Koncentracije beta-endorfina u serumu i mozgu kod štakora liječenih trazodonom
Brain and serum beta-endorphin concentrations in trazodone treated rats

Radivoj Jadrić[1], Sabaheta Hasić[1], Emina Kiseljaković[1], Jozo Ćorić[2], Jovan Radovanović[1], Mira Winterhalter-Jadrić[1]

[1]Institut za fiziologiju i biokemiju, Katedra za biokemiju, Medicinski fakultet Univerziteta u Sarajevu, Sarajevo, Bosna i Hercegovina
[1]Institute of Physiology and Biochemistry, Department of Biochemistry, Sarajevo University School of Medicine, Sarajevo, Bosnia & Herzegovina
[2]Institut za kliničku kemiju i biokemiju, Klinički centar Univerziteta u Sarajevu, Sarajevo, Bosna i Hercegovina
[2]Department of Clinical Chemistry, Sarajevo University Hospital Center, Sarajevo, Bosnia & Herzegovina

Sažetak

Uvod: Beta (β) endorfini otkriveni su u hipotalamusu i hipofizi, a u manjoj količini i u drugim organima. Cilj ove studije bio je utvrditi mogući utjecaj psihotropnih lijekova na β-endorfine u serumu i mozgu kod štakora kao eksperimentalnog modela.

Materijal i metode: Studija je provedena na albino Wistar štakorima (200-250 g tjelesne težine) uz primjenu antidepresiva trazodona. Tehnika RIA primijenjena je za kvantificiranje β-endorfina u serumu i mozgu.

Rezultati: Koncentracije serumskih β-endorfina izmjerenih 1. dana primjene trazodona bile su značajno više (72,3 ± 1,86 pg/mL; $\bar{x}$ ± SEM) od početnih koncentracija (45,83 ± 3,77 pg/mL; P = 0,001). Međutim, trazodon je doveo do značajno nižih koncentracija β-endorfina 9. dana liječenja (33,4 ± 1,91 pg/mL) u usporedbi s koncentracijama izmjerenim 1. dana davanja lijeka (P = 0,001). Koncentracije zabilježene 28. dana (38,62 ± 1,42 pg/mL) bile su više u usporedbi s onima izmjerenim 9. dana (P = 0,439). Koncentracija β-endorfina u mozgu pokazala je značajno sniženje 1. dana davanja trazodona (431,03 ± 11,57 pg/g) u usporedbi s kontrolnim životinjama (873,5 ± 18,32 pg/g; P = 0,001). Usporedba nižih koncentracija zabilježenih 9. dana liječenja (433,65 ± 14,67 pg/g) i onih u kontrolnoj skupini životinja također je dala statistički značajne vrijednosti (P = 0,001). U skupini životinja na trazodonu 28. dana su koncentracije β-endorfina u mozgu bile značajno više 28. dana (929 ± 18,13 pg/g) od koncentracija izmjerenih 1. i 9. dana (P = 0,001 oboje) liječenja, i te su koncentracije bile više od onih zabilježenih u kontrolnoj skupini, međutim, bez statističke značajnosti (P = 0,137).

Zaključak: Kronično liječenje trazodonom uzrokuje porast sinteze β-endorfina u mozgu, dok akutno davanje ovoga lijeka dovodi samo do brzog oslobađanja β-endorfina u krvotok.

Ključne riječi: β-endorfini, štakor, psihoaktivni lijekovi, trazodon

Abstract

Introduction: Beta (β) endorphins have been detected in the hypothalamus and pituitary, and in a small amount in other organs. The aim of our study was to establish the possible influence of psychotropic drugs on serum and brain β-endorphins in rats as experimental model.

Material and methods: The study was performed on albino Wistar rats (200-250 g body weight), using the antidepressant trazodone. RIA technique was employed for quantification of serum and brain β-endorphins.

Results: Serum β-endorphins measured on day 1 of trazodone application were significantly higher (72.31 ± 1.86 pg/mL; $\bar{x}$ ± SEM) compared to baseline values (45.83 ± 3.77 pg/mL; P = 0.001). However, trazodone produced significantly lower β-endorphin concentrations on day 9 of treatment (33.4 ± 1.91 pg/mL) compared to the values measured on day 1 of trazodone administration (P = 0.001). Endorphin concentrations recorded on day 28 (38.62 ± 1.42 pg/mL) were higher compared to those measured on day 9 (P = 0.439). Data on brain β-endorphin concentration showed a significant decrease on day 1 of trazodone administration (431.03 ± 11.57 pg/g) compared to data obtained from control rat brains (873.5 ± 18.32 pg/g; P = 0.001). Statistical significance was also recorded by comparison of the lower data obtained on day 9 of treatment (433.65 ± 14.67 pg/g) and those observed in the control group (P = 0.001). In trazodone treated rats, brain β-endorphins were significantly higher on day 28 (929 ± 18.13 pg/g) compared with the levels measured on day 1 and day 9 of treatment (P = 0.001 both), showing slightly higher values than in control rats, yet without statistical significance (P = 0.137).

Conclusion: Chronic trazodone treatment causes an increase in the brain β-endorphin synthesis, while acute drug administration results only in a rapid release of β-endorphins into the circulation.

Key words: β-endorphins, rat, psychoactive drugs, trazodone

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Uvod

Utjecaj morfinu sličnih psihoaktivnih tvari dugo je već predmetom je znanstvenog zanimanja, poglavito njihov terapijski učinak u liječenju psihijatrijskih poremećaja, anksioznosti, depresije itd. Istraživanje odnosa između endorfina i depresije započelo je pronalaskom encefalina i opioidnih receptora smještenih u područjima mozga odgovornim za reakcije u raspoloženju. Ranija ispitivanja postavila su pitanje uzrokuju li depresiju povišene, nedostatne ili ustaljene koncentracije endorfina. Endorfini vjerojatno moduliraju aktivnost živčanog sustava kroz duže, a ne kratko razdoblje.

Endorfini se oslobađaju u stanjima šoka, straha, u krajnje pogibeljnim situacijama, kod traume, fizičkog bola te kod stresa uključujući psihološki stres. Oni služe kao analgetici, anestetici, te uzrokuju disocijaciju, imobilizaciju i gubitak svijesti o samome sebi. Depresori izazivaju povišenje koncentracija stresnih hormona u krvi. Kako se endorfini oslobađaju zajedno s ACTH u odgovoru na bilo koji stresni poticaj, smatra se kako depresori "povisuju" i koncentraciju endorfina.

Istraživanja na području psihofarmaceutike pružila su dosta saznanja o njihovim pozitivnim učincima, kao i o nuspojavama. Najprije su se počeli rabiti triciklični antidepresivi koji su imali dodatni učinak uz njihovu primarnu ulogu, a to je inhibicija preuzimanja norepinefrina i serotonina u živčanim završecima (1,2).

Iako je učinkovitost selektivnih inhibitora ponovnog preuzimanja serotonina (SSRI) i tricikličnih antidepresiva slična, SSRI imaju bolji profil neškodljivosti i podnošljivosti, što im daje prednost kod svih anksioznih poremećaja. Triciklični antidepresivi su pak poglavito neprikladni za primjenu kod starijih osoba zbog znatnih nuspojava, mogućeg nastanka antikolinergičnog delirija i doprinosa učestalosti padova i prijeloma kuka, pa ih više ne preporuča (3).

Trazodon je učinkovit antidepresiv širokog terapijskog spektra, uključujući anksiolitično djelovanje. Ovaj triazolopiridinski antidepresiv je danas drugi najčešće propisivani lijek za liječenje nesanice, i to zbog njegovih sedativnih svojstava. S obzirom na široku primjenu trazodona proveden je pažljiv pregled literature kako bi se procijenila njegova učinkovitost i nuspojave kad se daje za liječenje nesanice. Iako se o trazodonu govori kao o inhibitoru ponovnog preuzimanja serotonina (5-HT), ovaj farmakološki učinak je preslab da bi mu se u potpunosti pripisala klinička djelotvornost ovoga lijeka (4,5).

Cilj ove studije bio je utvrditi mogući utjecaj psihotropnih lijekova na koncentraciju β-endorfina u serumu i mozgu štakora kao eksperimentalnog modela.

Introduction

The effect of morphine-like psychoactive drugs has long been a subject of scientific interest, especially considering their therapeutic effects in the treatment of psychiatric disorders, anxiety, depression, etc. The research into the relation between endorphins and depression began with the findings of encephalin and opioid receptors located in the mood-response areas of the brain. Previous studies have raised a question whether excess, deficient, or static levels of endorphins cause depression. Endorphins are likely to modulate the nervous system activity over a long-term rather than short-term period.

Endorphins are released in the conditions of shock, freeze, "fight or flight", trauma, physical pain, and in all stress situations including psychological stress. They serve as an analgesic, anesthetic and cause dissociation, immobilization and loss of self. Depressors induce elevation of stress hormone levels in blood. Since endorphins are released along with ACTH in response to any stressor, depressors are supposed to "elevate" endorphin levels as well.

Research in the field of psychopharmaceuticals has provided considerable knowledge about their favorable effects as well as side effects. Tricyclic antidepressants were introduced first, showing effects as a supplement for the primary role of inhibition of norepinephrine and serotonin uptake by the nervous ends (1,2).

Although the efficacy of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants is similar, the SSRIs have better safety and tolerability profile, making them preferable agents for all anxiety disorders. The considerable side effect burden, the potential of producing anticholinergic delirium, and their contribution to the occurrence of falls and hip fractures make tricyclic antidepressants especially unsuitable for the elderly and are therefore no longer recommended (3).

Trazodone is an effective antidepressant with a broad therapeutic spectrum, including anxiolytic efficacy. Because of its sedative effect, this triazolopyridine antidepressant is currently the second most commonly prescribed agent for the treatment of insomnia. Considering the widespread use of trazodone, careful review of the literature was performed to assess its efficacy and side effects when used for the treatment of insomnia. Although trazodone is usually referred to as a serotonin (5-HT) reuptake inhibitor, this pharmacological effect appears to be too weak to fully account for its clinical effectiveness (4,5).

The aim of our study was to establish the possible influence of psychotropic drugs on serum and brain β-endorphins in rats as experimental model.

Materijali i metode

Životinje

Studija je provedena na muškim albino Wistar štakorima (tjelesne težine 200 - 250 g). Ukupno 30 životinja podijeljeno je u skupine od 6 životinja. Trazodon (5 mg/kg/dan) se davao životinjama u eksperimentalnoj skupini, a 0,95%-tna otopina NaCl životinjama u kontrolnoj skupini. Uzorci krvi, oko 0,5 mL na dan liječenja, uzimali su se iz velike repne vene. Nakon 30 minuta na sobnoj temperaturi serum je dobiven centrifugiranjem na 3000 okr/min kroz 10 minuta, odvajanjem od ugruška, te zamrznut na -20 °C do analize. Kvantificiranje β-endorfina u serumu provedeno je prije (0. dan) te 1., 9. i 28. dana davanja trazodona, pri čemu je svaka životinja služila kao vlastita kontrola.
Proveli smo dodatno određivanje koncentrycije β-endorfina u mozgu kako bismo utvrdili širinu psihotropnog djelovanja. Sve životinje su propisno žrtvovane prije prikupljanja uzoraka mozga. Kod kontrolne skupine mozak se uzorkovao odmah, a u eksperimentalnoj skupini 1., 9. i 28. dana davanja trazodona. Nakon homogenizacije u Potterovom homogenizatoru tkivni uzorci su centrifugirani na 8000 okr/min kroz 20 minuta. Čisti supernatanti su stavljeni u epruvete i zamrznuti na -20 °C do analize.
Pokus je odobrilo Etičko povjerenstvo Medicinskog fakulteta Univerziteta u Sarajevu.

Metode

Koncentraciju β-endorfina u serumu i mozgu mjerili smo metodom radioimuno testa (RIA) (Nichols Institute, San Juan, Capistrano, SAD (6). Razinu radioaktivnosti mjerili smo β-brojačem s izvorom gama-zračenja (LKB Wallac, Švedska). Koncentracije β-endorfina izravno su proporcionalne radioaktivnosti izmjerenoj u uzorcima. Koncentracije su izražene u pg/mL za serum i u pg/g za vrijednosti β-endorfina u mozgu.

Statistička analiza

Statistička analiza koncentracije endorfina u serumu izvedena je pomoću programa SigmaStat 2.03 (SPSS Inc. 1995). Opetovano izmjerene vrijednosti analizirane su pomoću Friedmanove metode RM ANOVA kako bi se utvrdili glavni učinci na koncentracije β-endorfina tijekom razdoblja davanja lijeka. Tukeyev *post hoc* test za višestruke usporedbe primijenjen je za utvrđivanje značajnih razlika u serumskim koncentracijama β-endorfina u određene dane davanja lijeka (0. dan – 28. dan).
U statističkoj procjeni koncentracija β-endorfina u mozgu između skupina primijenili smo Kruskal-Wallisov jednosmjerni test ANOVA, dok smo za značajne razlike u koncentraciji β-endorfina u mozgu primijenili Bonferronijev t-test za višestruke usporedbe. Svi rezultati su izraženi kao srednja vrijednost, standardna devijacija (SD) i standar-

Materials and methods

Animals

Thirty male albino Wistar rats (200–250 g body weight) were divided into groups of 6 animals. Trazodone (5 mg/kg/day) was administered to the experimental group, and 0.95% NaCl solution to the control group. Blood samples, about 0.5 mL *per* day of treatment, were collected from the great tail vein. After 30 minutes at room temperature, serum was obtained by centrifugation at 3000 rpm for 10 minutes, separated from clot and frozen at -20 °C until analysis. Quantification of serum β-endorphins was performed before (day 0), and on days 1, 9 and 28 of trazodone administration, whereby each animal served as its own control.
To establish the extent of psychotropic influence, we performed an additional study of brain β-endorphins. Prior to the collection of brain samples, all animals were properly sacrificed. Collection of whole brain was performed immediately in control group, and on days 1, 9 and 28 of trazodone administration in experimental group. After homogenization in a Potter's homogenizer, tissue samples were centrifuged at 8000 rpm for 20 minutes. Clear supernatants were placed in tubes and frozen at -20 °C until analysis.
The experiment was approved by the Ethics Committee of the School of Medicine, University of Sarajevo.

Methods

The radioimmunoassay (RIA) kit (Nichols Institute, San Juan, Capistrano, USA) was employed for quantification of serum and brain β-endorphins (6). For radioactivity level measurement, β-counter with a gamma-radiation source (LKB Wallac, Sweden) was used. The concentrations of β-endorphins are directly proportional to the radioactivity measured in the samples. Concentrations are given in pg/mL for sera, and in pg/g of brain material for brain β-endorphin concentrations.

Statistical analysis

Statistical evaluation of serum endorphin concentrations was performed using the SigmaStat 2.03 (SPSS Inc. 1995) software. Repeatedly measured values were analyzed using Friedman RM ANOVA to determine major effects on serum β-endorphin concentrations over time after drug application. Tukey's post hoc test for multiple comparisons was used to determine significant differences in serum β-endorphin levels on particular days of drug application (day 0 – day 28).
On statistical evaluation of brain β-endorphin concentration between the groups, we used Kruskal-Wallis one-way ANOVA. Bonferroni t-test for multiple comparisons was used to determine the significance of differences in the brain β-endorphin concentration. All data are expressed

Tablica 1. Koncentracije β-endorfina u serumu i mozgu u određene dane liječenja trazodonom (srednja vrijednost ± standardna devijacija)

Table 1. Serum and brain concentrations of β-endorphins according to days of trazodone treatment (mean ± standard deviation)

	Control/Day 0 $\bar{x}$ ± SD	Day 1 $\bar{x}$ ± SD	Day 9 $\bar{x}$ ± SD	Day 28 $\bar{x}$ ± SD	P (ANOVA)
Serum (pg/mL)	45.83 ± 9.23	72.31 ± 4.55	33.4 ± 4.68	38.62 ± 3.49	P < 0.001
Brain (pg/g)	873.5 ± 44.89	431.03 ± 28.34	433.65 ± 35.95	929 ± 44.43	P < 0.001

First column: serum β-endorphin concentrations measured before the beginning of trazodone treatment (day 0), and β-endorphin concentration in control rat brain; Tukey's post hoc test for multiple comparisons showed all differences between results/days to be statistically significant, except for day 0 vs. day 28 and day 9 vs. day 28; Bonferroni t-test for multiple comparisons also showed all differences between results for particular day and control group to be statistically significant, except for control vs. day 28 and day 1 vs. day 9.

dna pogreška srednje vrijednosti (SEM). Razina značajnosti utvrđena je kao P < 0,05.

Rezultati

Rezultati dobiveni mjerenjem koncentracije β-endorfina u serumu i mozgu u određene dane davanja trazodona prikazani su u tablici 1. Serumske koncentracije izmjerene 1. dana davanja trazodona bile su značajno više (72,31 ± 1,86 pg/mL; $\bar{x}$ ± SEM) od početnih (45,83 ± 3,77 pg/mL; P = 0,001). Međutim, koncentracija β-endorfina izmjerena 9. dana liječenja (33,4 ± 1,91 pg/mL) bila je značajno niža od one izmjerene 1. dana (P = 0,001). Ove su vrijednosti također bile značajno niže od onih izmjerenih 0. dana (P = 0,011). I na kraju, koncentracije β-endorfina izmjerene 28. dana davanja trazodona bile su niže (38,62 ± 1,42 pg/mL) od onih izmjerenih prije početka davanja lijeka (P = 0,189) te značajno niže od koncentracija izmjerenih 1. dana davanja lijeka (P = 0,001). Međutim, koncentracije izmjerene 28. dana bile su više u usporedbi s onima zabilježenim 9. dana, no razlika nije bila statistički značajna (P = 0,439).
Rezultati dobiveni mjerenjem koncentracije β-endorfina u mozgu pokazali su značajno sniženje 1. dana davanja trazodona (431,03 ± 11,57 pg/g) u usporedbi s mozgom kontrolnih životinja (873,5 ± 18,32 pg/g; P = 0,001). Statistički značajna razlika zabilježena je i 9. dana liječenja (433,65 ± 14,67 pg/g) u usporedbi s kontrolnom skupinom (P = 0,001). Međutim, koncentracije β-endorfina u mozgu izmjerene 1. i 9. dana nisu se statistički značajno razlikovale (P = 1,00). I na kraju, koncentracije β-endorfina u mozgu izmjerene 28. dana davanja trazodona bile su značajno više (929 ± 18,13 pg/g) od onih zabilježenih 1. dana i 9. dana (P = 0,001 oboje). Koncentracije β-endorfina u mozgu izmjerene 28. dana davanja trazodona bile su nešto više od onih u mozgu kontrolnih životinja, no bez statističke značajnosti (P = 0,137).

as mean, standard deviation (SD), and standard error of mean (SEM). The level of significance was set at P < 0.05.

Results

Results of serum and brain concentrations of β-endorphins measured on particular days of trazodone application are given in Table 1. Serum concentrations measured on day 1 of trazodone application were significantly higher (72.31 ± 1.86 pg/mL; $\bar{x}$ ± SEM) compared to initial values (45.83 ± 3.77 pg/mL; P = 0.001). However, significantly lower β-endorphin concentrations were recorded on day 9 (33.4 ± 1.91 pg/mL) compared to day 1 of treatment (P = 0.001). These values were also significantly lower than the values measured on day 0 (P = 0.011). The last determination of serum β-endorphins was done on day 28 of trazodone application. These values (38.62 ± 1.42 pg/mL) were lower than the initial values (P = 0.189), and significantly lower than the values recorded on day 1 of treatment (P = 0.001). The values obtained on day 28 were higher compared to the values on day 9, however, without statistical significance (P = 0.439).
Data on the rat brain β-endorphin concentration showed a significant decrease on day 1 of trazodone administration (431.03 ± 11.57 pg/g) compared to control rat brains (873.5 ± 18.32 pg/g; P = 0.001). A statistically significant difference *vs.* control group was also recorded on day 9 of treatment (433.65 ± 14.67 pg/g; P = 0.001). However, there was no statistically significant difference in the concentrations of brain β-endorphins recorded on day 1 and day 9 (P = 1.00). Finally, the brain β-endorphin concentrations measured on day 28 of trazodone application were significantly higher (929 ± 18.13 pg/g) in comparison with the concentrations recorded on either day 1 or day 9 of treatment (P = 0.001 both). The brain β-endorphin concentrations measured on day 28 of trazodone application were

Rasprava

Ranija su ispitivanja ukazala na sinergistični utjecaj trazodona u kombinaciji s blatnim kupkama u poboljšanju psihološkog odgovora na stres. Desipramin i paroksetin primijenjeni u životinjskim modelima depresije nisu imali znatnijeg učinka na izvanstaničnu koncentraciju β-endorfina u *nucleus accumbens*. Kronično liječenje antidepresivima normaliziralo je serotoninom izazvano otpuštanje β-endorfina, kao i depresivne manifestacije u ponašanju (7,8).

Još je uvijek malo podataka koji pokazuju da akutno ili kronično liječenje antidepresivima ima različiti utjecaj na koncentraciju β-endorfina u serumu i mozgu kao mogući čimbenik u mehanizmu djelovanja ovih lijekova. U našem ispitivanju je 1. dana davanja trazodona zabilježen brz i značajan porast koncentracije β-endorfina u serumu (72,31 ± 1,86 pg/mL), nakon čega je 9. dana uslijedio pad (33,4 ± 1,91 pg/mL), dok su koncentracije izmjerene 28. dana liječenja bile nešto niže (38,62 ± 1,42 pg/mL) od početnih (45,80 ± 3,77 pg/mL). Rezultati objavljeni u literaturi također pokazuju promjene koncentracije β-endorfina u serumu nakon kronične primjene različitih antidepresiva (9,10). Rezultati dobiveni u našoj studiji s trazodonom sukladni su onima Đurovića i sur. (9,10). Brz porast serumskih β-endorfina te promjene zabilježene 9. i 28. dana ukazuju na akutni kao i kronični odgovor na davanje trazodona.

Prijašnja ispitivanja su pokazala kako akutno davanje amitriptilina i klomipramina dovodi do naloksonom reverzibilne antinocicepcije. Ovo očito opiodima slično djelovanje dalje se ispitivalo mjerenjem koncentracija β-endorfina u hipotalamusu nakon akutnog i kroničnog liječenja ovim antidepresivima. Dokazane su značajno povišene koncentracije β-endorfina. To govori u prilog pretpostavci da antidepresivi aktiviraju opioidne sustave kroz izravnu interakciju opioidnih receptora i neizravno kroz pojačano otpuštanje opioidnih peptida. Štoviše, pretpostavlja se kako izravno djelovanje antidepresiva na opioidne receptore i oslobođeni endogeni opioidni peptidi međusobno djeluju kao agonisti na μ- i δ-opioidne receptore te inhibiriaju nociceptivni prijenos, jer na tu aktivnost antagonistično djeluje i nalokson i naltrindol (11).

Nakon promjena koncentracija β-endorfina u serumu trebaju uslijediti promjene koncentracija β-endorfina u mozgu. U našem ispitivanju su koncentracije β-endorfina u mozgu bile značajno snižene 1. dana (431,03 ± 11,57 pg/g) i to je isto tako zabilježeno 9. dana neprekidnog davanja antidepresiva (433,65 ± 14,67 pg/g) u usporedbi s koncentracijama izmjerenim u kontrolnoj skupini (873,50 ± 18,32 pg/g). Koncentracija β-endorfina u mozgu 9. dana nije se razlikovala od one izmjerene 1. dana (tablica 1.). Suprotno tome, rezultati zabilježeni 28. dana kroničnog liječenja pokazali su značajan porast b-endorfina u mozgu (929 ± 18,13 pg/g) u usporedbi s ostalim danima liječenja trazodonom. Jednake rezultate objavili su Gray i sur., koji su

Discussion

Previous studies have demonstrated the synergistic influence of trazodone combined with mud bath in improving the psychological response to stress. Desipramine and paroxetine, used in animal depression models, did not significantly affect the extracellular levels of β-endorphins in nucleus accumbens. Chronic antidepressant treatment normalized serotonin-induced release of β-endorphins as well as behavioral manifestation of depression (7,8).

There still are relatively little data showing that the acute or chronic antidepressant treatment has different influence on serum and brain β-endorphin levels, as a potential factor in the mechanism of antidepressant action. In our study, serum β-endorphin concentrations showed a rapid and significant increase on day 1 of trazodone administration (72.31 ± 1.86 pg/mL), followed by a decrease on day 9 (33.4 ± 1.91 pg/mL) and reaching slightly lower values on day 28 of treatment (38.62 ± 1.42 pg/mL) as compared to initial values (45.8 ± 3.77 pg/mL). Data reported in the literature also point to changes in serum β-endorphin concentrations after chronic use of different antidepressants (9,10). Data obtained in the present study with trazodone are in concordance with the report by Đurović *et al.* (9,10). The rapid increase in serum β-endorphin concentrations and changes observed on days 9 and 28 are indicative of both acute and chronic response to trazodone administration.

Previous studies have shown 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, demonstrating significantly raised levels of β-endorphins. The support was provided for the suggestion that antidepressants activate opioid systems through both direct opioid receptor interaction and an indirect action through the enhanced release of opioid peptides. Moreover, it has been postulated that the direct action of antidepressants on opioid receptors and the endogenous opioid peptides released interact as agonists at both μ- and δ-opioid receptors to inhibit nociceptive transmission, since the activity is antagonized by both naloxone and naltrindole (11).

Changes in serum β-endorphin levels should be followed by changes in their brain levels. In our study, a significant decrease of brain β-endorphin levels (431.03 ± 11.57 pg/g) was recorded on day 1, and was also observed in rat brains on day 9 of continuous antidepressant administration (433.65 ± 14.67 pg/g), as compared to control group values (873.50 ± 18.32 pg/g). On day 9, brain concentratio-

primijenili druge antidepresive (11). To ukazuje na mogući porast sinteze β-endorfina u mozgu kao odgovor na kronično davanje trazodona.
Naša studija bila je ograničena činjenicom da se koncentracija β-endorfina u serumu nije mjerila kod životinja kod kojih je provedeno kvantificiranje β-endorfina u mozgu. Međutim, smatramo kako su naši rezultati za koncentraciju β-endorfina u mozgu kod životinja liječenih trazodonom vjerodostojni u usporedbi s vrijednostima dobivenim u kontrolnoj skupini.
Sve zabilježene promjene koncentracije β-endorfina u serumu i mozgu mogle bi biti uzrokovane razlikama u akutnom ili kroničnom djelovanju triazolopiridina (trazodona). To pak ukazuje na moguće razlike u intenzitetu sinteze i razgradnje β-endorfina u mozgu i mogućem otpuštanju u krvotok, sve to uslijed neprekidnog davanja antidepresiva.

Zaključak

Kronično liječenje trazodonom uzrokuje porast sinteze β-endorfina u mozgu, dok akutno davanje ovoga lijeka dovodi samo do brzog otpuštanja β-endorfina u krvotok. Smatramo kako bi koncentracije β-endorfina u serumu i mozgu mogle poslužiti za praćenje učinaka psihoaktivnih lijekova.

Adresa za dopisivanje:

Radivoj Jadrić
Čekaluša 90
71000 Sarajevo
Bosna i Hercegovina
e-pošta: rjadric@hotmail.com; medical_biochemistry@hotmail.com
tel/faks: +387 33 66 59 49/135

ns of β-endorphins were not different than the concentration measured on day 1 (Table 1).
In contrast, data obtained on day 28 of chronic treatment showed a significant increase in brain β-endorphins (929 ± 18.13 pg/g) compared to other days of trazodone treatment. Comparable results have been reported by Gray *et al.* (11), who used other antidepressants in their study. This suggests a possible increase in the brain β-endorphin synthesis in response to chronic trazodone administration.
Limitations of our study lie in the fact that serum β-endorphin concentrations were not recorded in animals used for quantification of brain β-endorphin concentration. However, we consider our results of brain β-endorphin concentration in trazodone treated animals relevant in comparison with the values obtained in control group.
The changes in serum and brain β-endorphins could be caused by differences in the acute or chronic triazolopyridine (trazodone) action. It points to possible differences in the rate of synthesis of β-endorphins, degradation of brain β-endorphins and their possible release to the blood stream, caused by continuous antidepressant administration.

Conclusion

Chronic trazodone treatment causes an increase in the brain synthesis of β-endorphins, while acute drug administration results only in a rapid release of β-endorphins into the circulation. We consider that serum and brain β-endorphin levels could be used for monitoring the psychoactive drug effects.

Corresponding author:

Radivoj Jadrić
Čekaluša 90
71000 Sarajevo
Bosnia & Herzegovina
e-mail: rjadric@hotmail.com; medical_biochemistry@hotmail.com
phone/fax: +387 33 66 59 49/135

Literatura/References

1. *Brunton LL, Parker KL, Buxton ILO, Blumenthal DK. Gudman & Gilman's The pharmacological basis of therapeutics, Eleventh edition, The McGraw-Hill Companies, New York, St. Louis, 2007.*
2. *Jadrić R, Zulić I, Hasić S, Kiseljaković E, Zečević B, Radovanović J, et al. Trazodone influence on rat sera beta-endorphins level. Bosn J Basic Med Sci 2004;4:33-6.*
3. *DeVane CL, Chiao E, Franklin M, Kruep EJ. Anxiety disorders in the 21st century: status, challenges, opportunities, and comorbidity with depression. Am J Man Care 2005;11:344-53.*
4. *Odagaki Y, Toyoshima R, Yamauchi T. Trazodone and its active metabolite m-chlorophenylpiperazine as partial agonists at 5-HT1A receptors assessed by (35S) GTP gammaS binding. J Psychopharmacol 2005;19:235-41.*
5. *Mendelson WB. A review of the evidence for the efficacy and safety of trazodone in insomnia. J Clin Psychiatry 2005;66:469-76.*
6. *Kaplan AL, Pesce AJ. Clinical chemistry – theory, analysis and correlation. Third edition, Mosby-Year Book, Inc., 1996.*
7. *Bellometi S, Galzigna L. Function of the hypothalamic adrenal axis in patients with fibromyalgia syndrome and undergoing mud-pack treatment. Int J Clin Pharmacol Res 1999;19:27-33.*
8. *Zangen A, Nakash R, Roth-Deri I, Overstreet DH, Yadid G. Impaired release of beta-endorphin in response to serotonin in a rat model of depression. Neuroscience 2002;110:389-93.*
9. *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; 53:143-4.*
10. *Đurović D, Milić-Aškrabić J, Majkić-Singh N. Serum beta-endorphin level in patients with depression on fluvoxamine. Farmaco 1999; 54:130-3.*
11. *Gray AM, Spencer PSJ, Sewell RDE. The involvement of the opioidergic system in the antinociceptive mechanism of action of antidepressant compounds. Br J Pharmacol 1998;124: 669-74.*