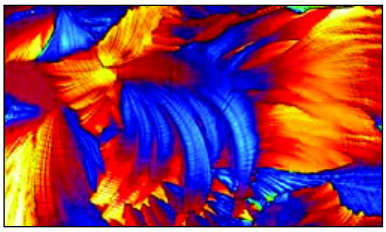
TRAZODONE INFLUENCE ON RAT SERA β-ENDORPHINS LEVEL

Radivoj Jadrić[2*], Irfan Zulić[1], Sabaheta Hasić[2], Emina Kiseljaković[2], Belma Zečević[2], Jovan Radovanović[2], Emina Ićindić-Nakaš[2], Mira Winterhalter-Jadrić[2]

1 Institute for Pharmacology and Toxicology, University of Sarajevo, Medical faculty, Bosnia and Herzegovina

2 Institute for Physiology and Biochemistry, University of Sarajevo, Medical faculty, Bosnia and Herzegovina

* Corresponding author



β -ENDORPHIN

ABSTRACT

Some 25 years ago it was found that parts of CNS could produce strong analgesic response on little morphine quantities. Later studies proved the existence for dozen of morphine-like substances, called opioids, which are normally produced in the brain. The most important are endorphins, met- and leu-encephalin and dinorphin produced both in hypothalamus and pituitary gland.

The aim of our study was to found whether and how strong produce of β-endorphins is to be expected when psychotropic drugs are used. Trazodon as antidepressant was used, and RIA technique for quantification of sera β-endorphins. The results showed significant difference in rat sera β-endorphins between certain days of drug application. These studies showed that β-endorphins could be of great importance, used as markers for evaluation of patient treatment and eventual abuse of psychotropic drugs.

Key words: β-endorphins, trazodon, rat, psychotropic drugs

INTRODUCTION

Influence of morphine-like psychoactive drugs is a subject of scientific interest for a long period, especially in expression of their therapeutic effects in treatment of psychiatric disorders, anxiety, depression, etc. Pert and Snyder (1973) found exogenous morphine cell receptors both in brain and guts (1). Investigating morphine-like endoactive substances, met encephalin and leu encephalin were discovered by Hughers and Kosterlitz (1975), with effects suppressed by morphine antagonist-naloxone (2). C-terminal-beta LPH was found in 1975 by Teschemacher at al., as a pituitary factor with opioid effects (3). Facts suggest that brain peptides are reminds from certain period, having a major role lost during evolution (1, 3, 4).

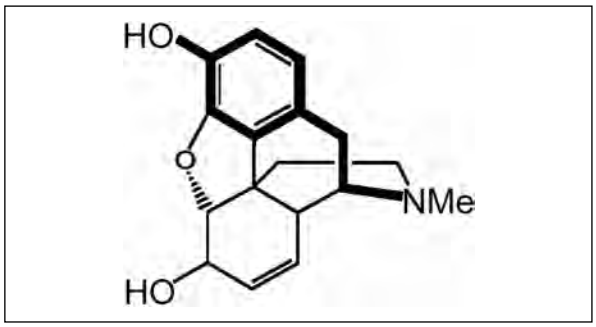


Figure 1. Morphin

Effects of opioid peptides are realized through opioid receptors (5, 6, 7). Using encephalin and opiates marked by radioactive isotopes, several different linking parts were found, and were marked as μ (for morphine) and (δ for encephalin) (8). Opioid receptors were finally classified in 1998 and marked as:

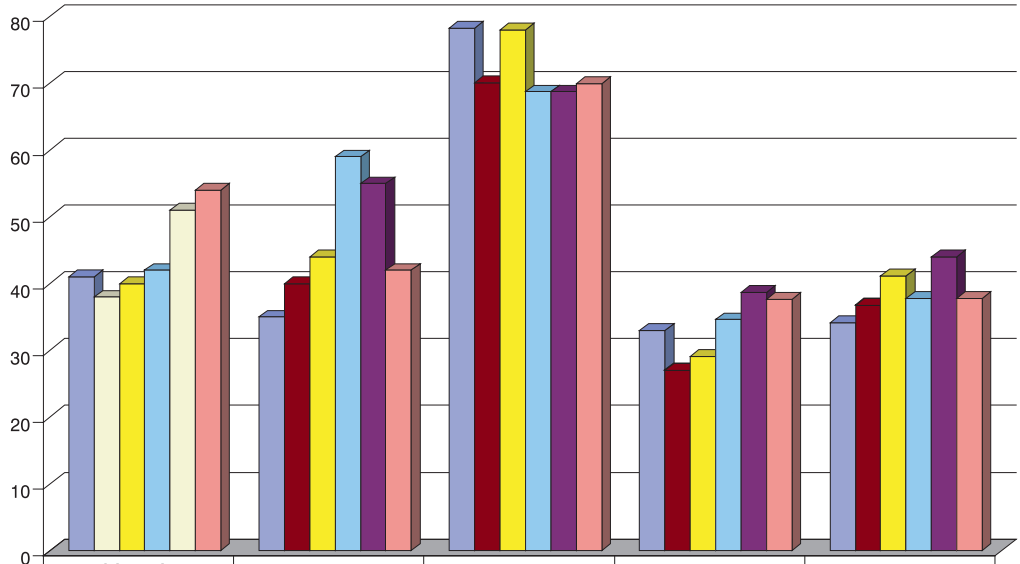
- OP_1 (delta)
- OP_2 (kappa)
- OP_3 (mu) (9).

In effects of the endogenous opioid system on pain perception and blood pressure sex differences were suggested (10).

Endorphins (α,β,γ and δ) have location in pituitary front lobe and pars intermedia and in hypothalamus, but were also found in testicles, seminal vesicles and prostate in different animal species (11), with beta-endorphins detectable also in serum. Unlike other mammals, cat brain shows different distribution of beta-endorphins immune-reactive parts, with possible involvement in different physiological functions of those peptides (12).

Beta-endorphins have a polypeptide structure, made of 31 amino acid, placed in beta-LPH C-terminal part, with high opiate activity, 3-5 time efficiently competing for opiate linking parts. Some facts are suggesting that beta-endorphins have a role in change of behavior, appetite

Graphic 2. β-endorphin sera levels in trazodon treated animals versus control group (pg/ml)



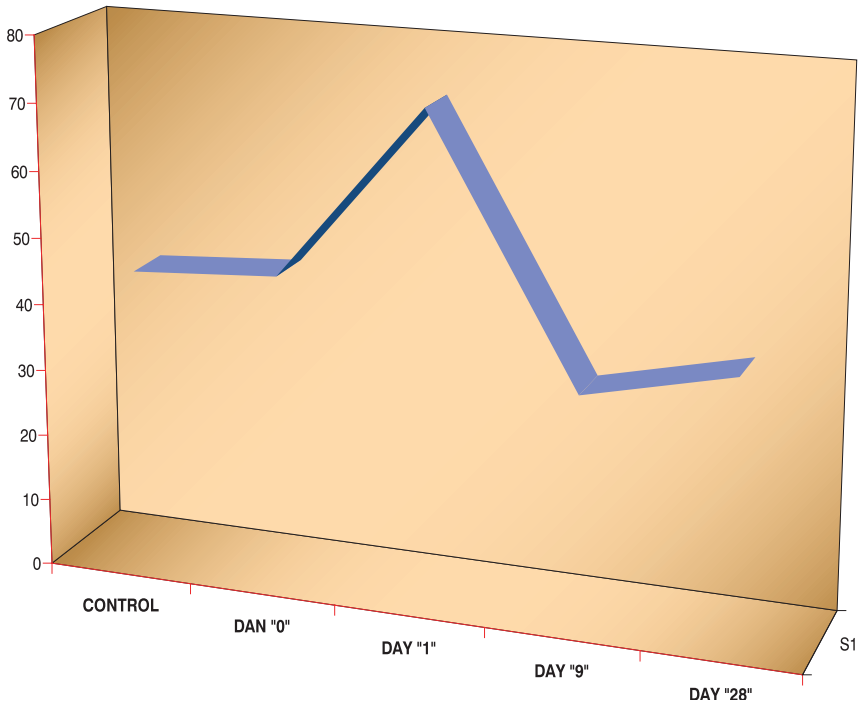
	CONTROL	DAN "0"	DAY "1"	DAY "9"	DAY "28"
Animal 1	41	35	78.29	32.97	34.15
Animal 2	38	40	70.14	27.02	36.8
Animal 3	40	44	78	29.07	41.19
Animal 4	42	59	68.75	34.6	37.8
Animal 5	51	55	68.74	38.74	44.06
Animal 6	54	42	69.95	37.7	37.78

control, and development of obesity and schizophrenia.
They are produced as well as ACTH, when adrenalectomy is performed, related to stress or administration of CRH, meaning both substances are produced by the same adenohypophyseal cells from the same glycoprotein precursor (13).
Beta-endorphins in brain are turned to gamma-endorphins with neuroleptic qualities, with alpha-endorphina originating from the last in low pH, expressing psycho stimulative effects, with number of proteolytic stages between changing process (14).
Given directly to animal central nervous system, they produce same effects as morphine and other opiates, also lowering pain and blocking respiration. With injections repeatedly given, addiction is produced, but quantities are thousand times bigger than those presumed to be resolved in the body. That is why there are no direct conclusions about the same effects of endogenous endorphins compared with injected ones (15).
It was presumed that they work as neurotransmitters, neuro modulators and even hormones. Anatomic pathways with endorphin and encephalin contents and also opioid receptors on cell surface gives a proof to neurotransmitter function (16), whereas pituitary and adrenomedullary opioid peptides speaks in favor of hormonal function (17).
Findings in the field of psycho-pharmaceutics gave us a lot of knowledge about their positive and side effects, as well as for brain function and nature of psychotic diseases; signal substances and their impact on health and illness of the brain (15).
Tricycle antidepressants were first in use, expressing their effects as a supplement for primary role - inhibition of norepinephrine and serotonin uptake by the nervous ends. Trazodon, nefazodon and bupropion has less defined neuropharmacology and are taken as atipic. Nevertheless, they have better efficiency and endurance, leading to better acceptance, even though there is no evidence of their superiority over alder drugs (18).
Research showed synergistic influence of trazodon, combined with mud bath in therapy of fibro-myalgic syndrome, bettering psychological response of homeostasis formation and systems as an answer to stress (19). Desipramine and paroxetin, used in animal depression models, did not significantly affect the extracellular levels of beta-endorphins in nucleus accumbens, but chronic antidepressant treatment did normalize serotonin-induced release of beta-endorphins, as well as behavioral manifestation of depressive behavior (20).

MATERIAL AND METHODS

Albino Wistar rats, weight 250 gr. were used, with experimental group of 6, and each animal was control for itself.
Trazodon was administrated to experimental (5mg/kg/

Graphic 3. Sera β-endorphin mean values (control versus trazodon treated group)



day), and 0.95% NaCl solution to control group.
Blood samples were collected from great tail vain, before beginning, and after 1st, 9th, and 28th day of trazodon administration. Analysing beta-endorphins level we used RIA technique for quantification of human serum beta-endorphins (Nichols Institute, San Juan, Capistrano, USA), and for radioactivity level beta-counter with gamma-radiation source (LKB Wallac - Sweden). Beta-endorphins concentrations are directly proportional to radioactivity measured in samples. Concentration is given in pg/ml, presented by charts and graphics. Statistic evaluation of obtained results was performed using Student's T test, and by counting mean value, standard deviation and standard error.

RESULTS AND DISCUSSION

Obtained experimental data were statistically evaluated. Individual results and mean value are given within graphs, and presented by lines and histograms.
Data shows individual animal sera beta-endorphins values, before beginning, and after 1st, 9th, and 28th day of trazodon administration. Beta-endorphins values obtained for each day were compared to the other (days marked as groups, from II - V), and versus those of control group. There are significant differences between group I vs. III, II vs. III, III vs. IV and III vs. V ($p \leq 0.05$). After 1st day of multiple trazodon administration results show rapid increase of sera beta-endorphins, lowering after 9th day, and reaching the same or a bit lower values 28th day of treatment. Data obtained by other authors, who were using different antidepressant drugs, speak in favor of beta-endorphins value changes got in our investigation (21, 22).

CONCLUSION

- Sera beta-endorphins values reach highest point at 1st day after trazodon administration
- Sera beta-endorphins values after a continuous trazodon treatment of animals are a bit lower then those in control group
- Endogenous beta-endorphins can be used in evaluation of psychoactive drug therapy
- Evaluation of beta-endorphins sera level could be of great importance used as markers for investigation of psychoactive drug effects

REFERENCES

(1) Pert C.B., Snyder S.H.: Opiate receptor: demonstration in nervous tissue; Science, 1973.,197: 1011-1014.

(2) Hughes J., Smith T.W., Kosterlitz H.W., Fothergill L., Morgan B.A., Morris H.R.: Identification of two related pentapeptides from the brain with potent opiate agonist activity; Nature, 1975., 258: 577-579.

(3) Teschemacher H., Opheim K.E., Cox B.M., Goldstein A. A peptide-like substance from pituitary that acts like morphine. I. Isolation. Life Sci., 1975., 16(12): 1771-1775.

(4) Terenius L.: Characteristics of the "receptor" for narcotic analgesic in synaptic plasma membrane fraction from rat brain.Acta Pharm. Toxic. 1973; 33: 377-384.

(5) Iwamoto E.T., Martin W.R. Multiple opioid receptors. Med.Res.Rev., 1981; 1: 411-440

(6) Yaksh T.L., Howe J.R. Opiate receptors and their definition by agonists. Anesthesiology, 1982; 56: 246-249.

(7) Snyder S.H. Drug and neurotransmitter receptors in the brain. Science, 1984; 224: 22-31.

(8) Pasternak G.W. Opioid receptors. Psychopharmacology, Raven Press, New York, 1987, p 283.

(9) Varagić V., Milošević M. Farmakologija, Elit Medica; 1998., p 200.

(10) al'Absi M, Wittmers L.E., Ellestad D, Nordehn G, Kim S.W., Kirschbaum C, Grant J.E. Sex differences in pain and hypothalamic-pituitary-adrenocortical responses to opioid blockade. Psychosom Med. 2004;66(2): 198-206.

(11) Morales Martinez M.E., Padron N. Beta-endorphines and male reproductive system, Ginecol.Obstet.Mex., 1999., 67: 183-187.

(12) Coveñas R., de León M., Narvaez J.A., Aguirre J.A., Tramu G., Gonzalez-Baron S. Anatomical distribution of beta-endorphin (1-27) in the cat brainstem: an immunocytochemital study. Anat.Embryol.(Berl.), 1999., 199:2: 161-167.

(13) Montgomery, R., Dryer, R.L., Conway, T.W., Spector, A.A. Biochemistry - A Case-Oriented Approach; The C. V. Mosby Cmpany, 1983., 698-700.

(14) De Wied, D. Proteolytic conversion of endorphins by brain synaptic membranes: Caracterisation of generated endorphin fragments and proposed metabolic pathway. J. Biol. Chem., 1982., 256, 12463-12469.

(15) Carlson A., Carlson L. Hemijski glasnici mozga, Savremena administracija, Beograd, 1990., p 7, 9, 11, 46, 47, 93, 94.

(16) Bloom F.E. The role of cyclic nucleotides in central synaptic function. Rev.Physiol.Biochem.Pharmacol., 1975., 74:1- p 104.

(17) Holaday J.W.: Cardiovascular effects of endogenous opiate systems. Ann.Rev.Pharmacol.Toxicol., 1983., 23: 541-594.

(18) Goodman & Gilman´s: The pharmacological basis of therapeutics, Ninth edition, McGraw-Hill: Health Professions Division, New York, St. Louis, 1996., p. 339-404, 432-433, 523.

(19) Bellometi S., Galzigna L.: Function of the hypothalamic adrenal axis in patients with fibromyalgia syndrom and undergoing mud-pack treatment. Int.J.Clin.Pharmacol.Res., 1999., 19(1): 27-33.

(20) Zangen A., Nakash R., Roth-Deri I., Overstreet D.H., Yadid G.: Impaired release of beta-endorphin in response to serotonin in a rat model of depression. Neuroscience. 2002;110(3): 389-393.

(21) Đurović D., Milić-Aškrabić J., Majkić-Singh N. Effect o fluvoxamine on the level of beta-endorphin in the sera and nervous tissue of rats, Pharmazie 1998, Feb;53(2): 143-144.

(22) Đurović D., Milić-Aškrabić J., Majkić-Singh N. Serum beta-endorphin level in patients with depression on fluvoxamine. Farmaco., 1999., 54:3; 130-133.