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ADAPTATION TO THE STRESS OF ACADEMIC EXAMINATIONS IN MEDICAL STUDENTS: INCREASED ANTIOXIDANT DEFENSE AND NEUROTROPHIC FACTOR DERIVED FROM THE BRAIN

ADAPTAÇÃO AO ESTRESSE DOS PROVAS ACADÊMICAS EM ESTUDANTES DE MEDICINA: AUMENTO DA DEFESA ANTIOXIDANTE E DO FATOR NEUROTRÓFICO DERIVADO DO CÉREBRO

CARLA PATRÍCIA CARLOS

Pós-Doutorado em Fisiopatologia Renal pela Faculdade de Medicina (FAMERP). Pós-Doutorado em Fisiopatologia Renal e Inflamação pelo Instituto de Biociências, Letras e Ciências Exatas, IBILCE, UNESP. Doutora em Ciências da Saúde pela FAMERP. Graduada em Ciências Biológicas e Mestre em Farmacologia pela Universidade Estadual Paulista (UNESP). Docente da FACERES Faculdade de Medicina. Pesquisadora e orientadora de projetos de pesquisa em Fisiopatologia Experimental.

PATRÍCIA MALUF CURY

Doutora, graduada e livre docente em Medicina pela Universidade de São Paulo. Coordenadora do curso de medicina da Faceres, em São José do Rio Preto. Presidente do Comitê de graduação da Academia Nacional de Cuidados Paliativos.

FERNANDA DO NASCIMENTO PESSATTO QUESSADA

Mestre em Psicologia da Saúde, Famerp-SP. Especialista em PSICOLOGIA CLÍNICA COGNITIVO COMPORTAMENTAL e Psicologia da Saúde. Instrutora

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de Mindfulness- Unifesp. Psicóloga clínica e docente na Faculdade de Medicina Faceres-São José do Rio Preto.

THAYSA CASTRO MOLINA

Mestre em Psicologia e Saúde pela Faculdade de Medicina de São José do Rio Preto (FAMERP) com estágio no exterior na Faculdade de Motricidade Humana em Portugal. Especialista em Psicologia Clínica Cognitivo-Comportamental e Especialista em Psicologia da Saúde pela FAMERP. Professora nos cursos de especialização e extensão do IPECS e FAMERP, professora convidada no curso de graduação de psicologia da FAMERP.

FLÁVIO PEREIRA DOS SANTOS JÚNIOR

Graduado em Medicina pela Faculdade de Medicina FACERES (SP)

HUGO AIDAR VICENTE DOS SANTOS

Graduado de Medicina pela Faculdade FACERES (SP)

LUIS FERNANDO BUENO DE BUENO

Graduado de Medicina pela Faculdade FACERES (SP)

ABSTRACT

Academic examination may cause stress and promote oxidative stress, producing metabolites that can lead to cell damage and death. On the other hand, it involves learning and memorization, requiring the production of neurotrophic factors. Thus, we aimed to analyze oxidative stress and neurotrophic factor markers in the plasma of medical students under academic assessments. For this, two blood samples were collected from 30 students in the 7th semester of their medicine degree, in the period immediately following the vacations, and minutes before academic assessments. The stress of students was investigated by applying Lipp Inventory of Stress Symptoms for Adults (ISSL) during blood samples collections. Oxidative stress was verified by

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measuring TBARS (thiobarbituric acid reactive substances) and TEAC (trolox equivalent antioxidant capacity); neurotrophic factor was measured by evaluating BDNF (brain-derived neurotrophic factor) concentration. No significant difference was found in the stress of the students in the two contexts studied, with the resistance phase predominating among the stressed students. The TBARS concentration did not differ between samples. However, TEAC was higher on the day of the assessments, with a positive correlation between these two parameters, accompanied by an increase in BDNF. We conclude that occurs elevation of antioxidant defense in order to maintain the redox equilibrium in plasma of medical students at pre-examinations. This is followed by increased BDNF that may favor the learning and academic performance.

Keywords: BDNF; Stress; psychological stress; oxidative stress; academic performance.

1 INTRODUCTION

It is noted that medical students are subject to high levels of stress, because of the considerable number of assignments, which they must complete across their lengthy degrees. Frequent assessments, an increase in responsibilities throughout the course and excessive workloads are some of the contributing factors, with stress symptoms being prevalent in 49.7% of graduates (Aguiar, Vieira, Vieira, Aguiar, & Nóbrega, 2009).

Studies show a correlation between chronological stress and an increase in the serum levels of reactive oxygen species in the organism. These reactive species are produced because of the oxidative metabolism of oxygen, which takes place mainly in the mitochondria during cellular respiration. Biochemical oxidation-reduction reactions that take place in these organelles are responsible for the synthesis of oxygen and nitrogen compounds ($O_2^{\cdot-}$, $NO^{\cdot-}$, $OH^{\cdot-}$, H_2O_2, among others), termed free radicals. When present in high levels, they pose a risk to homeostasis, triggering oxidation processes of biomolecules of cell organelles (lipids, proteins and nucleic acids), leading to a loss in their function, irreparable damages and cellular cell death (Lushchak, 2014; Pereira, 2011; Salim, 2017).

Molecules can be mobilized with an aim to contain the deleterious effects of free radicals action over cellular components, constituting the antioxidant defense. These molecules can be of endogenous origin such as glutathione and enzymatic such as superoxide dismutase or catalase, or stemming from diet such as vitamins, minerals or phenols.(Barbosa et al., 2010) Thus, oxidative stress occurs when there is a loss in balance between the production and neutralization of reactive species by antioxidants (Barbosa et al., 2010; Lushchak, 2014; Pereira, 2011; Salim, 2017).

Several circumstances are associated with the increased production of free radicals and oxidation caused by these compounds. It has been shown that psychological stress increases oxidative free radical levels, prompting oxidative stress (Eskiocak et al., 2005; Pani, Al Khabbaz, Bin Enayeg, & Bin Zouman, 2017; Sivoňová et al., 2004). When an individual is suffering from stress, the hypothalamic-pituitary-adrenal axis is activated, with an increase in the secretion of adrenaline and cortisol (Selye, 1950), which in turn leads to a greater demand for cellular respiration, intensifying the production of reactive oxygen species, even in situations of stress of academic assessments (Eskiocak et al., 2005).

On the other hand, assessment circumstances and stress, involve learning and memory. It is known that neurotrophic factors of neuron growth are produced in both situations that provoke stress, and during memory acquisition, modulating neural plasticity. One of these factors is BDNF (brain-derived neurotrophic factor), a member of the superfamily of neurotrophins, widely expressed in the brain. Some of the areas where expression is intense is the hippocampus, a structure that also participates in the neural circuits of stress, learning and memory acquisition, demonstrating the possible involvement of BDNF in these conditions (Komulainen et al., 2008; Leal, Bramham, & Duarte, 2017; Santos et al., 2018). It is known that intense cerebral activity stimulates the production of neurotrophic growth factors responsible for the neural plasticity involved in memory acquisition. However, chronic stress reduces BDNF(Leal et al., 2017), and

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medical students are continually subject to stress, especially assessment-related stress (Aguiar et al., 2009).

Learning and memory acquisition, as well as stress and assessments, require cerebral activity. Cerebral activity consumes high levels of oxygen, which makes the brain susceptible to oxidative stress. Therefore, our hypothesis is that it is possible that assessment situations can cause oxidative stress and changes in the levels of BDNF in medical students. The results obtained through the study could help educators with managing stress during academic assessments.

We aimed to assess oxidative stress and neurotrophic factor markers in the plasma of medical students taking academic tests.

2 MATERIALS AND METHODS

2.1. PARTICIPANTS AND CONTEXT

The project was submitted to the CEP (Research Ethics Committee) of FACERES School of Medicine, and approved under number 037/2020, CAAE 79845117.7.0000.8083. All invited participants signed the consent form to participate in the research. The study was cross-sectional, with the collection of two blood samples of 30 students in the 7th semester of their medicine degree (50% of the class), in a post-vacations period (the first two weeks of course), with no academic assessments taking place, and minutes before the students took a stressogenic practical test consisting of multiple stations with monitored time. They were requested to refrain from consuming vitamins for at least three days in advance of the blood sample collections.

2.2 ELIGIBILITY CRITERIA

Inclusion criteria were: medical undergraduates, over 18 years, from any of the stages of the course, who take academic performance evaluation tests. And, exclusion criteria were: students who withdraw consent at any time from the

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study, and who have used antioxidant medications/vitamins within less than 72 hours prior to blood collections. The study started with 31 participants. One student was excluded because he did not allow the second blood collection.

2.3 STUDY OF STRESS

The students completed a form to verify sociodemographic information at the time of the collection of blood sample and filled out Lipp Inventory of Stress Symptoms for Adults, ISSL (Lipp, 2000; Teixeira et al., 2015), at the time of the two blood sample collections. This questionnaire has been used to assess stress in medical students (Aguiar et al., 2009; Kam et al., 2019), and offers an objective measure of the symptomatology of young persons above the age of 15 and adults, classifying stress into four stages (alarm, resistance, near exhaustion and exhaustion). The instrument consists of three tables referring to each stage of stress, investigating physical and psychological symptoms experienced in the last 24 hours, week and month.

2.4. OXIDATIVE STRESS

We assessed oxidative stress levels in the serum by quantifying thiobarbituric acid-reactive substances (TBARS) and Trolox equivalent antioxidant capacity (TEAC), according to the described techniques (Brito et al., 2017) in an optical spectrophotometer (BIO-200S, Bioplus, São Paulo, SP, Brazil).

2.5. NEUROTROPHIC FACTOR

We dosed BDNF in the plasma sample using an ELISA with a commercial kit (RAB0026-1KT, Sigma-Aldrich, Missouri, USA).

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2.6. STATISTICAL ANALYSIS

A descriptive statistical analysis and a “D'Agostino & Pearson omnibus normality” test was used to analyze the results of the dosages. We compared the plasma results of the participants in both situations (control and assessment) by using Wilcoxon’s test. For the correlational analyses, we used Spearman's rank correlation coefficient. Lastly, for the proportional analysis of both contexts studied we used McNemar’s test. We set the significance level at 5%.

3. RESULTS

3.1. ASSESSMENT OF STRESS

Sixteen students were female and 14 were male, the average age being 22.5 ± 1.9 years (mean ± SD).

Upon analyzing the ISSL, we found that nine students were under stress at the beginning of classes, eight being in the resistance stage and one in the exhaustion stage, with physical symptoms predominating in the week preceding the data collection (Fig 1). Immediately before the academic evaluation test, thirteen students were stressed, three being in the alarm stage, nine in the resistance stage, and one in the exhaustion stage; the symptoms varying between psychological and physical. No significant difference was found in the proportional analyses of both situations of stress studied (p=034, McNemar’s test). On the day of the academic assessment test (Fig 1), all thirteen students stressed had been presenting with symptoms in the week and also 24 hours preceding the test. One student had been suffering with the symptoms for a month preceding the test, this student being the one who had been in the exhaustion stage of stress. However, he was not the same student who was in the exhaustion stage of stress during an analysis carried out in the first week of class. The thirteen students experienced these periods of stress symptoms during the time in which they were studying for the assessment. There was no significant difference in the score obtained by students who were stressed

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compared to those that were not in the academic evaluation test (7.81 ± 0.99 stressed vs. 7.69 ± 1.35 not stressed, mean ± SD, p=0.7749, unpaired *t* Student test).

3.2. OXIDATIVE STRESS

The plasmatic concentration of TBARS did not differ between samples. However, TEAC was higher on the day of the assessment (median 1.32 Control vs. 1.48 test, mMol/L, p<0.0001, Figure 2), a positive correlation occurring between the two parameters assessed on the day of the test (r=0.4806, p=0.0072, Spearman's correlation coefficient).

3.3. BDNF

BDNF concentration increased on the day of the assessment (median 9.2 Control vs. 13.9 Test, ng/mL, p=0.0047, Figure 3).

4. DISCUSSION

We conducted this analysis by applying the ISSL questionnaire, a tool that contains questions, which generate a total score based on the totality of the individual's symptoms, based on Selye's model of the stages of stress (Lipp, 2000; Teixeira et al., 2015). The results showed no significant difference in the level of stress at the time of the assessment compared to the initial period of the semester (control). Of the thirty examined students, 30% showed stress symptoms at the beginning of the semester, 88.9% being in the resistance phase, physical symptoms being predominant. These symptoms can perhaps be related to the students' re-adaptation to the routine of classes following a long period of rest, given that they presented with these symptoms in the week preceding the taking of the questionnaire. Immediately before the test, 43% of students were stressed (23.1% in the alert stage, 69. 2% in resistance and 7.7% in exhaustion),

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with symptoms varying between physical and psychological. The reason for there not being an increase in the proportion of stressed students on the day of the test might be that the students were in the 7th semester of their degree and had thus become used to the routine of assessments. In fact, studies have shown that students in the more advanced stages of their medical degree have lower levels of stress compared to those who are in the initial stages (Kam et al., 2019; Lima, Soares, Prado, & Albuquerque, 2016). In moderate levels, stress can be a source of motivation, improving learning; however, excessive stress can lead to physical, emotional and mental health issues, and is linked to an increase in the prevalence of mental illnesses in medical students, such as anxiety, burnout, depression and substance abuse (Hundertmark, Alvarez, Loukanova, & Schultz, 2019; Selye, 1950).

Stress appears in three consecutive phases: alarm, resistance and exhaustion. These stages are characterized by effort (alarm), persistence (resistance) and failure of adaptation mechanisms in coping with stressor agents. The alert stage is triggered by reactions of the hypothalamic–pituitary- adrenal axis, consisting of a fight or flight response that intends to preserve life. When the stressor agent remains for a longer period of time, the resistance stage occurs, which attempts to recover homeostasis. The exhaustion stage takes place when the organism is unable to adapt to the stressor agent, and is linked to illnesses (Loricchio & Leite, 2012; Selye, 1950). Events commonly referred to as stressors are pointed to as the causes of stress. The stressor factor that we analyzed in this study was learning assessments, which accounts for a significant portion of the stress experienced by students.

Parallel to the analysis of stress of assessments, we conducted a study of the oxidative stress in the plasma of students. We aimed to standardize the stress of the population used to collect the samples, and we used the collection of blood of all students on the day of the exams as the criterion (they were the same students in the two moments used for evaluation purposes). The metabolites generated as a result of the oxidation reactions producing free radicals, for example TBARS, can be measured and are useful when estimating

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possible damage to the cells (Barbosa et al., 2010). The students exposed to the stress of the assessment did not show higher levels of TBARS, contrary to what expected, given that this type of stress has been linked to oxidative stress (Eskiocak et al., 2005; Pani et al., 2017; Silva & Jasiulionis, 2014), causing damage to the DNA of lymphocytes (Sivoňová et al., 2004).

On the other hand, oxidative stress occurs when there is a loss of balance between production and neutralization of reactive species by antioxidants (Barbosa et al., 2010; Pereira, 2011). Molecules can be called into action to counteract the harmful effects of free radicals on cells, constituting antioxidant defense (Barbosa et al., 2010; Lushchak, 2014; Salim, 2017). The stress of academic assessments has been linked to a decrease in antioxidant defense of plasma (Sivoňová et al., 2004) and of saliva (Pani et al., 2017), with a reduction of glutamine in semen (Eskiocak et al., 2005). Our study did not find an increase in TBARS; surprisingly, we found a greater level of antioxidant defense in plasma. The equilibrium apparently kept could be linked to the resistance stage of stress, which predominated in 69.2% of students. In turn, the fact the students were in an assessment context can explain this result.

As previously mentioned, the exam was an assessment component of a 7th semester module. Although the format of the assessment, a practical examination consisting of multiple stations, was a stressful situation through the eyes of students, seemingly they had become used to being routinely assessed. This is demonstrated by the ISSL results, which showed that the resistance stage was predominant among students. We can correlate this hypothesis with recent studies that have shown that students in the 4th to the 6th year of medical degree have a lower level of stress, compared to students in the initial stages (Kam et al., 2019; Lima et al., 2016).

This data shows the development of an adaptive response to the stress of recurrent academic assessments, triggering the resistance stage and an organic response of heightened antioxidant defense. According to relevant literature, organic adaptation takes place in the resistance stage; this is confirmed by this study, which shows a positive correlation between TBARS and TEAC at

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the time of the assessment. This occurs to protect, by improving antioxidant defense, against reactive species produced by an increase in cellular respiration caused by the stress of assessments. Increased antioxidant defense was accompanied by elevated BDNF levels. This factor is widely expressed in the human brain in areas linked to stress, learning and memory (Komulainen et al., 2008; Leal et al., 2017; Santos et al., 2018), such as the amygdala, prefrontal cortex and hippocampus, constituting a marker of neural plasticity (Bathina & Das, 2015; Gray, Milner, & McEwen, 2013; Leal et al., 2017; Santos et al., 2018). Long-term potentiation is the main form of synaptic plasticity that takes place in the nervous system, connected to processes of information storage, the main hypothetic cellular response attributed to learning and memory. BDNF has been linked to this response, being secreted by dendrites and axons in response to neural activity. It plays a fundamental role in learning and long-term potentiation in the hippocampus, including pre and postsynaptic effects connected to the action of glutamine and GABA (Gray et al., 2013; Leal et al., 2017), and structural changes in the synapses (Leal et al., 2017).

Hormones and neurotransmitters released following a stressor event are the main modulators of the processes of learning and memory, with critical implications in educational contexts. Stress during learning is linked to the formation of memory; however, it can also hamper it, leading to poor academic performance (Vogel & Schwabe, 2016). The interaction between BDNF and glucocorticoid has been the subject of various studies, although the results of these have proved controversial (Gray et al., 2013; Leal et al., 2017). Glucocorticoids have a trophic effect on the hippocampus, via interaction with the TrKB receptor of BDNF. A lack of glucocorticoid leads to a reduction in hippocampal plasticity, whereas excess levels of the hormone causes cell death in this area (Gray et al., 2013), which points to a need for balance in the levels of this hormone. On the other hand, the release of glucocorticoids at the beginning stages of stress leads to an increase in BDNF in the amygdala, despite this, in the long term, this hormone seems to be linked to a decline in BDNF levels in the hippocampus (Gray et al., 2013; Leal et al., 2017).

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Thus, it is suggested that a greater expression of BDNF (resulting from corticoids) in the amygdala, is linked to the acquisition of fear memory in the acute phase. However, in the long term, greater BDNF expression and an increase in corticoids in the hippocampus disadvantages memory and learning in this area of the brain (Gray et al., 2013). This supports the theory in various studies, which sustains that prolonged period of stress harms memory and learning processes (Gray et al., 2013; Leal et al., 2017; Vogel & Schwabe, 2016). Nevertheless, we found a significant increase in BDNF levels of around 19.2% in students in assessment situations, compared to the post-holiday period. In addition, despite being subject to a stressful situation, the marks they obtained were not negatively impacted. These results are similar to those of a study which examined the academic performance of Brazilian university students (Mondardo & Pedon, 2005) and opposing to what is suggested in pertinent literature (Leal et al., 2017; Vogel & Schwabe, 2016). Indeed, our results are supported by a study that shows that the academic performance of medical students improves over the course of their degrees, especially from the 5th semester onward (Leal et al., 2017; Vogel & Schwabe, 2016). 73.3% of students stated that they tended to prepare for the assessments in the week preceding the test, or in the hours before it was due to take place, meaning that the stress symptoms identified in the ISSL predominated in this period where students were in the alarm/resistance stage of stress. Just one student, who was in the exhaustion stage, declared that he had prepared for the assessment many weeks in advance.

Our results reinforced what is proposed by Gray and collaborators (Gray et al., 2013), that changes in BDNF levels are not solely dependent on the type and duration of stress, given that its action occurs in tandem with other neurotrophic factors, which aim to modulate to the response to this situation. Thus, the increase of BDNF in students suffering from stress due to academic assessments can be related to the performance of those students like what happens to students not stressed during the assessments.

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4.1. LIMITATIONS AND FUTURE INVESTIGATIONS

It would be interesting to quantify cortisol levels, in addition to conducting a more structured analysis of memory and academic performance, in order to correlate this with BDNF concentration and the stress of assessments in future studies. Moreover, our study involved a small number of participants. However, previous studies also used small sample sizes, with quantification of oxidative stress markers and significant results in 15 (Sivoňová et al., 2004) and 34 (Eskiocak et al., 2005) students. Besides, the samples were obtained from the same students examined in the two periods (non-stress and stress conditions), which decreases variability and improves the sensitivity of statistical analysis.

5 CONCLUSION

We conclude that occurs elevation of antioxidant defense in order to maintain the redox equilibrium in plasma of medical students at pre-examinations. This is followed by increased BDNF that may favor the learning and academic performance.

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Disclosure statement

The authors declare that there is no conflict of interest.

Ethics

Ethics Committee consent (FACERES School of Medicine 037/2020) received to perform the study.

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