β-Endorphin

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β-Endorphins are peptides that exert a wide variety of effects throughout the body. Produced through the cleavage pro-opiomelanocortin (POMC), β-endorphins are the primarily agonist of mu opioid receptors, which can be found throughout the body, brain, and cells of the immune system that regulate a diverse set of systems. As an agonist of the body's opioid receptors, β-endorphins are most noted for their potent analgesic effects, but they also have their involvement in reward-centric and homeostasis-restoring behaviors, among other effects. These effects have implicated the peptide in psychiatric and neurodegenerative disorders, making it a research target of interest.

Keywords: β-Endorphin,Behavior

1. Introduction

β-Endorphins are peptides that exert effects throughout the body. In the brain, they are considered to be both neurotransmitters and neuromodulators, as they have the ability to elicit more stable and long-lasting effects on more distant targets than typical neurotransmitters [1]; β-endorphins exhibit a notably high degree of degradation-resistance in the brain [1]. β-Endorphins are produced primarily by both the anterior lobe of the pituitary gland [2][3], and in pro-opiomelanocortin (POMC) cells primarily located in the hypothalamus [3][4]. β-Endorphin and other cleavage products are produced in the multistage processing of POMC primarily involving prohormone convertases (PC) 1 and 2. PC-1 cleaves POMC into adrenocorticotrophic hormone biosynthetic intermediate and β-lipotropic hormone. PC-2 cleaves β-lipotropic hormone into β-endorphin and γ-lipotropic hormone [5]. Carboxypeptidase-E (CPE) is also involved in the processing of POMC and with the removal of C-terminal basic residues (arginine/lysine) which are left after PC cleavage. Notably, however, mice with inactive CPE (CPE^{fat}/CPE^{fat}) produce greater quantities of β-endorphin(1–31) than wild-type mice, indicating that CPE is not required for its synthesis [6]. Additional processing, such as the acetylation of some β-endorphins, and shortening, may also occur [7][8][9].

In the brain, the peptide and other related proteins are most prevalent in the hypothalamus, thalamus–midbrain, amygdala, hippocampus, and brainstem [1]. Though the primary source of peripheral β-endorphin is the pituitary gland [3], β-endorphins, POMC, and PCs 1 and 2 have been identified in the skin [10][11][12], as well as cells of the immune system [13], though transcripts of POMC are notably found only at very low levels in the latter [14]. Though there is evidence that peptides such as β-endorphins can penetrate the blood–brain barrier to a degree, based on studies of radiolabeled, intracarotidally injected peptides [15], and P-glycoprotein notably is involved in the efflux of β-endorphin from the brain [16], peripheral and central CSF levels of the peptide are not necessarily related [3].

There are multiple forms of endorphins, though β-endorphin(1–31) is the only form with a potent analgesic effect. The other, more inactive forms are shorter, such as β-endorphin(1–27); notably, β-endorphin(1–31) is the primary form found in the anterior pituitary gland and brain regions such as the hypothalamus, midbrain, and amygdala [17][18], while the shorter forms are more common in the intermediate pituitary and brain regions, such as the hippocampus, colliculae, and brain stem [17][18]. Typical antibodies against β-endorphin will recognize 1–31, 1–26, 1–27, and the acetylated forms [18]. β-Endorphin(1–27) has notably reported to be an antagonist of β-endorphin(1–31) in in vivo animal studies [19][20][21], though this has been refuted in more recent in vivo studies [22] and in vitro [8][23], indicating that the shorter forms of β-endorphin are full agonists, and the studies indicating antagonistic activity were somewhat flawed [8]. There is evidence that receptors with opiate activity that preferentially bind β-endorphin(1–31) are present [1].

β-Endorphins are part of the system of opioid receptor agonists. The endorphin family includes β-endorphin, α-neoendorphin, enkephalins, and dynorphins [24]. β-Endorphins exert an analgesic effect that is more potent than morphine [1][2], and act primarily on the mu family of opioid receptors [25], which are, like the two other opioid receptors, delta and kappa, G-protein coupled receptors [24]. Naloxone, a typical antagonist of other opiates, has been found to reduce β-endorphin binding as well, and is commonly used in opioid-related studies [1]. β-Endorphins, along with other opioids, appear to attenuate cyclic adenosine monophosphate levels, and decrease calcium uptake [2]. The peptide is typically

released to the periphery in response to a painful or stressful event, where they inhibit somatosensory fibers, with a focus on nociceptors [2]. It should be noted that, while β-endorphin has the highest affinity for the mu receptor, it also acts on other opioid receptors [24], particularly the delta opioid receptor [26]. Other opioid receptor agonists, such as the enkephalins and endomorphins, can also activate the mu-receptors [24][26][27][28], so all mu-receptor activity cannot necessarily be attributed to β-endorphin. It should also be noted that endomorphins are peptides which have been isolated in brain and immune tissue that exhibit the highest affinity for the mu opioid receptor [29][30][31][32], but as no precursor has yet been identified, it is unclear if they are truly endogenous [33].

β-Endorphins are related to the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis, which governs a wide range of functions, including metabolic and immune responses [34][35], is heavily involved in the body's stress-response, with stress being defined as the perception of a threat, real or imagined, to one's well-being or homeostatic state [36]. The HPA is first stimulated when a stressful event induces production of corticotropin-releasing hormone (CRH). This results in the simultaneous release of Adrenocorticotropic hormone (ACTH) and β-endorphins, both of which are produced from the cleavage of POMC, and are stored and released together in secretory vesicles [37]. As the initial cleavage generates a β-endorphin precursor, β-lipotropic hormone (LPH), which requires further processing to form β-endorphin, the two are not necessarily present in a 1:1 ratio [4]. The effects of the HPA can be tied to a variety of behaviors, including exercise, drug-use, sexual behaviors, among others [38].

2. β-Endorphins and Behavior

Much of β-endorphin's governance of behavior has to do with either brain reward-system pathways, among other changes in food-consumption, sexual behaviors, among others [39]. Though much focus on reward systems, and how it relates to many of the same behavioral changes as β-endorphin, is given to dopamine [40][41][42][43][44][45], β-endorphins are also active in various reward-system pathways. In fact, β-endorphins appear to exert regulatory effects on serotonin, inhibiting its release and modulating its turnover in a region-dependent manner that can be nullified with opioid antagonists [46][47][48]. Reciprocally, serotonin appears to regulate the secretion of β-endorphins in a similarly region-dependent way. Notably, secretion is increased in the hypothalamus and decreased in the hypothalamus in response to serotonin [49][50][51].

While not necessarily independent of other factors, the peptide is heavily involved in certain reward pathways. It is known that β-endorphins inhibit the release of gamma-aminobutyric acid (GABA) [52], the primary inhibitory neurotransmitter of the brain [53], which can lead to excess accumulation of dopamine, a key agent associated with feelings of pleasure [52]. Indeed, binding of opiates in general to their respective receptors is associated with feelings of well-being and euphoria [54]. Rats given access to levers that administer endorphins directly to their brain will self-administer the peptide to themselves regularly [55]. Injections of endorphins and exogenous opioids such as heroin can produce conditioned place preference, a common test for drug-reward [56], in rats, suggesting opioids' involvement in reinforcement and reward [55][57]. Consumption of highly palatable foods in non-food-deprived rats has been observed to increase binding of β-endorphin in the hypothalamus, further reinforcing β-endorphin's role in reward pathways [58].

2.1. Addiction

Much of the research on β-endorphin's human effects has to do with addictions, particularly those involving drug use and alcohol abuse. It is integrally involved in producing the feelings of euphoria associated with certain drugs and has been implicated in the development of alcoholism [59]. Consumption of cocaine, for example, leads to an increase in plasma concentrations of β-endorphins [60]. Opioid antagonists have been found to alleviate cocaine-addiction behaviors, as cocaine-induced reinforcement of conditioned place preference (CPP) was reduced through the administration of naltrexone, and reinforced by methadone [61]. Interestingly, the rewarding action of cocaine does not appear to be mediated by the mu-opioid receptor; mu-receptor knockout mice exhibit cocaine induced CPP, but β-endorphin deficient mice do not [62]. β-Endorphin has been suggested to interact with the delta opioid receptor in cocaine addiction, which may not only mediate the direct reward, but also the incubation of craving that can induce relapses in abstinent recovering cocaine addicts [63]. Opioid drugs such as heroin directly interface with opioid receptors, inducing pain relief and stimulating reward centers [64]. Opioid antagonists, in particular naloxone, are frequently used in the treatment of heroin addiction, through tandem treatment with a low-risk opioid such as buprenorphine [65], and heroin overdoses [66]. Certain variations of the mu-opioid receptor have been found to influence the condition and treatment outcome of heroin addicts [67]. Alcohol consumption appears to stimulate the release of β-endorphin, but habitual consumption ultimately results in a reduction in β-endorphin levels [68]. Those with genetic deficiencies in β-endorphin levels are more likely to become alcoholics [68], and excessive alcohol consumption in rats can be curbed through the use of opiate antagonists [69], further cementing the peptide's role in the development of alcoholism. β-endorphin has also been suggested to be related to the

phenomenon of exercise addiction; increases in plasma levels of the peptide is often observed in strenuous exercise, and is associated with feelings of well-being and euphoria similar to that observed in drug addiction [70][71]. However, difficulties in relating circulating β-endorphins to brain levels of the peptide makes verification difficult [70].

2.2. Food Consumption

Many opioid receptors, which can be found throughout the brain, are localized in brain regions that pertain to food/energy homeostasis [72]. A 1979 study found that administration of the opioid antagonist naloxone suppresses eating even in food-deprived rats [73], and successive studies have gone on to confirm this, and note that opioid antagonists reduce overall food intake in mice, including those that are genetically obese [72]. Single nucleotide polymorphisms of the mu-receptor gene have been found to be correlated to BMI in humans [74]. Total knockout of the mu-receptor gene decreases motivation to eat in mice, while showing no significant impact on the hedonic processing of food intake [75]; this is somewhat contradictory to β-endorphin's role in food reward-pathways, and could indicate an alternative reward path, or that the β-endorphin reward pathway is not mediated by the mu receptor. In support of this, while knocking out β-endorphin's primary receptor appears to have little effect on food hedonism, rats ingesting oil were found to have significantly increased levels of β-endorphin in serum and CSF. Interestingly, overall intake of the oil was found to be lowest where β-endorphin levels were highest, suggesting an inverse relationship. Pretreatment with naloxone decreased initial affinity for the oil based on licking-tests, suggesting a possible hedonic disruption [76].

Though it would seem that β-endorphins promote food consumption, with disruptions limiting food intake, the longer-term implications are quite different. Mice lacking the ability to produce β-endorphin were found to weigh significantly less than their wild-type counterparts after several weeks with food provided freely, suggesting that the peptide simultaneously has appetitive and anorexic effects, limiting excessive food consumption [77]. β-Endorphins appear to have peripheral function on taste and overall gastrointestinal function, suggesting that CNS action is not the only route through which β-endorphins modulate food intake [78].

2.3. Sexual Behavior

Exogenous opioids are known to have an overall inhibitory effect on sexual behaviors [79], but the impact of opioid receptor agonists including β-endorphin are considerably more nuanced. In both male rats and humans, administration of the opiate antagonist naloxone has been shown to induce copulatory behavior and improve sexual performance [80][81][82]. It would seem, however, that β-endorphins still have their place in the mechanisms of sexual reward. Rats with access to a preferred and non-preferred chamber would, when allowed to copulate to ejaculation in a non-preferred chamber, shift their preference toward the originally non-preferred chamber even following castration. This shift in preference was reversible with naloxone, with the extent of this reverse increasing over time [83].

Females have been found to experience similar inhibition of sexual behavior by β-endorphin. Numerous studies involving the lordosis reflex of female rats note that it is diminished following infusions of β-endorphins [84][85][86][87]. However, Torii et al. found that the inhibitory effect becomes a facilitatory one if β-endorphin administration occurs within 6 h of priming with estrogen [86]. Pfaus et al. found that the inhibitive effect of β-endorphins on lordosis is dose dependent, noting that it is likely that high-affinity mu-receptor activity inhibits lordosis, whereas low-affinity receptor activity facilitates it [87]. While it is fair to say that β-endorphin follows the trend of exogenous opioids in inhibiting sexual behavior, interactions and the multiplicity of the pathways β-endorphins influence allow for notable exceptions to the rule.

2.4. Other Effects

Aside from these regulatory effects on behavior, β-endorphins have their hand in other actions as well. Injection of β-endorphins to the brain has been found to induce tremors and jerking movements of the head, ocular fixation on empty space, pupillary dilation, and overall excitation in cats. The duration and severity of these effects was dose dependent, with the effects of a 12.5 μg dose lasting approximately one hour [88]. Intraventricular injections have also been observed to induce wet-dog shakes in rats [89][90], with the frequency and occurrence of the shakes depending on the ambient temperature; correlation of the wet-dog shake behavior to increased body temperature suggests a possible role in thermoregulation [90]. However, levels of β-endorphins have not been found to increase in proportion to heat loss in cold water immersion tests [91].

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