The β-Endorphin Role in Stress-Related Psychiatric Disorders

Avia Merenlender-Wagner, Yahav Dikshtein and Gal Yadid*

Neuropharmacology Section, The Mina and Everard Goodman Faculty of Life Sciences and The Leslie and Susan Gonda (Goldschmied) Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat-Gan, Israel

Abstract: Long known for its anti-nociceptive effects, the opioid β-endorphin is also reported to have rewarding and reinforcing properties and to be involved in stress response. In this manuscript we summarize the present neurobiological and behavioral evidence regarding the role of β-endorphin in stress-related psychiatric disorders, depression and PTSD. There is existing data that support the importance of β-endorphin neurotransmission in mediating depression. As for PTSD, however, the data is thus far circumstantial. The studies described herein used diverse techniques, such as biochemical measurements of β-endorphin in various brain sites and behavioral monitoring, in two animal models of depression and PTSD. We suggest that the pathways for stress-related psychiatric disorders, depression and PTSD, converge to a common pathway in which β-endorphin is a modulating element of distress. This may occur its interaction with the mesolimbic monoaminergic system and also by its interesting effects on learning and memory. The possible involvement of β-endorphin in the process of stress-related psychiatric disorders, depression and PTSD, is discussed.

Keywords: Anxiety, depression, post-traumatic stress disorder (PTSD), opioids.

INTRODUCTION

The involvement of the opioid system in depression and PTSD (post traumatic stress disorder) has been previously studied by several groups. Most of these studies employed pharmacological means, and examined the involvement of the different opioid receptors in these psychiatric diseases. However, an exclusive role for a specific opioid in these diseases had not been thoroughly assessed. Long known for its anti-nociceptive effects, the opioid β-endorphin is now known to induce reinforcing properties and to decrease feelings of distress. In this manuscript we provide new data, using animal models, which support the involvement of β-endorphin in stress-related psychiatric disorders, depression and PTSD.

THE OPIOID SYSTEM

Opioid Peptides and their Biosynthesis

The first endogenous opioids were discovered in the mid-80s [1]. Later, researchers succeeded in isolating and characterizing the enkephalins [2], dynorphins [3, 4] and also β-endorphin [5]. The behavioral and physiological effects of these opioids, such as rewarding and sedative sensations, are similar to those displayed by morphine as they all interact with post-synaptic opioid receptors [6-8]. Most of the endogenous opioids are enzymatically generated from three precursor proteins, proopiomelanocortin (POMC) [9]; prodynorphin (PDYN) [10] and proenkephalin (PENK) [11]; which undergo specific cleavage by proteolytic enzymes to give opioid as well other as non-opioid peptides. The final product is dependent on the enzymes present and can also involve posttranslational processing as in the case of POMC, to produce several opioid peptides, including β-LPH and β-endorphin [12].

The Opioid β-Endorphin

β-lipotrophin is a fat-mobilizing pituitary hormone [5] which contains an N-terminal fragment known as Met-enkephalin and a C-terminal fragment known as β-endorphin. The cleavage of POMC generates β-lipotrophin, which is later cleaved to produce β-endorphin [9]. The cleavage enzyme L-cathepsin has been recently linked with the production of β-endorphin through a protease gene knockout and expression study [13].

β-endorphin is an endogenous opioid peptide consisting of 31 amino acids which has been demonstrated to be involved in stress-related disorders as well as in other disorders such as obesity, diabetes, and altered immune responses [14-16].

β-endorphin can act as a neurotransmitter in the central nervous system and neurons in the brain that synthesize and release β-endorphin are located mainly in the arcuate nucleus of the hypothalamus (ArN), the anterior and neurointermediate lobes of the pituitary gland and the nucleus tractus solitaries, and these neurons’ extensions terminate in diverse brain regions [17, 18]. In both humans and rodents, injection of exogenous β-endorphin into the intracerebrospinal fluid causes a stronger analgesic effect than that of morphine [19-22]. Since it is produced in some regions in the brain that are associated with stress response its role was suggested in the manifestation of some psychiatric diseases [23-25].

Interaction of β-Endorphin with the Monoaminergic Systems

Several studies show that activation of the opioid system can alter dopamine release. Ventricular infusions of β-
**β-endorphin and stress-related psychiatric disorders**

Endorphin were shown to increase dopamine release in the nucleus accumbens via μ- and δ-opioid receptors [26]. β-endorphin inhibits the GABA-blocking dopaminergic neurons and lead to increase in dopamine release [27]. Furthermore, β-endorphin at doses that stimulate dopamine release in the nucleus accumbens is rewarding, as tested by the conditioned place preference paradigm [28]. Interestingly, accumbal β-endorphin has a reinforcing effect [24, 29, 30], which suggests that β-endorphin is an endogenous mediator of reinforcement, which is a measure of reward feelings using opertant conditioning, and can increase mesolimbic dopaminergic neurotransmission as a secondary target. These findings indicate an opioid-dopaminergic interaction wherein opioid receptor agonists act at a site upstream from the dopamine synapse in the nucleus accumbens. The dopamine-endorphin interaction is the evidence of enhanced locomotor response and reward sensitivity to opioid receptor agonists, given systemically or intra-accumbal, following mesolimbic dopaminergic lesions or chronic treatment with dopamine blockers [31, 32]. Our demonstration of a decrease (to ~35% of controls) in β-endorphin basal levels in 6-hydroxydopamine-treated rats may be relevant for the understanding of this dopamine-endorphin interaction [33]. This result indicates that the basal opioid tone in the nucleus accumbens is under dopaminergic control.

The relevance of the dopaminergic system to depression was previously suggested (for review see [34]). Therefore, if β-endorphin is modulated by dopamine, it may be a relevant chain in the neurochemical cascade that affects the manifestation of depressive like behavior. Other data [35], as well as those presented herein, demonstrate that extracellular β-endorphin levels in NAcc (nucleus accumbens) and ArN were altered in response to 5-HT (5-hydroxytryptamine). 5-HT₁A is the most widespread serotonin receptor. It is present in both the central and peripheral nervous systems, and controls a variety of different biological and neurological functions. Activation of 5-HT₁A receptors has been shown to increase plasma β-endorphin levels in animal studies and in healthy humans. In depressed patients who were treated with citalopram for 8 weeks, a reduction was shown in the β-endorphin response to a 5HT₁A agonist. Moreover, the reduction was parallel to the improvement in the patient’s condition. Since 5-HT is involved in many psychiatric diseases it is hypothesized that β-endorphin might mediate the development of these diseases. There are additional studies that indicate an interaction between β-endorphin and 5HT. Treating pregnant rats with β-endorphin caused a long-lasting reduction of 5-HT levels in the frontal cortex, hypothalamus and brain stem in the offspring [37].

The evidence of an interaction between β-endorphin and monoamines may facilitate the understanding of the role that β-endorphin plays in hedonia and motivation, since monoamines were established as key players in both hedonia and motivation. Decreased motivation and anhedonia are core symptoms in depression and are also involved with other psychiatric diseases.

**β-Endorphin, Opioid Receptors and their Knockout Models**

There are 3 major types of opioid receptors: μ (mu), δ (delta) and κ (kappa) and they were originally described by in-vivo and in-vitro pharmacology [38]. Several different neural systems are modulated by the opiate receptors.

The mu-Opioid receptor gene, OprM, is alternatively spliced into many variants and distributed in the Raphe nucleus and different limbic regions. Studies provide evidence for the region- and neuron-specific processing of the OprM gene and support the possibility of functional differences among the variants [39]. β-endorphin has the highest affinity to mu-Opioids receptor. mu-Opioids inhibit GABAergic and the glutamatergic afferents, thereby indirectly affect 5-HT efflux in the dorsal raphe nucleus. In contrast, kappa-opioids inhibit 5-HT efflux independent of their effects on glutamatergic and GABAergic afferents [40].

Mutant mouse strains lacking the genes encoding opioid receptors have been generated utilizing homologous recombination technology. Theses have aided in obtaining evidence suggesting that mu and delta receptors are responsible for reinforcement and that stimulation of kappa receptors triggers aversive effects [41-43]. A β-endorphin knockout mouse model has also been generated [44] and these mice demonstrate a selective reward deficit [45]. The examination of this mouse model in stress-related disorders is warranted.

**STRESS-RELATED PSYCHIATRIC DISORDERS**

Depression, anxiety and PTSD are the most prevalent psychiatric disorders in the general population. Whereas stressful events are the etiological trigger to develop PTSD, they were also suggested as a concept to explain the etiological and pathophysiological mechanisms of anxiety and major depression. Moreover, vulnerability to depression has been linked to the interaction of genetic predisposition with stressful life events [46-51]. During stress, the synthesis of central corticotropin-releasing hormone (CRF) in the paraventricular (PVN) increases and is released into the hypothalamic–hypophysial portal vascular system [52]. When the peptide reaches the anterior pituitary gland, it binds to CRF-receptors and causes a cascade of intracellular steps that increases POMC gene expression. POMC is a large gene that is translated into many POMC-derived peptides such as ACTH (adrenocorticotropic hormone) and β-endorphin (Fig. 1). Thus, activation of the stress system by CRH stimulates the secretion of hypothalamic β-endorphin and other POMC-derived peptides, which reciprocally inhibit the activity of the stress system [15, 53].

**Depression**

Depression is a mental illness which poses a major public health problem. Major depression usually develops early in life and can last for a lifetime, during which it will impair the overall function (with regard to occupation and social roles), and affect the quality of life [54, 55] of the affected individual. Lifetime prevalence rates of up to 20% for depression have been reported for the mild form of the illness, and
2%–5% of the U.S. population will suffer from the severe form of major depression [56]. Major depression is defined as a chronic state (at least 2 weeks) of a patient suffering from at least one core symptom and at least four of the following secondary symptoms. The core symptoms are: (i) lack of motivation and loss of interest in practically everything, and (ii) inability to experience pleasure (anhedonia). The secondary symptoms are: (i) loss of appetite, (ii) insomnia [increased amount and decreased latency of rapid eye movement (REM) sleep, as determined by EEG measurements], (iii) motor retardation or agitation, (iv) feelings of worthlessness or guilt, (v) continuous fatigue, (vi) cognitive difficulties, and (vii) suicidal thoughts [57]. The following physiological and biochemical characteristics are often observed in depressed patients: (i) chronic pain [50% of the depressed patients suffer from chronic pain [58, 59], (ii) high levels of plasma cortisol [60, 61], (iii) resistance in the dexamethasone suppression test [62], (iv) supersensitivity to cholinergic agonists [63-66], and (v) first degree relatives that also suffer from depressive disorders, i.e., a genetic component [67].

There are several available treatments for depression, which seem to benefit about 50% of patients. These patients show some improvement after receiving antidepressant medications, usually in combination with psychotherapy involving cognitive and behavioral therapies, which together can exert a synergistic effect [68, 69]. The antidepressants are classified into three classes or three generations. The first generation is divided to two main groups: 1. The tricyclic antidepressants that are generally thought to treat depression by inhibiting the synaptic re-uptake of the neurotransmitters norepinephrine and serotonin. 2. The monoamine oxidase inhibitors (MAOI) that inhibit the activity of monoamine neurotransmitters and thereby increasing their bioavailability. The agents of these classes were discovered by accident. However, the fact that agents that undoubtedly change the chemical balance in the brain can benefit the patients, paved the way to the assumption that there may be chemical changes in the brain that regulate depressive symptoms to begin with. Further research has lead to the development of the second generation of agents, the serotonin-selective reuptake inhibitors (SSRIs) which are widely used today. SSRIs act by inhibiting the reuptake of serotonin after being released into the synapse [70]. The SSRIs are the most commonly used drugs to treat depression [71]. One of the main reasons that the SSRIs are widely used is due to their minority of side effects compared to the first generation drugs.

Fig. (1). The Opioid's Precursor Proopiomelanocortin and its Cleavage Products. The gene that codes for the precursor proopiomelanocortin (POMC) is transcribed into mRNA which is then translated to a pro-hormone of 241 amino acids. Post translational processing of the large precursor peptide produces several smaller opioid peptides, including β-lipotropin, β-endorphin and non opioid peptides such as adrenocorticotropic hormone (ACTH), corticotrophin-like intermediate peptide (CLIP) and α-, β- and γ- melanocyte-stimulating hormone (MSH).
Later, a combination of neurotransmitters was suggested to express faster onset on behavior [72]. It has been suggested that dual-action antidepressants acting on both serotonin and noradrenaline pathways in the brain may offer superior therapeutic benefit over classical antidepressants, particularly in severe depression. This third generation includes agents such as venlafaxine, reboxetine, nefazodone and mirtazapine. Studies showed no convincings differences between third-generation agents and comparators in terms of overall efficacy, relapse prevention and speed of onset [73-76].

The precise mechanism of action of antidepressant medications is yet unknown. Altering neurotransmission should be expected to have an immediate effect on mood. However, all available antidepressants exert their mood-elevating effects only after prolonged administration (several weeks), which means that the mechanism probably involves some sort of drug-induced neuroplasticity. This is consistent with the ability of these agents to benefit a wide range of syndromes besides depression, such as anxiety disorders [77] and PTSD [78].

Post Traumatic Stress Disorder (PTSD)

PTSD is a chronic and disabling anxiety disorder that may develop in survivors of a traumatic event [79]. About Twenty percent out of those that were exposed to a traumatic event will develop PTSD. PTSD is currently defined by the coexistence of three clusters of different stress paradigms (re-experiencing, social avoidance and hyperarousal) persisting for at least one month [80]. Previous studies indicated that there are several risk factors for developing PTSD [81, 82]: (i) genetic background in monozygotic twins studies that were exposed to a traumatic event there was 48% correlation in PTSD symptoms. (ii) gender-females have higher risk to develop PTSD as a result of a traumatic event (ii) personal history background (child abuse etc) (iii) Family history of psychopathology (depression, bipolar disorder) (iv) The impact of the traumatic event (v) socioeconomic status (vi) environmental assistance dealing with the trauma. The most common and effective of current treatments are SSRI [83]. Research has pointed out that during the last decade, SSRIs have proven to be effective in reducing PTSD symptoms with the most effective ones being sertraline, fluoxetine, paroxetine and citalopram [83-86]. Other studies do not agree with this statement [87, 88]. The amygdala has been postulated as a crucial site in expression of traumatic stimuli or hidden traumatic stimuli [89-91] and the destruction of this region prevent expression of PTSD [92].

Animal Models for Depression and PTSD

Animal models, although limited in their ability to comprehend human complexities, are an invaluable tool in the research of markers for psychiatric disorders in general. A good animal model of clinical conditions should fulfill 4 criteria [93, 94]: Etiological validity, Face validity, Construct validity and Predictive validity.

So far the following 18 animal models for depression in humans have been developed: (i) predatory behavior [95, 96], (ii) yohimbine I potentiation [97, 98], (iii) kindling [99-101], (iv) dopa potentiation [102, 103], (v) 5-HTP-induced behavioral depression [104, 105], (vi) olfactory bulbectomy [106-108], (vii) isolation-induced hyperactivity [109-111], (viii) exhaustion stress [112], (ix) circadian rhythms [113], (x) behavioral despair [114-117], (xi) chronic unpredictable stress [118-121], (xii) separation models [118, 122-124], (xiii) incentive disengagement [125], (xiv) intracranial self-stimulation [126-130], (xv) learned helplessness [131, 132], (xvi) chronic mild stress (CMS) [133], (xvii) Swim Low-Active (SwLo) line rat [134], and (xviii) FSL rats [135].

The behavior of the FSL rats (Flinders Sensitive Line) resembles that observed in many depressed patients [136], thus the model has face validity. Both FSL rats and depressed individuals are sensitive to cholinergic agonists (cholinergic supersensitivity; [65, 137] and have serotonergic and dopaminergic abnormalities [182,136], thus the model has construct validity. Both FSL rats and depressed individuals respond positively to chronic treatment with antidepressants, thus the model has predictive validity. Since the FSL rat has fulfilled all three major criteria for determining the validity of an animal model of depression (face, construct, and predictive validities), it appears to be a suitable animal model for studying the neurochemical basis of depression and the neurochemical consequences of antidepressant agents.

Unlike most other mental disorders, the diagnostic criteria for PTSD in DSM IV specify an etiological factor, which is an exposure to a life-threatening traumatic event [138].

A number of animal models have been developed, mimicking many of the behavioral and physiological changes seen in PTSD-like behavior. These models use an electric shock [139-142], underwater trauma [143] and restraint stress [144, 145], are the most widely used method of applying a stressor to laboratory animals. Nevertheless, the use of exogenous stimuli that closely mimic those seen in the wild such as exposure to a live predator [146-148], a predatory cue [149-152] or psychological stress [153, 154] might have greater ethological relevance, thereby leading to improved modeling and analysis of fear and anxiety states.

Stressed rats tend to show PTSD-like behavior such as increased immobility, decreased grooming and rearing [152], decreased exploratory behavior and decreased food consumption [155]. The freezing response has been used as a behavioral measure of anxiety or fear [156]. Amongst all the unconditioned stressors, the predator stress seems to be the most potent stressor, since its effects on fear/anxiety potentiation can last for 3 weeks [147].

Most studies in animal models for PTSD-like behavior refer to the maladapted group as a uniform population. Others developed an animal model that categorizes PTSD-like behavior individually and in addition they applied it to further monitor the animal over a month in order to determine whether it had PTSD-like behavior. This adapted model includes re-exposure to the traumatic cue in a time-course manner, and showed high face-, contract- and predictive-validities [157].
Opioids and Stress-Related Disorders

Endogenous opioid peptides and their receptors are represented throughout corticolimbic structures [158, 159] and their high sensitivity to acute and prolonged aversive stimuli has been documented [160-164]. Herein we will summarize their possible role in depression, anxiety and PTSD.

(+/-)-Tramadol, an opioidergic- monoaminergic agent, conceivably displays antidepressant actions in a variety of rodent models [165-169], although the precise contribution of monoaminergic as compared to opioidergic mechanisms to its antidepressant properties remains unclear. Since it has a dual mechanism of action by which analgesia may be achieved via µ-opioid receptor activation, and enhancement of serotonin and norepinephrine transmission may conceivably exert a degree of antidepressant effect and it was suggested to be of particular value in patients with chronic pain who also suffer from depression [170].

Recent literature supports a potent role of methadone, buprenorphine, tramadol, morphine, and other opioids as effective, durable and rapid therapeutic agents for anxiety and depression [171]. Some studies showed that codeine produced an antidepressant-like effect when administered alone and even an accentuated anti-depressant like effect when administrated at subeffective doses in combination with selective serotonin reuptake inhibitors (fluoxetine or citalopram). In contrast, when codeine was combined with a noradrenaline reuptake inhibitor (desipramine) or with a noradrenaline-serotonin reuptake inhibitor (duloxetine), no such effect was observed. The anti-depressant like effect also remained unchanged with the combination of subeffective doses of codeine and (+/-)-tramadol (the weak µ-opioid agonist with serotonin/noradrenaline reuptake inhibitor properties) or (-)-tramadol (noradrenaline reuptake inhibitor properties only). Conversely, the combination with (+)-tramadol (µ-opioid agonist with serotonin reuptake inhibitor properties) produced an increase of the anti-depressant like effect [172].

The existing information indicating the possibility of opioids' neurotransmission in controlling PTSD is mostly circumstantial. Only recently a direct examination of central nervous system opioid function in PTSD was reported, using positron emission tomography (PET) and the selective µ-opioid receptor radiotracer [173] carfentanil. The study separated trauma exposed combat veterans who developed PTSD after combat experience, from trauma exposed combat veterans without PTSD, as well as non-exposed controls indicating changes in µ-opioid receptor occupancy in limbic forebrain and cortical regions involved in emotional regulation. These alterations are likely to reflect adaptive responses to trauma or stress, or alternatively potential adaptation failures that may be related to PTSD pathophysiology [173]. Another study of acute administration of morphine reported limited fear conditioning in the aftermath of traumatic injury and may serve as a secondary prevention strategy to reduce PTSD development [174].

Involvement of β-Endorphin in Depression

The results obtained from depressive patients not receiving drug therapy on plasma or CSF β-endorphin levels, were inconsistent [66, 175-179]. Later, using microdialysis, it was enabled to determine of the local release of β-endorphin in specific brain regions in vivo. This may lead to a more accurate understanding of the neurophysiological basis of behavioral abnormalities in depression, and the mode of action of drugs used for treating them. The neuronal mechanisms that mediate the beneficial effect of several antidepressants on depressive behavior [180] are not known, but may involve the 5-HT-β-endorphin interaction in NAcc and ArN, since some findings [35] demonstrate that extracellular β-endorphin levels in these areas are altered in response to 5-HT. Antidepressants, such as tricyclics and SSRIs, increase 5-HT neurotransmission in the brain [181]. Therefore, this increase in 5-HT neurotransmission should facilitate the release of β-endorphin in brain regions, such as the above-mentioned, where this opiate can mediate hedonia or motivation [19, 22, 35]. Extracellular levels of β-endorphin in the NAcc, as well as behavioral deficiencies associated with depressive behavior, were assessed in animal model of depression and control rats, before and after chronic antidepressant treatment. Using microdialysis, [35] it was demonstrated that extracellular β-endorphin levels were dose dependently increased when artificial cerebrospinal fluid (aCSF) containing 5-HT was applied to the NAcc (Fig. 2). This response was attenuated in FSL rats showing a shift to the right in the dose-response curve [208] (Fig. 3). In FSL rats exposed to the same 5-HT treatment, the β-endorphin levels increased only slightly, but not significantly. Chronic treatment (18 days) with desipramine or paroxetine, exogenous administration of 5-HT via the microdialysis probe induces increases in extracellular levels of β-endorphin, similar to those observed in controls (Fig. 4). In FSL rats chronically injected with saline, exogenous application of 5-HT appeared to slightly affect β-endorphin release. However, this 5-HT-mediated effect was minimal compared to that observed in the FSL rats treated with the antidepressants. 5-HT-mediated release of β-endorphin in the control Sprague-Dawley rats was not significantly affected by chronic administration of saline or the antidepressants [208]. The basic characteristic symptoms of depressed patients are anhedonia and a lack of motivation, both of which are expressed in the absence of an immediate response to environmental stimuli [182]. Responses to environmental stimuli that activate specific neuronal circuits in the brain involved in mediation of motivation or hedonia (and are likely to involve release of β-endorphin) are probably impaired in depressive patients [183]. Chronic, but not acute, treatment with antidepressant drugs, which is necessary for effective treatment of depressive behavior [136] normalizes the 5-HT-β-endorphin interaction, probably by affecting neuronal plasticity [184].

Injection of β-endorphin into the brain has also rewarding effects [24, 29] and impairment of the reward system was suggested to occur in depression [185]. Therefore a complementary way to address β-endorphin role in depression is by its modulating the reward system.
Fig. (2). Increments of β-endorphin levels in extracellular fluid of nucleus accumbens in response to exogenous serotonin. Rats were implanted with a microdialysis probe (2 mm length, 20 kDa cutoff value, CMA/10; Carnegie Medicine; Stockholm, Sweden) in their nucleus accumbens using the Paxinos & Watson the rat brain in stereotaxic coordinates [207]. Artificial cerebrospinal fluid (aCSF; 145 mM NaCl, 1.2 mM CaCl₂, 2.7 mM KCl, 1.0 mM MgCl₂, pH 7.4) was pumped continuously (1.5 μl/min) through the dialysis probe using a microinjection pump (CMA/400, Carnegie Medicine). Experiments were initiated 24 h after surgery in awake, freely moving rats. After collecting baseline, various concentrations of 5-HT were applied locally via the probe for 30 min. Data are mean ± SEM values from six rats. Two-way ANOVA with repeated measurements was conducted. *p<0.001 compared with basal levels by Student–Newman–Keuls post hoc test [35].

Fig. (3). Attenuated effect of exogenously added 5-HT on the extracellular levels of β-endorphin in the nucleus accumbens of an animal model of depression (FSL) rats. FSL and Sprague–Dawley (control) rats were implanted with a microdialysis probe in their nucleus accumbens. The microdialysis probe was perfused with aCSF before and after a 30 min perfusion with aCSF containing 5-HT (bar). (A) A dose–response curve when the peak of the response to each 5-HT concentration (mean±S.E.M. values of five rats in each group) was plotted. ANOVA with repeated measure over time applied to each 5-HT dose separately revealed that only at the 5 μM 5-HT (B) a significant strain–sample interaction was obtained (control group: F(4,8)=7.78, P<0.001); FSL group: F(4,8)=1.22, P=0.31), strain x treatment interaction (F(1,8)=2.34, P=0.028). *P<0.05 [208].
It is worth to mention that Tramadol, an opioidergic monoaminergic (NA and 5-HT re-uptake inhibitor) agent displays antidepressant actions in a variety of rodent models [165-169], although the precise contribution of monoaminergic as compared to opioidergic mechanisms to the antidepressant properties of tramadol remains unclear.

We suggest that impaired 5-HT-induced release of β-endorphin may be involved in the etiology of depression, and that normalization of this induction by chronic antidepressant treatments mediate, at least in part, the therapeutic action of antidepressant drugs.

Involvement of β-Endorphin in Anxiety

The role of neuropeptides in general and β-endorphin in particular in anxiety-related disorders is largely unknown. In humans, acute stress, which is associated with higher anxiety levels, had increased plasma levels of β-endorphin [186]. In animal studies, mice with selective deletion of β-endorphin demonstrated lower anxiety levels in the zero-maze, a model for a mildly stressful situation [187]. Several others studies address the issue of alcohol-withdrawal induced anxiety and its possible connection to β-endorphin in both humans and mice. β-endorphin plasma levels were significantly lowered on day 1 and day 14 of alcohol withdrawal relative to control subjects and levels of β-endorphin were inversely correlated with anxiety levels [188]. In mice, a direct inverse relationship was noted between β-endorphin plasma levels and anxiety behavior measured using the elevated plus maze, suggesting that this peptide normally inhibits anxious behavior. However, mice lacking β-endorphin demonstrated an exaggerated anxiolytic response to alcohol in this assay [189]. Together, these studies suggest that lowered β-endorphin may contribute to anxiety-related behaviors.

Involvement of β-Endorphin in PTSD

In animals exposed to a scent of predators, a prolonged 25% increase in of β-endorphin in the ArcN was observed [190]. Exposure to stress enhances release of the endogenous opioid receptor, dynorphin, in several cerebral structures, including the hippocampus and nucleus accumbens [162, 163, 191-193]. An earlier report found lower plasma β-endorphins in PTSD patients [194], however later findings [195, 196] suggested higher levels of immunoreactive β-endorphins. Treatment with the opioid antagonists nalmefene and naltrexone has reduced PTSD symptoms like flashbacks and dissociations, intrusions, and hyperarousal [89, 197, 198], whereas activation of opioid receptors by morphine reduced the risk of subsequent development of PTSD symptoms [199]. Only one study directly examined the role of the central nervous system opioid function in PTSD [173].

However, a direct evidence for a specific opiate involvement in PTSD was only recently available by the use of microdialysis and a unique animal model of PTSD. A recent study has measured β-endorphin levels both in tissue and in
the extra cellular fluid in the amygdala. Table 1 demonstrates the basal levels of tissue content. PTSD rats demonstrated a significant lower concentration of β-endorphin then the non-PTSD rats and the naive rats. When extracellular fluid was sampled by microdialysis in freely moving rat during re-exposure the traumatic remainder only (without cat scent), the PTSD rat had increased the extra cellular β-endorphin which remained high for two hours post re-exposure to the cue associated with the traumatic event (Fig 5). This may indicate that the mechanism underlying heighten behavioral reaction to the traumatic cue involve inability to maintain a threshold of basal β-endorphin release. Hence, β-endorphin levels may increase in order to moderate the distress reaction. Massive extracellular release of the β-endorphin may further lead to depletion of its cellular storage. Despite the increase in the extracellular fluid β-endorphin levels in the amygdala, they did not reach the basal levels of control rats, but they approximate the basal extra cellular fluid β-endorphin level of non-PTSD rats. These findings support Grisel et al. finding that β-endorphin have a significant role in moderating anxiety. Inability to increase β-endorphin levels in PTSD might explain the behavioral symptoms of trauma re-experiencing.

β-Endorphin and Memory

The process of learning and memory is obviously involved in stress-related disorders. An involvement of β-endorphin in post-operative memory in the amygdala was suggested [200, 201]. Additionally, retrieval of avoidance learning is modulated by β-endorphin and enhanced by naloxone [202]. In humans, opioid receptor blockade, using a single oral dose of naltrexone, may specifically improve incidental recognition memory following physiological arousal [206]. These findings demonstrate that opioid peptides in general, and β-endorphin in particular, mediate alterations in specific aspects of human memory during heightened emotional states and that learning-based interventions can create new memories that may modify existing ones [203]. These studies support a role for β-endorphin in learning and memory that may be associated with memory-related stress disorders.

### Table 1: β-endorphin content in the amygdala PTSD rats

<table>
<thead>
<tr>
<th></th>
<th>Naive</th>
<th>non-PTSD</th>
<th>PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-endorphin (μg/ml)</td>
<td>157.06±38.71</td>
<td>* 75.86±20.7</td>
<td>**15.32±4.9</td>
</tr>
</tbody>
</table>

* (*p<0.01 vs naive, **p<0.0 vs non-PTSD, ANOVA)*

---

**Fig. (5). Extracellular (CSF) β-endorphin level in the amygdala in PTSD and non-PTSD rats re-exposed to cue.** Rats underwent a stressful procedure (exposure to a predator scent) over eight weeks experiment as described [157]. On the eighth week rats were defined as maladapted (PTSD-like) or non maladapted) non PTSD-like rats. A week after, microdialysis probes were co-implanted into their basolateral amygdala. During microdialysis sampling, rats were re-exposed to a cue (same bedding without a predator scent). Re-exposure to the cue, increased β-endorphin concentration in the extracellular fluid of PTSD rats. This increment stayed significantly higher for two hours following the re-exposure (ANOVA for repeated measure revealed significance. *p<0.05 PTSD vs non PTSD).
CONCLUDING REMARKS AND PERSPECTIVES

Current pharmacological treatment for depression is based on the use of drugs that act mainly by enhancing brain serotonin and noradrenaline neurotransmission. Although complete remission of symptoms is the goal of any depression treatment, many patients fail to attain or maintain a long-term, symptom-free status. In view of this, there is an intense search to identify novel targets for antidepressant therapy. Some antidepressants which increase the availability of noradrenaline and serotonin through the inhibition of the reuptake of both monoamines lead to the enhancement of the opioid pathway [204]. Endogenous opioid peptides are co-expressed in brain areas known to play a major role in affective disorders and in the action of antidepressant drugs. Therefore, opioid peptides and their receptors are potential candidates for the development of novel antidepressant treatment. Actually, opioids have been used for centuries to treat a variety of psychiatric conditions with much success but lost popularity in the early 1950s with the development of non-addictive tricyclic antidepressants and monoamine oxidase inhibitors. The combination of monoamine agents with opioid's agents even at subeffective doses may increase the antidepressive and anxiolytic efficacy. Tramadol has dual mechanisms of action by which analgesia may be achieved via μ-opioid receptor activation, enhancement of serotonin and norepinephrine transmission may conceivably exert a degree of antidepressant effect. Therefore, it was suggested to be of particular value in patients with chronic pain who also suffer from depression [170]. Nonetheless, recent literature supports the potent role of methadone, buprenorphine, tramadol, morphine, and other opioids as effective, durable, and rapid therapeutic agents for anxiety and depression [171]. Some studies showed that codeine produced an antidepressant-like effect when administered alone and even an accentuated anti-depressant-like effect when administered at subeffective doses in combination with selective serotonin reuptake inhibitors (fluoxetine or citalopram)[172].

The existing information indicating the possibility of opioids' neurotransmission in controlling PTSD is far circumstantial [173]. One study, acute administration of morphine, limited fear conditioning in the aftermath of traumatic injury and may serve as a secondary prevention strategy to reduce PTSD development [174].

β-endorphin is a potent μ- and δ- receptors agonist. It was demonstrated to induce motivation and hedonia, the two main symptoms lacking in depression, and as such may have a role in controlling depressive behavior. β-endorphin has also interesting effects on post-operative memory and retrieval of avoidance [205]. In humans, opioid receptor blockade improves incidental recognition memory following physiological arousal, indicating its role in memory during heightened emotional states [206]. This may explain why memories can be selectively modified under stressful events, such as those experienced by PTSD patients.

While abuse of opioids may occur, several large studies have demonstrated that the incidence of abuse is rather low, about one case per 100,000 patients [170]. As well, all reported combinations of antidepressants with opioid-receptor's activation were without effects on motor behavior in animal models.

Currently, some evidence supports the possibility of β-endorphin neurotransmission in controlling depression and PTSD. Therefore, understanding the role of β-endorphin in the modulation of the anti-distress and post-operative memory may assist in providing potential therapeutic strategies for the prevention of relapse to depressive state and PTSD. Such treatments may be more efficient compared to currently available treatments.

REFERENCES

null
tematic review and meta-analysis. Arch Gen Psychiatry 2006; 63: 1217-23.


β-endorphin and stress-related psychiatric disorders


