutic response (Nikolac Perkovic et al., 2017). In PTSD there are numerous types of physiological markers (such as neuroimaging and psychophysiological measures and behavioural and neurocognitive responses), but the majority of biomarkers are different parameters that can be determined in peripheral bio-fluids. Since a variety of markers were proposed for PTSD, an attempt has been made to organize these metadata in one PTSD Biomarker Database (Domingo-Fernandez et al., 2019). However, specific and validated biomarkers for PTSD are still missing (Lehrner & Yehuda, 2014). Most biomarkers are related to the major neurotransmitters dopamine, noradrenaline (Pan, Kaminga, Wen & Liu, 2018) and serotonin, but also to the major stress response system, i.e. the hypothalamic-pituitary-adrenal (HPA) axis, immune system and metabolic and glycomic markers (Kao, Stalla, Stalla, Wotjak & Anderzhanova, 2015; Olff & van Zuiden, 2017; Nedic Erjavec et al., 2018; Konjevod et al., 2019, VanDyke, Burton, Hanidovic & Burke, 2017). Biomarkers have military applications (i.e. they might be used to confirm PTSD diagnosis and severity, to predict risk, for validation of trauma exposure, to predict recovery, to verify the recovery and for subtyping PTSD) but there must also be consideration of the potential ethical, social, clinical and legal implications (Lehrner & Yehuda, 2014).

Dopaminergic markers in posttraumatic stress disorder

One of the most elaborated hypotheses of the neurobiological underpinning of PTSD is a dysfunction of the dopaminergic system (Lee, Wang & Tsien, 2016). The dopamine signalling system regulates several neurological processes, including fear-conditioning in different brain areas (Aubry, Serrano & Burghardt, 2016). Neuroimaging studies reveal dopamine dysregulations in individuals with PTSD as a response to stressful stimuli (Charney, 2004). Also, a higher response of the dopaminergic system after the stress exposure often occurs, and it is associated with PTSD symptoms such as restlessness, nightmares, fear memories and impulsivity (Pezze & Feldon, 2004), as well as alterations in memory and other cognitive functions, anhedonia and hypervigilance (Sher et al., 2005). Systematic levels of dopamine were measured in order to investigate how they relate to PTSD. In a study dealing with PTSD in mothers of childhood cancer survivors (Glover et al., 2003), an increased concentration of urinary dopamine in women with PTSD was found compared to values in women without PTSD and in healthy control women. However, another

study (Osuch et al., 2009), and a recent meta-analysis of seven studies accounting for a total of 656 participants (Pan et al., 2018), reported no significant changes in dopamine levels between individuals with PTSD and healthy control subjects.

Genetic variations in the dopaminergic system involved in signalling transduction may affect the ability to cope with stress stimuli in people who have been exposed to traumatic events (Cornelis, Nugent, Amstadter & Koenen, 2010). A SNP in dopamine receptor D2 (DRD2) gene (rs6277) has been reported as significantly associated with PTSD where war veterans with PTSD were more likely C allele carriers than healthy control subjects (Voisey et al., 2009). Another polymorphism (rs1800497) of the DRD2 gene was significantly associated with PTSD according to meta-analysis, which examined six studies with a total of 597 PTSD patients and 1155 controls (Li et al., 2016). Further on, a long (seven or more repeats) allele (considering VNTR in the third exon of dopamine receptor D4 [DRD4] gene) was found to be associated with significantly intense avoidance/numbing symptoms and PTSD symptoms in general, but not with the PTSD diagnosis itself, among flood survivors (Dragan & Oniszczenko, 2009). There are contradictory reports about the association of PTSD and a variable number of tandem repeats (VNTR) in a dopamine transporter gene (DAT1). According to some studies, there is an increased risk of PTSD in grown-up individuals (Segman et al., 2002) and preschool children (Drury, Theall, Keats & Scheeringa, 2009) with 9 repeats (9R) of 40-bp sequence when compared with individuals/children carrying 10 repeats-allele (10R). On the other hand, a study carried out on a group of people suffering from PTSD after exposure to an earthquake found no association between DAT1 VNTR and PTSD risk (Bailey et al., 2010). Due to the scarce presence of DAT in prefrontal cortex (PFC), dopamine degradation in this area mostly depends on catechol-O-methyltransferase (COMT) activity, which is altered by its functional polymorphism rs4680 (Val108/158Met substitution), also affecting the overall dopaminergic signalling (Goldberg & Weinberger, 2004). Namely, the Met allele is associated with reduced COMT activity and dopamine degradation, causing higher dopamine availability in the PFC (Chen et al., 2004). Therefore, it is not surprising that there is a certain association of COMT rs4680 and PTSD, manifested either in reduced hippocampal volume in Val homozygotes (Hayes et al., 2017) or in better cognitive performance in veterans with PTSD (Mestrovic et al., 2018), increased endocrine stress reactivity (Alexander et al., 2011) and deficits in fear conditioning (Deslauriers et al., 2018) in Met carriers or homozygotes. On the other hand, a meta-analysis (Li et al., 2016) including five studies dealing with COMT rs4680 found no association between this polymorphism and PTSD risk. In complex diseases such as PTSD, some genetic effects are often more pronounced in certain combinations with other genetic or environmental factors. For example, it was reported that men carrying a combination of Met/Met COMT rs4680 genotype and 10R/10R DAT1 VNTR have higher cortisol responses and impaired stress recovery during public speaking (Alexander et al., 2011).

Another important dopamine degrading enzyme is monoamine oxidase (MAO) that exists in two isoforms, MAO-A and MAO-B, and participates in the regulation of important processes such as mood, emotions and behaviour (Edmondson, Binda, Wang, Upadhyay, & Mattevi, 2009). Its role in the pathophysiology of different mental and neurodegenerative disorders was also reported (Adolfsson, Gottfries, Oreland, Wiberg & Winblad, 1980; Brunner, Nelen, Breakefield, Ropers & van Oost, 1993; Sandler, Glover, Clow & Jarman, 1993). Considering the role of MAO in PTSD, literature data are inconsistent. In contrast to one earlier study (Davidson, Lipper, Kilts, Mahorney & Hammett, 1985) that found platelet MAO-B activity to be reduced in PTSD, another study reported no difference in platelet MAO-B activity between war veterans with or without PTSD (Pivac, Muck-Seler, Sagud & Jakovljevic, 2002) or increased platelet MAO-B activity in veterans with psychotic PTSD compared to veterans with non-psychotic

features (Pivac et al., 2007; Svob Strac et al., 2016). Additionally, altered MAO-B activity was found in platelets of veterans with more severe PTSD symptoms according to the Clinician Administered PTSD Scale (CAPS) and in veterans with agitation assessed by the Positive and Negative Syndrome Scale (PANSS) (Svob Strac et al., 2016). Polymorphisms of MAO-A and MAO-B genes were found to be associated with different pathologies (Bortolato & Shih, 2011), but a lack of association of the most studied MAO-B (rs1799836) (Pivac et al., 2007) and MAO-A (MAOA-uVNTR) (Svob Strac et al., 2016) polymorphisms with combat related PTSD was reported. A methylation of MAO-A gene exonI/intronI region was recently suggested as a disease status and severity (according to CAPS) marker of PTSD in men (Ziegler et al., 2018). Namely, a hypermethylation of 3 CpGs was found in male subjects with current PTSD when compared with remitted PTSD patients and healthy control subjects, while symptom severity significantly correlated with MAO-A methylation (Ziegler et al., 2018).

It seems that there are several potential dopaminergic biomarkers of PTSD, but still more extensive studies are needed to overcome the effects of severity of PTSD symptoms, race and ethnicity and type and duration of traumatic events on overall mechanisms of development and course of PTSD.

Serotonergic biomarkers of posttraumatic stress disorder

Various studies have investigated the role of serotonergic system in PTSD. A variety of data suggested that serotonergic dysregulation might be related to PTSD symptoms such as hypervigilance, exaggerated startle, irritability, impulsivity, aggression, intrusive memories, depressed mood and suicidality (Southwick et al., 1999). Findings supporting the role of serotonin (5-HT) in PTSD include clinical efficacy of selective serotonin reuptake inhibitors (SSRIs), (Marshall, Beebe, Oldham & Zaninelli, 2001; Martenyi, Brown, Zhang, Prakash & Koke, 2002; Davidson, Rothbaum, van der Kolk, Sikes & Farfel, 2001) and blunted prolactin response to 5-HT–releasing drug fenfluramine (Davis, Clark, Kramer, Moeller & Petty, 1999), as well as exaggerated reactivity to m-chloro-phenyl-piperazine, the 5-HT agonist (Southwick et al., 1997).

A number of studies have addressed serotonergic function in PTSD by investigating the peripheral markers. Since blood platelets store 5-HT and possess many other serotonergic components, including serotonin transporter (5-HTT), enzyme MAO-B, as well as various 5-HT receptors, they are considered an easily available, limited peripheral model of central 5-HT function (Muck-Seler & Pivac, 2011). Studies measuring 5-HT uptake into platelets (Cicin-Sain et al., 2000; Mellman & Kumar, 1994) and platelet 5-HT concentrations (Muck-Seler et al., 2003; Pivac et al., 2002), as well as [3H] paroxetine (Maguire, Norman, Burrows, Hopwood & Morris, 1998) or [3H] imipramine (Weizman et al., 1996) binding to platelet membranes demonstrated no alteration of peripheral 5-HT function in PTSD. On the other hand, diminished 5-HT activity was suggested by studies demonstrating lower platelet paroxetine binding (Arora, Fichtner, O'Connor & Crayton, 1993; Maes et al., 1999), decreased 5-HT concentration in platelets (Guo et al., 2016, Li et al., 2016) and decreased platelet-poor plasma 5-HT levels (Spivak et al., 1999) in PTSD patients.

Lower platelet 5-HT concentration was also found in suicidal PTSD patients compared with non-suicidal patients or healthy controls (Kovacic, Henigsberg, Pivac, Nedic & Borovecki, 2008). These results might explain different findings (Guo et al., 2016, Li et al., 2016) from the literature, since suicidality is frequently associated with PTSD and the presence of suicidal behaviour might have affected platelet 5-HT data. On the other hand, higher platelet 5-HT concentration was observed in PTSD veterans with psychotic features compared to veterans with PTSD who did not develop psychotic symptoms (Pivac et al., 2006) and in non-depressed veterans with PTSD

and early insomnia compared to veterans with PTSD who did not develop insomnia (Kovacic Petrovic et al., 2019). Therefore, the presence of psychotic symptoms or insomnia affected platelet 5-HT concentration in veterans with PTSD.

Regarding genetic variants of the components of the serotonergic system, most of the PTSD studies focused on 5-HTT encoded by the *SLC64A* gene. Reduced 5-HTT binding has been observed in the amygdala of PTSD patients (Murrough et al., 2011). In a PET study, Frick et al. (2016) found both higher and lower 5-HTT and neurokinin-1 (NK1) receptor availability in several brain regions of PTSD patients; however, lower expression overlap between 5-HTT and NK1 receptors has been associated with higher PTSD symptom severity.

Frequently investigated *SLC64A* promoter polymorphic region (5-HTTLPR) has two common functional variants. The S (short) allele, in comparison to L (long) allele, is associated with lower gene transcription, decreased 5-HTT activity and lower 5-HT reuptake from the synaptic cleft (Morey et al., 2011; Kolassa, Illek, Wilker, Karabatsiakis & Elbert, 2015), resulting in increased amygdala reactivity to emotional stimuli and consequently higher fear conditioning (Hariri et al., 2002). However, since a third functional allele L_G has been identified (Nakamura, Ueno, Sano & Tanabe, 2000), the 5-HTTLPR polymorphism is now considered triallelic. This A > G substitution at nucleotide 6 of the first of two extra 22-bp repeats in the L allele results in a transcriptional level comparable with that of the S allele. Many studies found an association of 5-HTTLPR polymorphism with PTSD (Goenjian et al., 2012; Kilpatrick et al., 2007; Koenen et al., 2009a; Lee et al., 2005), which was consistently observed in combat related studies (Kimbrel et al., 2015; Liu et al., 2015; Wang et al., 2011). However, the reported findings have been contradictory (Gressier et al., 2013; Kolassa et al., 2010; Kovacic Petrovic, Nedic Erjavec, Nikolac Perkovic, Peraica & Pivac, 2016; Navarro-Mateu, Escámez, Koenen, Alonso & Sánchez-Meca, 2013). For example, in some studies, increased risk of PTSD was associated with the 5-HTTLPR low expression S allele (Lee et al., 2005; Kolassa et al., 2010; Kilpatrick et al., 2007; Koenen et al., 2009a, Xie et al., 2009; Mellman et al., 2009), whereas other studies report association with the high expression L allele (Thakur, Joober & Brunet, 2009; Grabe et al., 2009). In addition, the LL genotype of 5-HTTLPR was associated with more severe early insomnia in veterans with PTSD compared to veterans with PTSD who did not develop early insomnia (Kovacic Petrovic et al., 2019). Nevertheless, recently, Zhao et al. (2017) performed a meta-analysis of 14 studies with 15,883 subjects and found strong evidence that 5-HTTLPR significantly influenced the relationship between stress and PTSD. Another meta-analysis demonstrated an association between the SS genotype and PTSD only in high trauma-exposed participants (Gressier et al., 2013). The review of meta-analyses on PTSD candidate gene research confirmed the association of 5-HTTLPR with PTSD, but only in an interaction with environment (Sheerin, Lind, Bountress, Nugent & Amstadter, 2017). Namely, for 5-HTTLPR, a significant G × E effect was found to be associated with PTSD. The 5-HTTLPR genotype interacted with adult traumatic events and childhood adversity to increase the risk for PTSD, especially in individuals exposed to high rates of both types of trauma (Xie et al., 2009). Consistently with the plasticity gene hypothesis (Belsky et al., 2009), the S allele was associated with increased risk of PTSD when combined with high rates of crime and unemployment, whereas it was associated with decreased PTSD risk in low-risk environments (Koenen et al., 2009a). Various animal studies also demonstrated that 5-HTT gene variations are associated with changes in serotonergic function following early stressful experiences (Murphy et al., 2001; Bennett et al., 2002).

In addition, *SLC6A4* methylation was shown to modify the effect of the number of traumatic events on PTSD risk. Koenen et al. (2011) reported that individuals with more traumatic events were at increased risk for PTSD, but only at lower *SLC6A4* methylation levels, whereas at higher methylation levels, subjects with more traumatic events were protected from PTSD. Methylation

patterns of 5-HTTLPR have also been associated with an increased risk of unresolved loss or trauma, but only for individuals with the L allele (Van, Caspers, Bakermans-Kranenburg, Beach & Philibert, 2010), suggesting an interaction between methylation density and the 5-HTT genotype. Such 5-HTTLPR genetic–epigenetic interactions have been shown to influence circulating cortisol levels in response to stress (Alexander et al., 2014).

Moreover, Bharadwaj et al. (2016) suggested rs363276 polymorphism, located in intron 14 of the *SLC18A2* gene, coding for a transporter of monoamines serotonin, dopamine and noradrenaline, as a new candidate polymorphism associated with PTSD risk.

Some studies suggested a significant role of 5-HT receptors in PTSD. The G allele of the -1438A/G substitution polymorphism (rs6311), located in the promoter region of 5-HT2A receptor gene, was significantly associated with increased risk of PTSD (Mellman et al., 2009; Lee, Kwak, Paik, Kang & Lee, 2007). Additionally, another 5-HTR2A genetic variant (rs7997012) was shown to moderate the association between PTSD severity and reduced default mode network (DMN) connectivity (Miller et al., 2016). In a PET study, Sullivan et al. (2013) observed higher brainstem and forebrain 5-HT1A binding in PTSD. However, no change in 5-HT1A receptor binding was found in a study by Bonne et al. (2005).

Regarding PTSD research assessing the 5-HT synthesis and metabolism, observed association of PTSD symptoms with the T allele of rs2108977 and rs11178997 polymorphisms, located in the *TPH1* and *TPH2* genes, respectively, suggested that variants in the genes coding for tryptophan hydroxylase (TPH), the enzyme involved in 5-HT synthesis, represent risk factors for PTSD symptoms (Goenjian et al., 2012). In subjects with war-related chronic PTSD, the CSF concentrations of 5-hydroxyindoleacetic acid (5-HIAA), a main 5-HT metabolite, tend to decline during presentation of a trauma-related video, suggesting its association with laboratory-induced PTSD symptoms (Geracioti et al. 2013).

In conclusion, these data summarize an important role of serotonergic system, its components and genetic variations of the 5-HT system's components in the development of PTSD and its symptoms.

Neurotrophic factors in posttraumatic stress disorder

During development and in adulthood, neurotrophins have an important role in regulating neurogenesis, differentiation, maintenance and growth of neuronal cells. Neurotrophins, like nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are also the key modulators of brain plasticity and their expression is under strong influence of psychophysical stress (Bothwell, 2014). BDNF is widely expressed in various types of tissues and cells, including the limbic system where it is involved in the regulation of stress and fear responses (Peters, Dieppa-Perea, Melendez & Quirk, 2010; Rosas-Vidal, Do-Monte, Sotres-Bayon & Quirk, 2014). Studies involving animal models (Faure, Uys, Marais, Stein & Daniels, 2007) support the theory of BDNF over-expression, in plasma and in hippocampus, as a compensatory mechanism which is induced by the traumatic stress (Zhang et al., 2014). Brain-derived neurotropic factor (BDNF), although not a conventional CVD risk factor, has also drawn attention. Namely, low peripheral levels of BDNF were associated with an increased risk of stroke (Pikula et al., 2013) and was proposed as a biomarker of heart failure (Takashio et al., 2015). In line with this, higher serum BDNF levels were protective, suggesting decreased risk of CVD (Kaess et al., 2015). Studies have reported either decreased BDNF levels in patients with different types of non-combat related trauma (Dell'Osso et al., 2009; Stratta et al., 2016), no difference in BDNF levels in subjects after traffic accidents (Su et al., 2015; van den Heuvel, Suliman, Malan- Müller, Hemmings & Sedat, 2016), and elevated BDNF levels in subjects severely injured in traffic accidents (Matsuoka, Nishi,

Noguchi, Kim & Hashimoto, 2013), in those with trauma not specified (Hauck et al., 2010) and in young male veterans with PTSD (Blessing et al., 2017). It seems that peripheral BDNF levels are higher after the trauma, and decrease thereafter (Hauck et al., 2010). Higher methylation within the BDNF promoter I region, in peripheral leukocytes, was reported in veterans with PTSD, even 45 years after combat exposure, relative to non-psychiatric controls (Kim et al., 2017).

Recent findings propose that up-regulated BDNF release might help to prevent the development of PTSD since it induces fear extinction and mediates more successful trauma processing (Dincheva, Lynch & Lee, 2016). Data from animal studies suggest that stress, along with BDNF up-regulation, leads towards startle response abnormality (Zhang et al., 2014), one of the main symptoms of PTSD, i.e. hyperarousal (Jovanovic, Norrholm, Sakoman, Esterajher & Kozarić-Kovacić, 2009).

Different genome-wide association studies (GWAS) and candidate gene studies (Koenen, Amstadter & Nugent, 2009b; Miller &Wiener, 2014) have pointed out the importance of BDNF in the pathology of PTSD. A common SNP in the BDNF gene, which results in a valine to methionine substitution at position 66 (Val66Met), has been associated with poorer memory performance and reduced hippocampal volumes (Brooks et al., 2014; Zhang et al., 2006). Compared to Val/Val homozygotes, the Met allele carriers show less activity-dependent release of BDNF in the hippocampus (Hashimoto et al., 2008; Miller & Wiener, 2014; Sanchez et al., 2011). Study by Zhang and colleagues (2014) detected a higher frequency of Met/Met genotype carriers and a twofold higher frequency of Met allele carriers in subjects diagnosed with PTSD, compared to individuals without PTSD symptoms, which fits with the findings of smaller hippocampal volume in Met allele carriers (Bueller et al., 2006; Harrisberger et al., 2014; Szeszko et al., 2005). Results also indicate that Met allele carriers have poorer memory performance compared to Val/Val genotype carriers (Hariri et al., 2003). Our study further supports the interaction between BDNF Val66Met polymorphism and PTSD, showing a higher frequency of Met allele carriers in veterans with psychotic PTSD, compared non-psychotic veterans with PTSD or veterans without PTSD (Pivac et al., 2012). BDNF Met allele was also associated with exaggerated startle, linking Met/Met genotype to hyper-arousal vulnerability (Zhang et al., 2014). However, there are also studies that suggest no association between PTSD and BDNF Val66Met polymorphism (Zhang et al., 2006), which emphasizes the need for further research evaluating the genetic association between BDNF and PTSD, also taking into account BDNF central/peripheral levels and epigenetic patterns that influence BDNF gene expression. In addition, as demonstrated by Zhang and colleagues (2014), it is very important to have in mind different environmental conditions, trauma exposure type and trauma severity, time passed since exposure, treatment approach, and age.

In the last decade BDNF blood levels (plasma and serum levels) were proposed as potential biomarkers in PTSD diagnosis (Angelucci et al., 2014; Grassi-Oliveira, Stein, Lopes, Teixeira & Bauer, 2008; Hauck et al., 2010; Matsuoka et al., 2013). Data suggested that individuals diagnosed with PTSD have significantly higher BDNF serum levels, compared to controls (Hauck et al., 2009; Hauck et al., 2010), with BDNF levels being higher in Met allele carriers then in Val/Val genotype carriers (Harris et al., 2006). However, some studies showed opposite results (Dell'Osso et al., 2009). These contradictory results might be a consequence of differences in the sample population and different time points during the course of the disease in which the analyses were done. Nevertheless, peripheral BDNF levels could contribute to development of less invasive diagnostics in PTSD (Zhang et al., 2014).

NGF is another key member of neurotrophin family (Bothwell, 2014), but there is still not enough effort to investigate the diagnostic potential of NGF in PTSD in details. Study by Tural and colleagues (2018) showed lower serum NGF levels in individuals with chronic PTSD, compared

to trauma exposed non-PTSD individuals. In addition, the authors reported that after 12 weeks of treatment with escitalopram, the NGF production was restored, hippocampal activity was decreased and there was a significant improvement in Clinician-Administered PTSD Scale (CAPS) scores in individuals with PTSD (Tural, Tamer Aker, Turan Sodan, Ünver & Akansel, 2018).

In summary, neurotrophic system, with BDNF and NGF and genetic variants of the BDNF are associated with PTSD. However, the clear relationship still needs to be elucidated.

Conclusion

The most frequent data on the biomarkers in PTSD are biomarkers related to components of the dopaminergic, serotonergic and neurotrophic systems, especially BDNF. It is difficult to conclude on the specificity of these biomarkers since in the literature there are mixed results regarding the changes of biomarker findings in PTSD. Namely, the same biomarkers were reported to be increased, decreased, or unchanged in PTSD. The comparison with corresponding control samples might also contribute to these divergent findings, since for veterans with PTSD studies should include combat exposed veterans who did not develop PTSD. More data regarding PTSD biomarkers will lead to improved knowledge on the biological underpinning of PTSD. Notwithstanding the alterations in dopaminergic, serotonergic and neurotrophic systems, development of PTSD depends on the complex interactions between these and other biological factors, environmental and trauma-related factors, psychological factors, presence or absence of early stress, and/or social and family support. This review focused on the most frequently studied markers of the dopaminergic, serotonergic and BDNF systems. However, due to the complexity of PTSD, efforts of the future studies should be to offer a panel of biomarkers that will more appropriately reveal alterations in PTSD.

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