COMPARISON OF TRAZODONE, DIAZEPAME AND DIBENZEPINE INFLUENCES ON RAT BRAIN BETA-ENDORPHINS CONTENT

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Abstract

The aim of our study was to establish the extent of influence of different psychotropic drugs to brain β-endorphins in experimental animals. The study was performed on albino Wistar rats (weight 250 g), treated with different psychoactive drugs. RIA technique was employed for quantification of brain β-endorphins. Brain β-endorphins were higher in experiment group treated with trazodone (929 pg/g ± 44,43; X±SD), and dibenzepine (906,63 pg/g ± 74,06), yet with lower brain content in rats treated with diazepame (841,55 pg/g ± 68,47), compared to brain β-endorphins content of control group treated with saline solution (0,95% NaCl) (873,5 pg/g ± 44,89). Significant differences were obtained comparing brain β-endorphins of trazodone vs. diazepame treated animals, with diazepame group having lower values ($p<0,02$). This study showed differences in changes of rat brain β-endorphins contents when different psychoactive drugs are used. Therefore, we consider that β-endorphins could be used for evaluation of effects of psychoactive drugs, as a useful parameter in therapy with these psycho pharmaceuticals.

KEY WORDS: β-endorphins, rat, psychotropic drugs, trazodone, diazepame, dibenzepine

Introduction

Investigations in the field of psycho pharmaceutical drugs gave us a lot of knowledge about their positive and side effects. Tricycle antidepressants were first in use, expressing their effects as a supplement for primary role – inhibition of norepinephrin and serotonin uptake by the nervous ends. The research of relation between endorphins and psychiatric disorders began with findings of enkephalin and opioid receptors located in mood-response areas of the brain (1, 2). Antipsychotics, also known as neuroleptics (dibenzepine, Figure 1.), are a heterogenous group of medications used to treat psychotic disorders such as schizophrenia, depression, dementia, and non-specific agitation. Antidepressants (trazodone, Figure 2.), given systemically, are widely used for the treatment of various chronic and neuropathic pain conditions in humans. There are numerous antidepressant medications, which are specifically designed to mimic the effects of endorphins in the brain to make a depressed person feel better or cope with stressful situations. In animal studies, antidepressants exhibit analgesic properties in nociceptive, inflammatory and neuropathic test systems, with outcomes depending on the specific agent, the particular test, the route of administration and the treatment method used. Anxiolytics are a group of medications used for treatment of anxiety disorders. The medications included in this group are benzodiazepines and buspirone. All benzodiazepines share the same three ring structure, but differ mainly in substitution on the heptagonal ring. There are three established subgroups: 1) 2-ketobenzodiazepines (diazepame, Figure 3.), 2) 3-hidroxybenzodiazepines and 3) triazolobenzodiazepines (3, 4). β-endorphins are cleaved from the prohormone proopiomelanocortin (POMC), which is a protein found in the pituitary gland and the brain. POMC undergoes cleavage to give way to a number of hormones, including melanocortins and the opiate peptides. β-endorphins, a class of opiate peptide, share a common N-terminal sequence, function as neuromodulators and are cleaved from C-terminus of the POMC protein. When β-endorphins bind to their receptors in neural membranes, cyclic adenosine monophosphate (cAMP) levels in the neurons are reduced, and the conductance of voltage-gated Ca2+ channels is decreased. Although β-endorphin is not known to cross the blood-brain barrier, levels of plasma β-endorphin-like immunoactivity may indirectly reflect central opioid activity. Importantly, β-endorphins can influence neurogenesis and other hippocampal functions (5). A vide range of techniques have been described, investigating various characteristics of human and rat specific antibodies. β-endorphins radioimmunoassays are widely performed following physical, emotional and environmental challenges in rat (6). Endorphins serve as an analgesic (pain killing), anesthetic and cause dissociation, immobilization and loss of self. They are released in shock, freeze, "fight or flight", trauma, physical pain and in all stress including psychological stress (1). The aim of our study was to establish the extent of influence of different psychotropic drugs to brain β-endorphins in experimental animals.

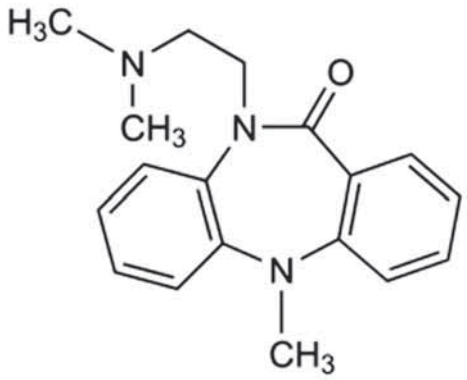

FIGURE 1. Structure of dibenzepine

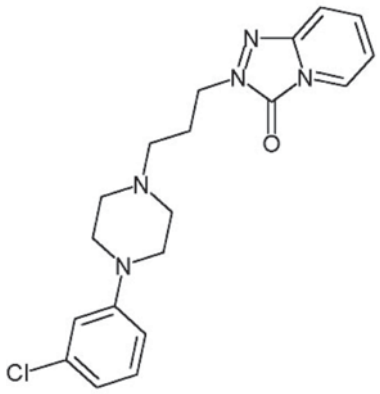

FIGURE 2. Structure of trazodone

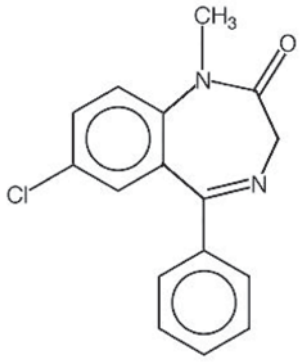

FIGURE 3. Structure of diazepame

Material and Methods

Albino Wistar rats, weight 250 g were used, divided in groups of 6. Ethical Committee of Faculty of Medicine, University of Sarajevo approved the experiment. Dibenzepine (3.5mg/kg/day), trazodone (5mg/kg/day) and diazepame (0.5mg/kg/day) were administrated to experimental, and 0,95% NaCl solution to control group. Before brain samples were collected, all animals were properly sacrificed. Collection of brain samples was performed immediately for control group, and after 28th day of drugs administration. For analyzing β-endorphins levels we used RIA method, for quantification of human serum and brain β-endorphins (Nichols Institute, San Juan, Capistrano, USA), and for radioactivity level β-counter with gamma-radiation source (LKB Wallac – Sweden). β-endorphin concentration is directly proportional to radioactivity measured in samples. Concentration is given in pg/g for brain β-endorphin values. We performed statistic evaluation of obtained results by counting mean value (X), standard deviation (SD) and standard error of the mean (SEM). The level of significance was determined by use of Student's T test, with values $p \leq 0,05$ considered as significant.

Results and Discussion

O Previous investigations showed that acute amitriptyline and clomipramine produce naloxone-reversible antinociception. This apparent opioid-like involvement was further investigated by measuring β-endorphin levels in the hypothalamus following acute and chronic treatment with these antidepressants. They demonstrated significantly raised levels of β-endorphin. The support was provided for the suggestion that antidepressants activate opioid systems, through both a direct opioid receptor interaction and an indirect action through enhanced release of opioid peptides (7). Desipramine and paroxetin, used in animal depression models, did not significantly affect the extra cellular levels of β-endorphin in nucleus accumbens, but chronic antidepressant treatment did normalize serotonin-induced release of β-endorphin, as well as behavioral manifestation of depressive behavior (8). Our data, presented by graphic (X±SD), show brain β-endorphins values after 28-day period of different drugs administration. Obtained values for each drug were compared to the other, and to those of control group treated with saline solution. Results after chronic treatment show increase of brain β-endorphins, as was described in other studies (7). Antidepressant trazodone produced strongest response in brain β-endorphins content (929 pg/g ± 44,43). Those results were higher then those of control group (873,5 pg/g ± 44,89). Also, content of brain β-endorphins was higher in trazodone treated rats, compared to changes obtained in rat brains after other drugs were used, yet significantly higher only compared to diazepame treated group (841,55 pg/g ± 68,47; $p<0,02$). Dibenzepine produced higher β-endorphins concentration in rat brains (906,63 pg/g ± 74,06) compared to values of diazepame treated rats and control rats, but without significance (Figure 4). We consider that all of these changes can be caused by differences in mechanism of triazolopyridine (trazodone), dibenzepine and benzodiazepine (diazepame) action on brain β-endorphins content. That points at possible differences in synthesis intensity of β-endorphins, degradation of brain β-endorphins and possible releasing into blood stream, caused by constant psychotropic drugs administration. Limitations of this investigation are in fact that starting values (serum, cerebrospinal fluid) were not obtained for animals used for quantification of brain β-endorphins content. However, we consider our results of brain β-endorphins in treated animals as eligible, compared with values obtained for control group, and previous studies (7) showing that chronic treatment with different drugs produced β-endorphins content changes in CNS, as was presented in our study.

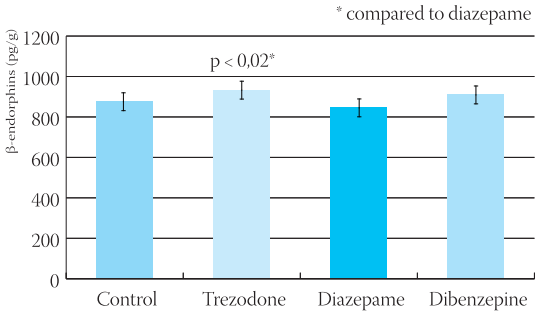

FIGURE 4. Brain β-endorphins values in psychotropic drugs treated animals

Conclusion

As a result of our study, we obtained changes in brain β-endorphins content in psychotropic drugs treated animals. Strongest response was produced by chronic trazodone administration (929 pg/g ± 44,43), significantly higher only compared to values of diazepame treated animals (841,55 pg/g ± 68,47; p<0,02). Dibenzepine produced higher β-endorphins concentration in rat brains (906,63 pg/g ± 74,06) compared to results of diazepame administration, and to control group (873,5 pg/g ± 44,89), but without significance.

This study showed differences in changes of brain β-endorphins concentrations when different psychoactive drugs are used. Therefore, we consider that β-endorphins could be used for evaluation of effects of psychoactive drugs, as a useful parameter in therapy with these psycho pharmaceuticals.

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