The role of beta-endorphin in horses: a review

M. Golynski[1], W. Krumrych[2], K. Lutnicki[1]

[1]Faculty of Veterinary Medicine, University of Life Sciences, Lublin, Poland
[2]National Veterinary Research Institute, Pulawy, Poland

ABSTRACT: Opium alkaloids counterparts are secreted by human and animal organisms but the role of endogenous opioid peptides in horses has not yet been fully elucidated. Endogenous opioids are involved in regulating food intake, sexual and social activity, pain relief and pain threshold regulation in horses as well as in regulating the functions of the immune system. The aim of this review is to describe the endogenous opioid system in the horse and its function during stress, illness, reproduction, and its influence on immunity and on the formation of reactive oxygen species (ROS) in horses. What is currently known concerning beta-endorphin suggests that they can be a promising diagnostic or prognostic indicator of many pathologic states in horses.

Keywords: horse; endorphin; opioids

Contents

1. Introduction

Alkaloids originating from opium, used throughout centuries as common anaesthetics, are still widely used nowadays. It has long been presumed that these substances may have counterparts, which are secreted by animal and human organisms. This notion was supported by the research of Kosterlitz and Hughes, who in 1975 described the presence of the first endogenous ligands of opioid receptors; however, the role of endogenous opioid peptides in animals has not yet been fully explained (Kosterlitz and Hughes, 1975).

There are presently many substances included in the group of endogenous opioids, of which the most widely researched and best known are encephalins, endorphins and dynorphins. These bind to the following specific opioid receptors types: MOR (m), KOR (k) and DOR (d), and to the untypical orphan receptor NOR causing numerous biological effects in the entire organism as well as in specific organs.

Endogenous opioids are involved, among others, in regulating food intake as well as sexual and social activity. They also exhibit pain relieving properties and regulate pain threshold in horses, similarly to the way they do in people (Hamra et al., 1993). The pain relieving function of opioid receptors evolved as an element of the organismal defence system against stress. This function consisted primarily in regulating the immune system (Stefano et al., 1998). Thus, opioids may be ascribed the function of immunomodulators.

2. Secretion

Proopiomelanocortin (POMC) is a precursor of one of the endogenous opioid peptides – beta-endorphin, which is secreted in the horse by the pars intermedia of the pituitary gland. Additionally, proopiomelanocortin is a substance from which two others are formed: adrenocorticotropin (ACTH 18-39, corticotropin-like intermediate lobe peptide – CLIP) and α-melanotropin (α-melanocyte stimulating hormone, α-MSH) (Scott and Miller, 2003). Beta-endorphin is the strongest endogenous opioid along with the m- (MOR) and d-opioid (DOR) receptor ligand.

The daily rhythm of beta-endorphin secretion is similar to that of ACTH and cortisol. The highest values of opioid were noted in morning blood samples (peak level at 9.00) (Hamra et al., 1993). Different results were obtained by Mehl et al. (1999), who did not note statistically significant differences in the levels of beta-endorphin examined in mares every two hours between 8 a.m. and 8 p.m. Owing to the inconsistency of research results so far, the data published by Pell and McGreevy (1999) concerning the activity of beta-endorphin in horses with stereotypy, and the results of the study on foals by Fazio et al. (2009) should be interpreted with caution, taking into consideration such factors as seasonality. At present, data on the daily rhythm of beta-endorphin secretion in horses remains very limited.

3. Beta-endorphin and stress

The release of beta-endorphin into the blood in horses is particularly evident during the course of stress reactions. A study on 42 healthy pure blood stallions was aimed at determining the impact of transport stress on the levels of beta-endorphin, cortisol and ACTH (Fazio et al., 2008). An increase in the levels of circulating ACTH was observed after travelling distances of 100 and 200 kilometres and levels of cortisol were higher after traversing distances of 100, 200 and 300 kilometres. However, the concentration of beta-endorphin was raised when compared to the basic level only after the distance of 100 kilometres. After the next 100 and 200 kilometres a decrease was observed which may suggest an effect of negative feedback signalling. It may thus be assumed, on analysing the levels of beta-endorphin and ACTH that the release of the opioid into the blood occurs maximally one hour after the appearance of the stressor. The authors suggest that beta-endorphin modulates the activity of the hypothalamic-pituitary-adrenal axis, thereby regulating ACTH secretion. Yet, the evidence brought forward in support of this claim is inconclusive. It may cautiously be stated that beta-endorphin release from the pituitary gland in horses is synchronised with the initial phase of the stress reaction and may in this way mitigate the negative results of cortisol on the organism.

4. Beta-endorphin in illness

One of the best examples of hyperbetaendorphinemia in horses is ECS (Equine Cushing's Disease). Lowe (1993) reports that changes in the behaviour of affected individuals such as lethargy or submissiveness may result from increased concentrations of beta-endorphin. According to Millington et al. (1988), the concentration is 60 times higher in the plasma and 120 times higher in the cerebrospinal fluid of ECS-affected animals. Another cause of changes in animal behaviour connected with the opioid system is described by authors who compared the levels of endorphins in healthy horses and horses with stereotypy (Pell and McGreevy, 1999). They argue that the diseased horses exhibited a congenital increased sensitivity of opioid receptors. However, the claim is not fully proved as it is only based on the observation that there is a lack of statistically significant differences in beta-endorphin concentrations between healthy and diseased horses.

The concentration of beta-endorphin in blood was also assayed in the case of colic diseases. Recent research conducted by a group of Finnish scholars focussed on, among other questions, specifying the levels of circulating beta-endorphin using the RIA method in colicky horses. Additionally, the study was concerned with assessing the usefulness of the method as an indicator of pain intensity, prognosis and stress (Niinisto et al., 2009). Observations were made of 77 diseased horses divided into three groups according to the intensity of clinical symptoms – mild, moderate and acute. Groups were not uniform and included many horses with only intestinal obstruction and displacement. The control group consisted of 15 clinically healthy horses. Only ponies were excluded from the study; therefore, it may be assumed that horses of different types were used. Among the experimental groups a significant variability of results was observed due to the duration of the disease and

the different ages of the animals in question. It appears justified to trace the level of beta-endorphin in patients belonging to fairly uniform age groups and relate the results to such parameters as the duration of the disease. Moreover, many animals included in the study had been treated with pain relievers (mainly flunixine meglumine) prior to hospitalisation. The influence of the treatment on the results of the study was not explained by the authors. Therefore, it seems sound to examine only the horses which did not undergo any pain alleviation treatment. The concentrations of beta-endorphin in cured animals were lower than in the deceased ones as well as animals which had to be euthanized due to the lack of effect of the treatment (12.29 and 34.57 pmol/l, respectively). The assessment of the peptide concentration may have a vast prognostic significance. In healthy horses the value was 5.71 pmol/l, while in the diseased animals with mild, moderate and acute clinical symptoms the values were 11.43, 14.0 and 32.29 pmol/l, respectively. The results of the examination conducted after the animals were brought to hospital, with the abovementioned influence of transportation on the beta-endorphin concentration in plasma taken into account, may not be fully reliable. The measurement of beta-endorphin levels is therefore only useful in the case of non-transported horses, that is, if samples are collected prior to the appearance of transportation stress, on the site of colic occurrence. A high correlation of the obtained results with the intensification of clinical symptoms, including heart rate and mortality as well as ACTH and cortisol levels, constitutes evidence supporting the usefulness of determining the level of beta-endorphin in horses with colic symptoms as a prognostic indicator. The levels of opioid in plasma rises in the case of colic with endotoxemia, probably by means of serotoninergic mediation, as a shock effect (Niinisto et al., 2009). The obtained results may confirm the notion that measuring the concentration of plasma beta-endorphin is beneficial in monitoring visceral pain (McCarthy et al., 1993) and orthopaedic pain in horses (Raekallio et al., 1997), as beta-endorphin is an endogenous pain relieving substance secreted in response to stress, similarly to ACTH (Niinisto et al., 2009).

5. Beta-endorphin and the reproductive system

Beta-endorphin has also been a subject of inquiry for researchers in the field of reproduction,

although reports concerning horses are scarce. The impact of beta-endorphin on the activity of the reproductive system remains largely a point of theoretical debate, based mainly on comparisons drawn between different species. The role of the peptide in stallions, which is secreted by Leydig's cells in the testicles/testes, may be limited to suppressing the activity of Sertoli cells (Roser, 2008). This stands in partial contrast to the findings of other authors, who state that although POMC gene expression in epididymides and testes was not observed in stallions, the presence of beta-endorphin was found in these organs using immunocytochemical staining (Soverchia et al., 2006). These results may suggest plasma as the source of the peptide rather than testes or epididymides, and are not sufficient, in the light of the current state of knowledge, to fully explain the role of beta-endorphin in the functioning of the reproductive system in stallions.

The role of endogenous opioids in females appears to be complex. Reliable research, employing naloxone – an opioid receptor blocker, was conducted in mares (Behrens et al., 1993). The authors assert that opioid peptides influence FSH and LH release in the luteal phase of the ovarian cycle and may play a role in suppressing gonadotropin secretion by progesterone. It is interesting that an increase in FSH and LH levels in the luteal phase of the cycle after applying naloxone was observed both in breastfeeding and non-breastfeeding mares.

A pool of circulating beta-endorphin was studied in women during the menstrual cycle. No significant fluctuations in beta-endorphin levels were noted during the cycle. In addition to this, no relationship was found between its concentration in blood and estradiol, progesterone, luteinizing hormone and foliculotropin levels, despite the fact that ovaries contain considerable amounts of beta-endorphin. This leads to the supposition that ovaries exert no influence on the pool of circulating beta-endorphin (Martyn et al., 1986). Similar results, but with regard to beta-endorphin in the uterus and the placenta, were obtained in the case of sows. A raised level of beta-endorphin in plasma was observed during pregnancy, but not during the menstrual cycle, and its release during labour may be induced by prostaglandin F2-alpha (Aurich et al., 1993).

In women, increased secretion of beta-endorphin during pregnancy may stimulate the foetus to adapt to extrauterine life, and some amount of it may be transferred from the mother's bloodstream to

the foetus (Radunovic et al., 1992). In a study conducted in rats, it was determined that pregnancy and labour are connected with a considerable rise in beta-endorphin levels in the hypothalamus, the midbrain and the amygdala when compared to non-pregnant animals (Wardlaw and Frantz, 1983). The results suggest that beta-endorphin of central origin influences the level of pain perception and the behaviour of a female during pregnancy. Beta-endorphin, as a modulator of behavioural events, is thought to have a role in shaping perinatal activity in females (including mares).

6. The role of beta-endorphin in immunity

The results of research conducted so far indicates that there is a correlation between endogenous opioids and the immune system. However, data and observations pertaining to this correlation in horses are very limited.

The impact of endogenous opioids on receptors distributed in the central nervous system may lead to anti-inflammatory effects as a result of a suppression of cytokine secretion, as spleen macrophages in mice whose ability to produce beta-endorphin has been disabled secrete significantly more IL-6 after LPS stimulation than the cells of animals who are able to produce beta-endorphin (Refojo et al., 2002). Additionally, human peripheral blood polymorphonuclear cells (PMN), regardless of TNF-α stimulation, bred in the presence of beta-endorphin, exhibit greater apoptosis than cells incubated in the absence of opioids. Furthermore, the effect is reversible by naltrexone – an opioid antagonist (antagonist of opioid receptors) (Sulowska et al., 2002).

The immunomodulating effect of opioids is complicated by the fact that numerous inflammatory cells exhibit the ability to produce endogenous opioid peptides, which is of great significance for the process of inflammatory reactions. In rats with experimentally induced inflammation an infiltration of leukocytes containing beta-endorphin was observed (Machelska et al., 2003). These cells release the peptide in the inflammatory focus, which may not only have an immunomodulating, but also pain-relieving effect. This is clearly visible after the administration of corticoliberin (CRH) to rats with artificially induced inflammation. This supports the co-expression of beta-endorphin and corticoliberin receptors in inflammatory cells infiltrating

the inflammation site and in circulating leukocytes (Mousa et al., 2003). Furthermore, beta-endorphin may play a major role in the course of artificially induced peritonitis in mice in which it was detected in exudate (Chudzinska et al., 2005). It has a considerable significance in natural pain control, which may be completely neutralised through immunosuppression (Janson and Stein, 2003). It appears then that there is a great deal of evidence imlicating beta-endorphin as an immunomodulator and in some situations it may oppose the effects of cortisol. Therefore, the abovementioned changes in beta-endorphin levels during stress reactions may be extremely important in contributing to balance of the immune system in horses.

7. Prooxidative/antioxidative balance

In recent years there have been numerous papers published concerning free-radical processes and their role in the emergence and the course of many diseases, both in humans and in animals (Droge, 2002; Marlin et al., 2002). The scale of danger posed by excess reactive oxygen species (ROS) is manifested in the fact that they participate in the etiopathogenesis of around one hundred disorders, including cancers, cardiovascular and degenerative diseases (Bartosz, 2005). It is suspected that free radical damage which accumulates throughout life is the cause of ageing processes (Ji et al., 1998). Therefore, the influence of endogenous opioids on the formation of reactive oxygen in horses deserves further attention.

Owing to their intensive oxygen metabolism and their use in sport, horses appear to be especially sensitive to the consequences of induced oxidative stress, as during physical effort the demand for oxygen increases by up to 60 fold. It is widely known that in cell respiration at most 98% of the oxygen supplied is used. The remaining 2% undergoes incomplete reduction, leading to the formation of free radicals in the entire organism. Broadly speaking, the free radicals in question are reactive oxygen species (ROS), which are extremely active chemically and react with cell constituents. The ROS include, among others, hydrogen peroxide (H_2O_2), singlet oxygen ($[1]O_2$), hypochlorous acid (HOCl) and superoxide anion radical ($O_2^{\bullet-}$), as well as hydroxyl radical ($^{\bullet}OH$), hydroperoxil radical ($HO_2^{\bullet-}$) and nitrous oxide ($NO^{\bullet}$). Reactive oxygen species, principally hydroxyl radical and singlet oxygen,

cause damage to cellular structures through oxidation and reduction reactions and through the production of organic radicals. Reactive oxygen species mainly attack plasma membrane lipids, where the peroxidation of polyunsaturated and esterified fatty acids takes place, which leads to disturbances in network structure and the loss of transport abilities (Dinis et al., 1993). Another site of impact for ROS are proteins which may directly undergo denaturation, fragmentation, cross-linking and aggregation. Furthermore, reactions may take place indirectly, in the presence of peroxides (Davies, 1993). With regard to carbohydrates, a disruption of glycosidic bonds between monomers may occur as well as an increase in their proneness to hydrolysis. Damage processes may affect both carbohydrate structures of glycolipids and glycoproteins, which may lead to antigen changes on the cell surface (Hunt et al., 1988; Bartosz, 2004). Free radicals (hydroxyl radicals in particular) also react with nucleic acids, damaging their structure, disrupting DNA threads or even entire chromosomes (Breen and Murphy, 1995). Importantly, reactive oxygen species destroy cytotoxic and suppressor T lymphocytes, which may result in autoimmune phenomena (Walport and Duff, 1998). As far as blood cells are concerned, respiratory burst, characterised by increased production of reactive oxygen species, applies mainly to neutrophils, and the evaluation of their oxygen metabolism is widely taken into consideration in works describing numerous human and animal diseases. This occurs when there is an increased demand for oxygen after the shift from glucose metabolism to the pentose phosphate pathway as a result of glucose activation by chemotactic factors, components of the complement system and cytokines (Dahlgren and Karlsson, 1999).

Respiratory burst, which causes an increase in the production of free radicals, has been found to be inhibited by beta-endorphin in alveolar macrophages in rabbits, stimulated by phorbol myristate acetate (PMA). On the other hand, it has been observed that it is activated in the same cells when stimulated by opsonised zymosan (Billert et al., 1998). Additionally, experiments performed with the use of the lucigenin chemiluminescence reaction on human material revealed a stimulating effect of beta-endorphin on respiratory burst. It was found to stimulate the production of the superoxide anion radical in polymorphonuclear cells (circulating neutrophils) and peritoneal macrophages, while naloxone, which acts in a manner similar to naltrex-

one, effectively suppresses this activation (Sharp et al., 1985). In research conducted in rats, a significant influence of beta-endorphin has been observed on the expression of both induced and endothelial nitric oxide synthase (iNOS and eNOS respectively) during ovulation. NOS activity was excited indirectly through inhibiting the production of prostaglandins, and the effect was reversible after administering naltrexone (Faletti et al., 2003). This suggests that the abovementioned problems may also affect horses, in which the formation of reactive oxygen species could be of critical importance, especially in the conditions of considerable physical burden.

8. Conclusion

The opioid system is a subject of attention not only due to its complexity but also its impact on key functions of the organism. There is little known concerning beta-endorphin as a promising diagnostic/prognostic indicator in horses is and not all research results published so far allow the drawing of definite conclusions. For these reasons we propose that the questions raised above require further scientific attention.

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Corresponding Author:

Marcin Golynski, University of Life Sciences, Faculty of Veterinary Medicine, Department and Clinic of Animal Internal Diseases, Sub-Department of Internal Diseases of Farm Animals and Horses, Lublin, Poland
E-mail: marcelgo@op.pl