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Article

Maprotiline treatment differentially influences cardiac β-adrenoreceptors expression under normal and stress conditions

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Alterations in cardiac function were observed in antidepressants treated patients and published in several clinical reports. These detected changes could be either a consequence of the treatment or of depression itself, which has already been proved to be a risk factor in heart diseases. In order to determine a possible influence of chronic treatment with norepinephrinergic reuptake inhibitor, maprotiline, on the heart, we investigated gene expression of cardiac β-adrenoceptors both in controls and in animals with signs of depression. The rats were divided into two groups, unstressed controls and those exposed to chronic unpredictable mild stress (CUMS). The groups were further divided into two subgroups, one receiving daily intraperitoneal injections of vehicle (sterile water) and another one maprotiline (10 mg/kg) for four weeks. Tissue samples were collected after the last application. Gene expression of cardiac β_1- and β_2-adrenoceptor was determined using Real-time RT-PCR analysis. Our results show that in control animals expression of both adrenoreceptors was decreased in the right atria after 4 weeks of maprotiline application. Contrary, the same treatment led to a significant increase in expression of cardiac β_1-adrenoceptor in the stressed rats, with no change in the characteristics of β_2-adrenoceptor. Our findings might reflect the that molecular mechanisms are underlying factors involved in the development of cardiovascular diseases linked with antidepressant treatment.

Uniterms: Antidepressants. Depression/treatment. Cardiovascular diseases/associated with the use of antidepressants. ß-adrenoceptors/gene expression.

Vários relatórios clínicos observaram alterações de funcionamento cardíaco de pacientes depressivos que foram tratados com os antidepressivos. As alterações detectadas podem ser consequência do tratamento ou, por outro lado, da depressão que, como se tem provado, é um fator de risco no caso de doenças cardíacas. De modo a determinar a possível influência de tratamento crônico com o inibidor da recaptação de norepinefrina, maprotilina, no coração, foi investigada a expressão do gene aos receptores β-adrenérgicos cardíacos dos animais em grupos de controle e em grupos com sinais de depressão. Os ratos foram divididos em grupos de controle não estressados e os grupos de ratos submetidos ao estresse crônico moderado imprevisível (CUMS). Os grupos foram, ainda, divididos em dois subgrupos, que, durante quatro semanas, diariamente receberam injeções intraperitoneais de placebo (água estéril) ou de maprotilina (10 mg/kg). As amostras de tecido foram coletadas após a última aplicação. A expressão do gene aos receptores adrenérgicos β1 e β2 foi determinada utilizando a análise PCR quantitativa em tempo real (RT-PCR). Os nossos resultados demonstram a diminuição de expressão dos ambos os receptores adrenérgicos no átrio direito dos animais do grupo de controle depois de quatro semanas de aplicação de maprotilina. Em contraste, o mesmo tratamento conduziu ao aumento significativo na expressão do receptor β1-adrenérgico no coração dos ratos estressados, sem qualquer alteração nas características do receptor β2-adrenérgico. Estes resultados podem refletir os mecanismos moleculares envolvidos no desenvolvimento de doenças cardiovasculares associadas ao tratamento com os antidepressivos.

Unitermos: Antidepressivos. Depressão/tratamento. Doenças cardiovasculares/associação ao uso de antidepressivos. Receptores ß-adrenérgicos cardíacos/expressão do gene.

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INTRODUCTION

Depression is associated with the autonomic nervous system dysfunction that could have a negative impact on cardiovascular function (Carney *et al*., 2005). Several studies have demonstrated an exaggerated norepinephrine response in major depression (Lake *et al*., 1982; Veith *et al*., 1994; Yehuda *et al*., 1998; Mausbach *et al*., 2005). Chronic exposure to elevated levels of catecholamines, released from sympathetic nerve terminals and the adrenal gland, may cause pathologic changes, resulting in alterations in cardiac structure and function (Brum *et al*., 2002, Lohse *et al*., 2003). Activation of the closely related β_1- and β_2-adrenergic receptors (β_1-AR and β_2-AR) by released catecholamines is the primary trigger of molecular changes in the heart. These two subtypes are expressed in cardiac tissue at a ratio of 70:30, and their activation lead to an increase in contractile force and heart rate (Wallukat, 2002). The ratio of β_1-AR to β_2-AR subtypes depends on the type of animals and it is modified in pathological conditions (Brodd, Michel, 1999). Both receptors are highly homologous and activate the G protein stimulatory for adenylyl cyclase (Gs),yet they have distinguishable biological effects (Xiang, Kobilka, 2003). Thus, the β_1-AR plays the dominant role in stimulating heart rate and strength of myocyte contraction, whereas β_2-AR produces only modest chronotropic effects. Furthermore, chronic stimulation of β_1-AR produces myocyte hypertrophy and apoptosis, whereas β_2-AR signaling promotes cell survival (Xiao *et al.,* 2004).

Stress is a key etiological factor in anxiety and major depressive disorders (Caspi *et al.,* 2003). The chronic unpredictable mild stress (CUMS) procedure is an animal model that mimics the role of chronic stress in precipitating depression and induces various long-term physical, behavioural, neurochemical and neuroendocrine alterations that resemble those observed in depressed patients, which are reversed only by chronic antidepressants treatments (Wilner *et al*., 1992; Mineur *et al*., 2006; Yalcin *et al*., 2007). Maprotiline is a antidepressant with an atypical tetracyclic structure, which function is to prevent reuptake by blocking norepinephrine transporter. It is commonly used in elderly patients suffering from depression as long-term medication (Ahles *et al*., 1984). In the past, there have been only several clinical reports on the rise in heart rate (Hewer *et al*., 1995) and proarrhythmia (Lentini *et al*., 2001; Zuchner, 2002) linked to maprotiline.

This raises a question of a possible influence of maprotiline on β-adrenergic receptors gene expression in the heart of these animals. Applying TaqMan RT-PCR we have estimated the influence of long-term treatment with norepinephrinergic reuptake inhibitor, maprotiline, on gene expression of β_1 and β_2 adrenoreceptors, in the right and left atria as well as in the ventricle of unstressed controls and rats exposed to CUMS for 4 weeks.

MATHERIAL AND METHODS

Animals and study design

Adult Wistar rat males weighing 280-320 g at the onset of experiments and maintained in a temperature--controlled room (21±1.0 °C) and 12 h/12 h light/dark cycle, were used. Care was taken to minimise the pain and discomfort of the animals in accordance with the Guide for Care and Use of Laboratory Animals of the National Institute of Health, Bethesda, MD, U.S.A. Research investigations were approved by Ethical Committee of the "Vinca" Institute, Belgrade (Application No. 02/11). The rats were randomly divided into control (unstressed) and group subjected to CUMS according to the method by Grippo *et al*. (2006). These two groups were further divided into two subgroups each, and the animals were receiving daily injections of vehicle (sterile water) or maprotiline (10 mg/kg) by i.p. route. Exposure to CUMS and the vehicle, i.e. drug administration started on the same day and were continued for 4 weeks. Maprotiline (Sigma-Aldrich Chemie, Germany) solutions in sterile water, sonicated for approximately 10 min were prepared *ex tempore*. Upon completion of 4 weeks, the animals exposed to CUMS and the corresponding controls were decapitated, the right and left cardiac atria and ventricles rapidly dissected, frozen in liquid nitrogen and stored at −70 °C until analysed.

RNA isolation and cDNA synthesis

Total RNAs were isolated using TRIZOL reagent (Invitrogen, CA, U.S.A.). Reverse transcription was performed using Ready-To-Go You-Prime First- Strand Bead (AP, Biotech) and pd (N)6 primer according to manufacturer's protocol.

Real-time RT-PCR

TaqMan PCR assays were carried out using Assay-on-Demand Gene Expression Products (Applied Biosystems, USA) for β_1–AR (Rn 00824536_s1) and β_2–AR (Rn 00560650_s1). The reactions were performed in a 25 μL reaction mixture containing 1x TaqMan Universal Master Mix with AmpErase UNG, 1x Assay Mix (Applied Biosystems) and cDNA template (10 ng of RNA converted to

cDNA). PCR reactions were performed in the ABI Prism 7000 Sequence Detection System at 50 ◦C for 2 min, 95 ◦C for 10 min, followed by 40 cycles at 95 °C for 15 s and 60 °C for 1 min. A reference, endogenous control, was included in each analysis to correct the differences in the inter-assay amplification efficiency and all transcripts were normalised to cyclophyline A (ID:Rn 00690933) expression. Quantification was done using the $2^{-\Delta\Delta Ct}$ method according to Livak and Schmittgen (2001).

Statistical analysis

The results are reported as means ± S.E.M. Significance of the differences between the groups in gene expression levels of the examined β-AR were estimated by Two-way ANOVA test, followed by the Tukey post hoc test. Statistical significance was accepted at $p < 0.05$.

RESULTS

In our present study, we investigated the alterations in relative gene expression of β_1- and β_2-AR in the right and left atria and ventricles after chronic maprotiline application in rats exposed to CUMS for 4 weeks in comparison with unstressed controls. Results indicate that stress procedure induced a considerable effect ($F_{(1, 20)} = 17.87$, $p<0.001$) on β_1-AR gene expression in the left atria. Chronic stress increased β_1-AR mRNA levels by 75% ($p <0.01$) in the left atria. On the other hand, antidepressant treatment affected β_1-AR gene expression ($F_{(1, 20)} = 45.21$, $p<0.001$) in the right atria. In addition, maprotiline effect on the unstressed animals was quite different from that on the stressed ones. Thus, this antidepressant led to an increase in β_1-AR mRNA levels by 224% ($p<0.001$) in the right atria of CUMS rats, but decreased it by 47% ($p<0.001$) in controls. Analysis of data also displayed a significant interaction ($F_{(1, 20)} = 9.56$, $p<0.01$) between effects of chronic stress and antidepressant treatment on β_1-AR mRNA levels in the left ventricle. In animals subjected to CUMS for 4 weeks and parallelly treated with maprotilin, β_1-AR mRNA levels were increased by 76% ($p<0.01$) in the left ventricle (Fig. 1).

Two-way ANOVA test pointed to a significant difference in β_2-AR mRNA levels between unstressed and chronically stressed groups both in left atria ($F_{(1,20)} = 8.01$, $p<0.05$) and in the left ventricle ($F_{(1, 20)} = 43.52$, $p<0.001$). CUMS procedure increased β_2-AR mRNA levels in both left atria (by 34 %, $p<0.05$) and left ventricles (by 40 %, $p<0.01$). Maprotiline affected gene expression of β_2-AR ($F_{(1, 20)} = 5.71$, $p<0.05$) in right atria. Antidepressant treatment decreased β_2-AR levels by 21% ($p<0.05$) in controls, but had no significant effect in stressed rats (Fig. 2).

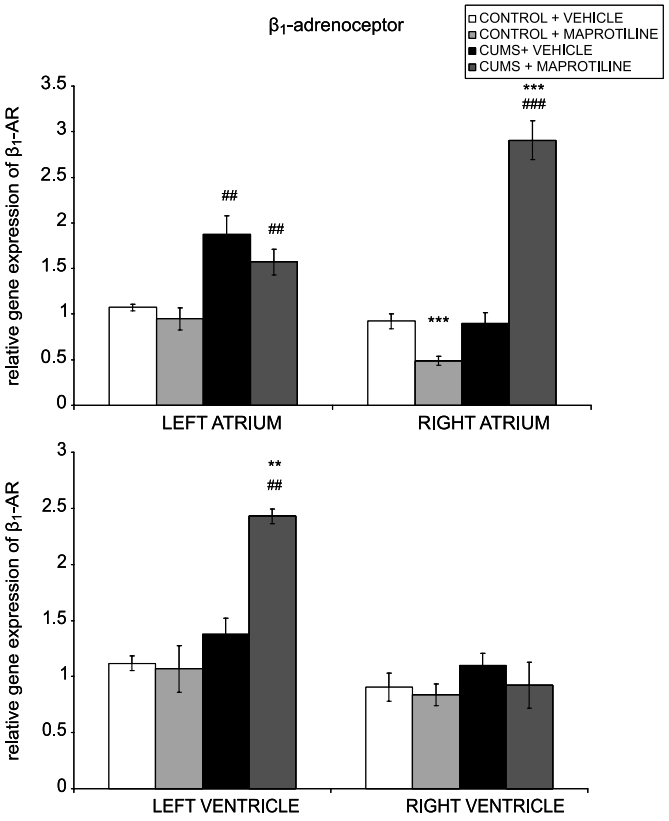

FIGURE 1 - The effects of chronic maprotiline treatment on β_1– adrenoceptors mRNA levels in left and right cardiac atrium and ventricle of unstressed and CUMS rats. The values are means ± S.E.M. of 7 rats. Statistical significance: ## $p< 0.01$; ### $p< 0.001$ CUMS vs. control (Tukey-test); **$p< 0.01$; ***$p< 0.001$ maprotiline vs. vehicle (Tukey-test). The final result was expressed as fold change relative to the calibrator and normalized to cyclophyline A.

DISCUSSION

Antidepressant prescriptions are often associated with an increased risk of heart disease (Rosenberg *et al*., 2010). Tata *et al*. (2005) reported that this risk is more likely associated to factors relating to depression itself than to specific adverse drug effects. Therefore, we examined whether the effect of maprotiline treatment on gene expression of β_1 and β_2-adrenoceptor in the heart of animals with depressive symptoms, which were induced by the 4 weeks exposure to CUMS, differed from that in unstressed rats. In control animals expression of both adrenoreceptors was decreased in right atria after four weeks of maprotiline application. Down-regulation of the β-adrenergic receptors appears to be a common effect of most tricyclic antidepres-

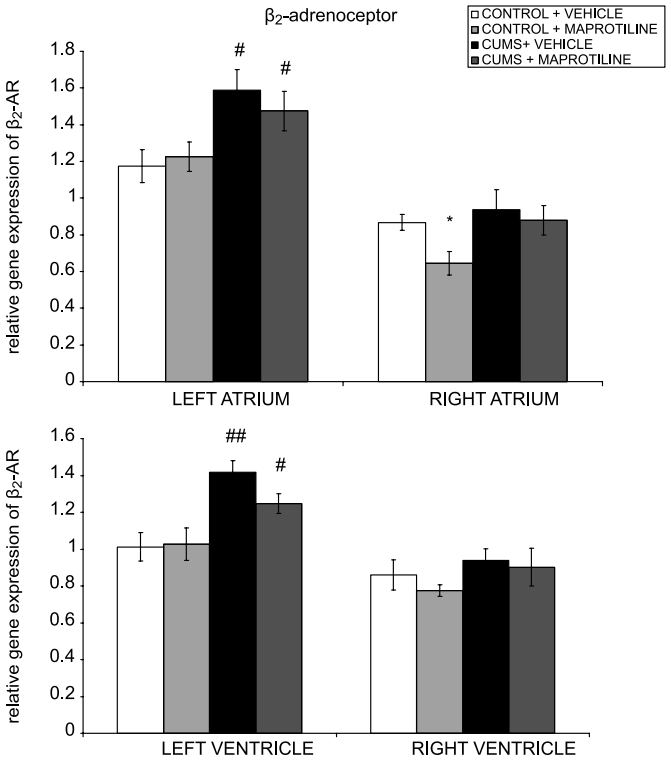

FIGURE 2 - The effects of chronic maprotiline treatment on β_2–adrenoceptors mRNA levels in left and right cardiac atrium and ventricle of unstressed and CUMS rats. The values are means ± S.E.M.of 7 rats. Statistical significance: # $p<0.05$; ## $p<0.01$ CUMS vs. control (Tukey-test); *$p< 0.05$ maprotiline vs. vehicle (Tukey-test). The final result was expressed as fold change relative to the calibrator and normalized to cyclophyline A.

sants (Duman *et al*., 1997; Deupree *et al*., 2007). This may be related to adaptive processes regarded as a secondary effect to the increased concentration of norepinephrine in the synaptic cleft. Similarly, prolonged agonist exposure decreases both β_1-AR binding activity and β_1-AR mRNA levels (Dunigan *et al*., 2002). Port *et al*.(1992) identifed a 35 kDa β-AR mRNA-binding protein (β-ARB protein) which is involved in agonist-induced destabilization of β_2-AR mRNA. They have shown that the amount of β-ARB protein correlates inversely with the decrease in β_2-AR mRNA during the treatment with agonists in hamster heart cells. Antidepressants might also affect β-adrenergic receptors transcription that is independent of the inhibition of norepinephrine uptake. An intact Sp1 site is required for the full activity of the β_1-AR promoter in heart cells. The conservation of this binding site across mammalian β_1-AR genes suggests that this element is crucial for the β_1-AR gene expression regulation (Bahouth *et al*., 2002). It has been observed that chronic desipramine produced a significant reduction in Sp1-binding activity (Frechilla *et al*., 1998). In our experiments, as a result of exposure to CUMS, a significant increase in β_1- and β_2-adrenoceptor mRNA levels was recorded in left atria whereas β_2-ARs mRNA levels were increase only in left ventricles. According to Ueyama and colleagues (2003) activation of β-ARs is the primary trigger of emotional stress-induced molecular changes in the heart. Glucocorticoids are known to affect expression of these receptors through GRE sequences in promotor region (Malbon, Hadcock, 1988). In these animals, as previously shown, plasma corticosterone levels were elevated (Dronjak *et al*., 2007). Similarly, Misliveček *et al*. (2003) noticed that after hydrocortisone treatment density of both β_1-AR and β_2-AR was increased. In contrast to control group of animals, maprotiline treatment led to a significant increase in the expression of β_1-AR but remained without effect on β_2-AR expression in stressed rats. Chronic antidepressant treatment, which enhances norepinephrine synaptic transmission, was shown to increase phosphorylation of CREB and CRE-mediated gene expression in several brain regions (Thome *et al*., 2000; Abdel-Razaq *et al*., 2007). Tseng and co-workers (1998) demonstrated that cAMP mediates the induction of β_1-AR gene expression by interacting with CRE within the promoter region. It has been also observed that glucocorticoids, which are present during chronic stress, interacting with transcription factor CREB, can prevent downregulation of β_2-AR number and mRNA expression (Mak *et al*., 1995; Adcock *et al*., 1996). According to Dangel and co-workers (1996), glucocorticoids also induce changes in the β_2-AR RNA stability by reducing the amount of β-ARB protein. In addition, antidepressants could also regulate mRNA stability. The studies conducted by Headley and coworkers (2004) demonstrated that stimulation of mitogen-activated protein kinases-MAPKs (JNK, p38) resulted in marked stabilization of β-AR mRNA. Budziszewska *et al.* (2010) observed that chronic treatment with antidepressant drugs attenuated the stress-induced decreased levels of MAPKs in the brain of rats subjected to prenatal stress, but had no effect on its concentration in control animals. Longer half-life may explain the higher levels of β_1-AR mRNA in stressed treated animals, in comparison to placebo group. The results of the mentioned authors can explain the different gene expression of these receptors in normal and stressed conditions. Norepinephrine-promoted destabilization and stress-induced transcription seem to be underlying factors for the interplay of the two opposing pathways controlling receptor mRNA levels. Further experiments on transcriptional activation and mRNA stability will be required to unravel the complexity of stress- and antidepressant-dependent regulation of beta-adrenoceptor gene expression. In chronically stressed individuals, treated with maprotiline, the increased expression of this

receptor might be a prerequisite in the development of cardiovascular disease given that it initiates irreversible damage to cardiac tissue.

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