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Beta-Endorphin Peptide and some Selected Psychiatric Disorders

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Abstract

Beta-endorphin, an endogenous opioid peptide seems to play an important role in some psychiatric disorders. Some researchers observed a correlation between this peptide level in plasma or cerebrospinal fluid and several diseases such as: major mood disorders, schizophrenia, autism, self-injurious behavior and addiction. However, there are also many inconclusive reports which do not evidently prove that a deficit or an excess of this peptide is related to specific diseases. These discrepancies may depend on methodological methods and patients' selection, who may present different subtypes of the same disease. It was also suggested to use beta-endorphin as an indicator of effectiveness of treatment in some psychiatric disorders.

Conclusion: Beta-endorphin measurement may help assessing the effectiveness of therapy in some psychiatric diseases as well predicting the development of some diseases related to beta-endorphin as postpartum depression or PTSD.

Keywords: Beta-Endorphin; Depression; Schizophrenia; Autism; Self-Injury Behavior; Post-Traumatic Stress Disorder

Introduction

Beta-endorphin is the most important peptide of the endogenous opioid system, which consists of 3 families of peptides: endorphins, enkephalins and dynorphins, as well as two additional peptides, endomorphin-1 and -2 [1,2]. The endogenous opioid system plays a relevant role in various functions of the organism, such as analgesia, regulation of respiration, control of the cardiovascular system, and eating behavior, as well as control of thermoregulation, learning, and memory [3]. This system is also involved in emotions and reactions of the body to stress factors such as anxiety, because during the stress reaction, the secretion of corticotropin-releasing hormone (CRH) stimulates proopiomelanocortin (POMC) to release ACTH and beta-endorphin [4-6].

Beta-endorphin belongs to the endorphins family, and is produced in the hypothalamus and pituitary gland. Neurons that synthesize and release β-endorphin are predominantly located in the hypothalamic arcuate nucleus [7]. Hence, beta-endorphin neurons project to various brain regions including the ventral tegmental area (VTA), nucleus accumbens, septum, amygdala, hippocampus, frontal cortex and periaqueductal gray [7,8]. Beta-endorphin plays an important role in the brain reward system both in controlling and modulating reward, as well as in reinforcing processes. This peptide is implicated in response to natural rewards such as food and fluid intake and sexual behavior, and also plays an important role in addiction [9,10]. Abnormalities of beta-endorphin secretion have been reported, most of all, in various stress related psychiatric disorders, such as depression or post-traumatic stress disorder (PTSD) and other conditions [11,12]. Aberrant beta-endorphin production has also been postulated in obesity, diabetes, and altered immune response or in response to peripheral inflammation [4,13-17]. Over the recent years, interest in beta-endorphin has weakened, however it was suggested to use the measurement of beta-endorphin concentration as a biological marker for effectiveness of therapy in some psychiatric disorders. The following overview concentrates on the role of beta-endorphin in various psychiatric disorders, such as depression, PTSD, schizophrenia, autism, and self-injurious behavior. This overview omits the role of beta-endorphin in addiction to psychoactive substances, because detailed discussion of this issue requires a separate review.

Methodology

The review was based on a primary literature search on the Medline/PubMed using the search terms "beta endorphin with the next descriptors: psychiatric disease, schizophrenia, depressive disorder, depression, PTSD, post-traumatic stress disorder, self-injury behavior, autism" Relevant articles were selected according to the professional judgement of the author, were applied and there were no restrictions on the types of studies and articles or date.

Depression

Depression is a serious mood disorder and the most frequent cause of disability in the world [18]. Some studies present opioid system as associated with mood regulation and, hence, with depressive disorders [19]. Preclinical studies have shown that beta-endorphin is involved in regulation of several processes which occur during depressive episodes. These include regulation of feeding behavior, motivation, and different types of physical activity [20]. Studies of the role of beta-endorphin in the development of depression have been undertaken for many years. Experimental and clinical research showed that beta-endorphin may play an important role in the pathophysiology of major depressive disorder [21]. Reports from experimental studies suggest a decrease in beta-endorphin neurotransmission as agonists of opioid receptors reduced depressive-like behaviors in several behavioral tests, such as forced swimming test, tail suspension test and learned helplessness test [22,24]. Moreover, the effectiveness of opioid agonists in reserpinized mice may suggest that the opioid system plays an important role in depression [25,26]. Additionally, the opioid system has been suggested as a target for treatment of this disorder [19,23]. Bernstein, *et al.* observed that the number of arcuate and paraventricular neurons containing beta-endorphin was significantly reduced in depressive patients [27]. Also, pain related to depression suggests, a low level of opioid peptides [28]. Some reports describe the effectiveness of oxycodone, oxymorphone and buprenorphine in patients with depression [29-31]. Moreover, studies by Berrocoso and Mico support the hypothesis that a combination of antidepressants with even at subeffective doses opioid receptor agonists, may be a helpful new strategy in the treatment of refractory depression [32]. However, this combination of antidepressants with opioids may increase the risk of dependence, abuse and withdrawal reactions what limited interest in their use for depression [33]. Conversely, the results of a recent study suggest that opioid analgesics used for longer than 30 days impose the risk of new-onset depression [34]. Authors suggested that new-onset depression may have developed during or after opioid use cessation. It seems that, given the above observations, the best option could be to balance the opioid system. Placebo controlled clinical studies showed that treatment of major depressive disorder in inadequate response to antidepressant used with mixed opioid agonists and antagonists may increase the effectiveness of therapy [35,36]. On the other hand, in some depressed patients higher than normal plasma and CSF levels of beta-endorphin were observed. The elevated beta-endorphin concentration was found in manic depressive patients in manic state [37].

Inconsistency of reports about beta-endorphin levels can be explained by the existence of various types of depression [38]. It seems that beta-endorphin concentration may be increased in some subtypes of depression, but not in others. It was observed that individuals with endogenous depression appear to have significantly lower levels of beta-endorphin compared with non-endogenous depressed subjects [20,39,40]. Djurovic, *et al.* observed the serum levels of beta-endorphin in patients with 'nonendogenous' depression (104.68 ± 5.29 pg/ml) and in those with 'endogenous' depression (36.34 ± 2.23 pg/ml) as well as in healthy volunteers (125.19 ± 1.64 pg/ml) [40]. They also observed that antidepressant treatment with fluvoxamine caused a statistically significant increase in beta-endorphin serum levels in all patients (nonendogenous depression 132.10 ± 2.38 pg/ml and endogenous depression 50.09 ± 2.45 pg/ml). It seems that an increase in beta-endorphin levels during therapy may be an indicator of its effectiveness. Kubryak, *et al.* observed increased beta-endorphin plasma level in patients with nonpsychotic unipolar depression after 2 weeks of antidepressant treatment [41]. This increase in the level of the peptide was accompanied by an improvement in mental condition of patients, estimated with 17-item Hamilton Depression Rating Scale (HDRS). A similar improvement was observed in patients who didn't receive antidepressants but underwent biofeedback treatment and rehabilitative exercises [41]. Another study by Zalewska-Kaszubska and Obzejta confirmed a correlation between the increase of beta-endorphin concentration and the alleviation of depression. They observed that in alcohol addicted subjects with depression treated with laser irradiation the increase in plasma beta-endorphin level was accompanied by the decrease of depression, assessed with Beck Depression Inventory-Fast Screen (BDI-F) [42].

Another prevalent type of depression often occurs in women after delivery. Although postpartum depression (PPD) etiology is still unclear, some authors hypothesize that abnormalities in plasma beta-endorphin concentration may be involved. In a prospective study of primiparous Australian women, Smith, *et al.* examined their mood changes using Profile of Mood States (POMS) and Montgomery Asberg Depressive Rating Scale (MADRS) [43]. At the same time they monitored beta-endorphin plasma levels both during pregnancy and the third postpartum month. They observed that beta-endorphin increased as pregnancy advanced, peaked at birth and fell after delivery. Larger falls were observed in women who also had significantly higher MADRS depression scores at third postpartum months, Yim, *et al.* have tried to identify the women at risk of postpartum depression as early as possible [43,44]. They observed that women who developed PPD symptoms had higher levels of beta-endorphin throughout pregnancy compared to women without PPD symptoms. These observations indicate that determination of beta-endorphin levels may be a useful early predictor of PPD symptoms in women who did not report depressive symptoms in mid-pregnancy. It seems that examining levels of beta endorphin during the course of pregnancy may help prevent occurrence of PPD and improve the efficiency of treatment in the early stages of pregnancy. About half of all postpartum depression cases occur in the first two weeks after childbirth. Some of these cases follow a period of early euphoria [45]. It is likely that high levels of beta-endorphins during pregnancy help women tolerate their state better as well as may be responsible for the initial euphoria. However, following the delivery the levels of this peptide decrease and beta-endorphin deficit may be the cause of postpartum depression. Babiss and Gangwisch reported that increased physical activity may protect against depression [46]. Results of some clinical trials have shown an increase in plasma beta-endorphin following acute and chronic exercise [47,48]. The effects of physical activity in depressed patients are comparable to antidepressant treatment, or at least can enhance its effectiveness [49,50]. Considering all the above cited studies, it seems that

determination of beta-endorphin blood levels could be a valuable laboratory test not only in the diagnosis of depression but may also be useful as an indicator of potential efficacy of antidepressant therapeutic strategy.

Post-Traumatic Stress Disorder (PTSD)

PTSD is a chronic anxiety disorder which may be developed by people who have survived traumatic events. The stress especially caused by traumatic events induces the release of beta-endorphin to promote adaptation of the organism [51,52]. Increased release of beta-endorphin during early periods of stress which help to suppress pain and emotional response, later gradually decreases and leads to depletion of this peptide, which may play a role in pathogenesis and continuation of PTSD [53,54]. Hoffman, *et al.* Proposed that plasma beta-endorphin concentration may be a marker for PTSD, as they observed significantly lower concentration of this peptide in PTSD [54]. It was observed that individuals with PTSD have a reduced pain threshold, which may indicate a decreased beta-endorphin release [55]. It was also observed that acute stress may induce analgesia [56], however, chronic stress may contribute to hypersensitivity to pain known as stress-induced hyperalgesia [57], probably because of beta-endorphin depletion [56,57]. Chronic pain has been shown to be highly comorbid in patients with PTSD, especially in veterans but also in civilian population [55,58,59]. However, not all individuals exposed to traumatic stress develop PTSD [60,61]. Kavushansky, *et al.* hypothesized that low level of beta-endorphin in traumatic stress, which may be caused by degradation of this peptide by enzymes metabolizing this opioid in brain, may contribute to vulnerability of individuals to develop PTSD [61]. Therefore it is possible that measuring beta-endorphin level in patients after traumatic events may identify individuals vulnerable to developing PTSD. Later it may also be a marker of treatment effectiveness.

Self-injury behavior

Self-injury behavior may refer to several different behaviors including both suicidal and non-suicidal self-injury (NSSI) [62]. This behavior is strongly associated with psychiatric disorders such as: depression, borderline personality disorder, dissociation and dissociative disorders, eating disorders or addiction [63]. A large number of cases of self-injury behavior are related to major depressive disorder [64,65]. Because pain appears to be associated with self-injury, it seems that individuals who injure themselves present significantly higher pain tolerance than subjects who do not engage in self-injury [66]. It was suspected that this condition can be associated with abnormalities in the endogenous opioid system [67,68]. Initially, in a post-mortem a study, Scarone, *et al.* observed reduced beta-endorphin levels in the left temporal cortex, frontal cortex, and caudate nucleus in 7 suicides compared to 7 dying a sudden natural death [69]. Later studies provided evidence that self-injury behavior is associated with increased beta-endorphin levels as endorphins are released in response to physical injury and act as natural analgesics, as well as induce pleasant feelings and can reduce emotional distress [70]. Stanley, *et al.* investigated the correlation between beta-endorphin level and the risk of suicide and self-inflicted multiple injuries, including cutting or burning [71]. They suggested that low levels of beta-endorphins may be a risk factor for developing self-injurious behavior, as during this process the level of this peptide increased and many self-injuring subjects did not feel any pain. Moreover, for some, intentional self-injury may become a means of seeking pleasure probably due to increase of beta-endorphin level. According to Stanley, *et al.* it can be assumed that measurement of beta-endorphin concentration during the therapy makes it possible to assess its effectiveness and reduce the risk of self-injury [71]. It was also suggested that beta-endorphin dysfunction may be involved in incidence of self-injury behavior among autistic individuals and may indicate the possibility of such behavior [72]. Further investigation into the role of beta-endorphin in self-injury behavior is necessary, as it may become one of important markers of potential suicidal behavior.

Schizophrenia

Various theories have been verified in order to explain the pathogenesis of schizophrenia. One of them pertains to endogenous opioid system, as it was observed that endorphin level in plasma may be elevated in this disorder [73]. However, the research concerning the beta-endorphin concentration in schizophrenics is inconclusive because both excess as well as deficiency of this peptide were observed irrespective of which body fluid was measured. Although cerebrospinal fluid analysis may reflect the activity of CNS endorphin system more directly, measurements of blood beta-endorphin levels are also used. Panza, *et al.* observed that beta-endorphin levels in brain autopsy samples or cerebrospinal fluid are consistent with concentrations of this peptide in peripheral blood mononuclear cells [74]. Nevertheless, inconsistency in schizophrenics' beta-endorphin concentration may be due to both methodologic differences in assay technique as well as differences in patients' selection. Watson, *et al.* supported the hypothesis that endorphins may play a role in modulating hallucinations in selected subgroup schizophrenics with chronic symptoms [75]. It was also observed that hallucinations accompanied by increased beta-endorphin concentration occurred in patients at some time during their recovery from surgery [76]. The idea that the hallucinations in schizophrenics may be connected with an increased level of beta-endorphin is supported by the observation of alleviation or disappearance of auditory or visual hallucinations after the application of naloxone, an opioid antagonist [77]. However, five-day long treatment of naloxone was ineffective in treating schizophrenia [78]. Other studies, involving the administration of naltrexone, also an opioid antagonist, to patients with schizophrenia found some improvements, or at least the lack of exacerbation of positive and negative symptoms [79-81]. In a different study, Pickar, *et al.* observed in schizophrenics with different types of schizophrenia significantly lesser opioid activity than in the healthy control group [82]. However, when considering schizoaffective patients, they did not observe differences between them and the control group. Recently, Urban-Kowalczyk, *et al.* studying patients with severe symptoms

of schizophrenia, observed higher concentration of beta-endorphin in schizophrenics with negative symptoms and lower in patients with positive symptoms in comparison to control group [83]. They also observed that individuals with predominant negative symptoms and higher beta-endorphin concentrations are most able to identify negative odors [84]. Furthermore, they observed that effective antipsychotic treatment results in "normalization" of beta-endorphin levels i.e. they were decreased in patients with negative symptoms and increased in patients with positive symptoms. Their study supports the hypothesis that normal level of this peptide is needed for psychological homeostasis [83]. Another reason for the discrepancy in the results of research on the role of beta-endorphin in schizophrenics was postulated by Gil-Ad, *et al.* [85]. They suggested that differences in beta-endorphin release may be the result of not only the different types of schizophrenia but also of the instability of diurnal beta endorphin secretion, which may contribute to the pathogenesis of schizophrenia. Gil-Ad, *et al.* observed that in the control group beta endorphin concentration was high in the morning (21.0 ± 3.5 pmol/l) and decreased in the evening, while in schizophrenics the concentration of this peptide fluctuated randomly, ranging from 9 to 40 pmol/l throughout the day [85]. Those conflicting results on beta-endorphin levels in schizophrenics may also be caused by possible interference of previous pharmacological treatment. Patients treated earlier with neuroleptics presented higher levels of beta-endorphin in peripheral blood mononuclear cells than untreated schizophrenics and healthy subjects [74]. Moreover, Naber, *et al.* observed significantly lower opioid levels in CSF in unmedicated schizophrenic men when compared with healthy men [37]. It seems that although neuroleptic therapy induced marked elevations of beta-endorphin in schizophrenics this effect was not correlated with therapeutic efficacy [86-88].

Autism

Initially, autism was defined as withdrawal from reality in people with schizophrenia but later it was redefined as a separate childhood psychiatric condition [89,90]. In the last several decades, considerable evidence has suggested that autism and schizophrenia are unrelated [38]. Autistic children often show self-injurious behavior, which has been suggested to be related to pain insensitivity. One of the theories explaining this behavior proposes dysfunction of endogenous opioid system, as in autistic children reduced pain sensitivity was reported [91]. Some studies support the suggestion that autism may result from hyperactivity of brain opioid system as they reported higher plasma and CSF beta-endorphin concentration in autistic children [92-94]. Moreover, higher beta-endorphin levels in autistic children were positively correlated with autism severity [93]. Tordjman, *et al.* suggested that plasma beta-endorphin derived from pituitary may indicate acute stress response in the more severely affected individuals [92]. One of the views on autism, suggesting that it may involve an excess of endorphins secretion, resulted from the observation that treatment with an opioid receptor antagonist, naltrexone, can ameliorate some but not all symptoms of this disorder [95,96]. In order to confirm the role of the elevated activity of the opioid system in autistic subjects, clinical and biological effects of naltrexone were assessed. Naltrexone attenuated the basic autistic symptoms and lead to several functional improvements, e.g. stereotype movements. Cazzullo, *et al.* observed in autistic children higher baseline beta-endorphin levels than in healthy age-matched controls, but after long-term naltrexone treatment they observed both a reduction (7/11) as well as an increase (4/11) of this peptide level [94]. Despite the difference in biochemical response to naltrexone they observed improvement of various autistic symptoms in all children, assessed by Clinical Global Impression (CGI) scores [94]. In spite of the fact that there was evidence that certain autistic individuals had elevated levels of beta endorphin, some clinical evidence on plasma and CSF levels was to the contrary [92,97,98]. Other studies showed opioid levels decreased or did not change in infantile autism [99,100]. Ernst, *et al.* observed lower than normal baseline plasma beta-endorphin level with strong correlation between the level of this peptide and severity of stereotypies [101]. As Nagamitsu, *et al.* did not observe any correlation between CSF levels of beta-endorphin and clinical symptoms of infantile autism, including self-injurious behavior, pain insensitivity, and stereotyped movement, they suggested that there is no relationship between dysfunction of brain opioid system and infantile autism [102]. Also Tordjman, *et al.* did not support opioid theories of autism [93]. Tordjman, *et al.* have assumed that reduced pain sensitivity in autism may have a practical implication. They studied behavioral and physiological pain responses, plasma beta-endorphin levels and their relationship in individuals with autism [93]. It was observed that most individuals with autism displayed absent or reduced behavioral pain reactivity at home (68.6%), at day-care (34.2%) and during venepuncture (55.6%). Despite their high rate of absent behavioral pain reactivity during venepuncture (41.3 vs. 8.7% of controls, $P<0.0001$), individuals with autism displayed a significantly increased heart rate in response to this procedure. The authors suggested strongly that reduced pain sensitivity in autism may be related to a different mode of pain expression rather than to insensitivity or endogenous analgesia resulted from the opioid system [93]. However, even if brain opioid activity is not a determining factor in autism, it may contribute to the development of this disorder. These results may suggest heterogeneity of autism.

Conclusion

The present paper discusses the role of beta-endorphin in several psychiatric diseases, especially stress-related, as abnormalities in this peptide secretion accompany several disorders of central nervous system. A correlation between the level of this peptide and clinical improvement has also been observed during pharmacological therapy. However, the inconsistency of measurement results and multitude of variables affecting the levels of beta-endorphin presently make it impossible to draw any definitive conclusions. Nevertheless, further investigation may confirm the observation of researchers aiming at determining the application of beta-endorphin measurement in assessing the effectiveness of therapy in some psychiatric diseases, as well as evaluating of some diseases severity. Further studies may also provide new possibilities for predicting the development of some diseases, for example postpartum depression or PTSD.

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