CHRONIC LITHIUM TREATMENT PREVENT ANXIETY-LIKE BEHAVIOR RELATED TO DIETARY RESTRICTION

TRATAMENTO CRÔNICO COM LÍTIO PREVINE COMPORTAMENTO RELACIONADO À ANSIEDADE INDUZIDA PELA RESTRIÇÃO DIETÁRIA

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ABSTRACT: Caloric intake reduction has been considered as the major experimental manipulation able to increase longevity in experimental models. Therefore, its effects upon cognition and mood like behavior are poorly explored. On the other hand, Li^+ is a re-emergent therapeutic drug used to treat mood disorders, mainly bipolar disorder, with antipanic and antidepressant actions. On the hypothesis that lithium treatment could attenuate the negatives effects of stress on Central Nervous Systems (CNS), we evaluated the role of chronic lithium treatment on anxiety-like behaviors in animals submitted to stress by chronic moderated feed restriction (FR). Male wistar rats were divided into four groups (n = 7-8/group) according to dietary and drug manipulation: *ad libitum* (AL) with unlimited access to standard rat diet, lithium treatment (AL + Li) which received approximately 50 mg/Kg animal/day of LiCl solved in water and *ad libitum* diet, FR that were fed with equivalent to 70% of total rat diet consumed by AL group, and FR + Li which received diet corresponding to FR and Li administration. After 12 weeks of drug and FR manipulation, anxiety like behavior was evaluated in elevated plus mazes (EPM). Chronic lithium treatment prevent the anxiogenic like effect of FR (open time, $F_{3,30} = 3.588$; $P = 0.0265$; percentage of open entries, $F_{3,30} = 6.004$; $P = 0.00029$; and open time at the first min, 2.35; $F_{3,30} = 4.937$; $P = 0.0073$, Duncan test $P < 0.05$) compared to AL diet. Ours results adding to evidences that moderate feed restriction my increase anxiety-like behavior; also suggest that chronic lithium treatment may be attenuated this effects.

KEYWORDS: Anxiety. Lithium. Dietary restriction.

INTRODUCTION

Since the dietary manipulation proposal by McCay and coworkers (1935), a mount of works have implicated the reduction of caloric intake, without impairment on nutritional state (MASORO, 2003), as the major experimental assay able to increase longevity (MASORO, 1995; MASORO; McCAY, 1995; WEINDRUCH, 1989). The systemic benefit probably is associated with the decrease in oxidative damage, and the enhancement of genomic stability and protein turnover (GEDIK, et al., 2005; GUO et al., 2002; LINDSAY, 1999; WACHSMAN, 1996). Beyond of the beneficial effects of feed restriction (FR) on biochemistry and physiological roles observed on animal models, highlight have sharpen the influence of dietary manipulation on Central Nervous System (CNS) superior functions as perception, cognition, learning and memory (WU et al., 2003). The neuronprotective effects associated with long term reduction of caloric intake were reported (DUAN et al., 2001; LEE et al., 2000; MATTSON et al., 2002). These effects adhere to the evidences which shown a reduction on the risk to neurodegenerative disease such as Alzheimer's and Parkinson's diseases in individuals under usual low caloric intake (CONTESTABILE et al., 2004; LUCHSINGER et al., 2002; NUNOMURA et al., 2006). Moreover, FR seam affect learning and memory types mediated by the hippocampus. Mild dietary restriction increase short and long term memory in punished Y maze task in male rats, and in female rat one same model (WU et al., 2003). This effect is probably associated with memory facilitation by serum glucocorticoid (CORT) by the activation of hypothalamic-pituitary-adrenal (HPA) axis (BELDA et al., 2005). Also, the modulatory effect of FR stress on anxiety and depression like behavior have been reported, with possible psychiatric implications (JAHNG et al., 2007; INOUE et al., 2004; CHANDLER-LANEY et al., 2007; FERREIRA et al., 2006).

On the other hand, Li^+ is a re-emergent therapeutic drug used to treat mood disorders, mainly bipolar disorder, with clinical profile including antipanic and antidepressant actions, as well as prophylaxis of both mania and depression (SHALDUBINA et al., 2001). Lithium treatment also modulates glucocorticoid receptor mRNA level in brain regions important for the regulation of the HPA axis, with possible role in modulation of

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CORT level by negative-feedback (SEMBA et al., 2000). The facilitation of CORT negative-feedback by chronic lithium administration may be related with the attenuation of the stress effects found in studies with model of restraint (WOOD et al., 2004), forced and cold swimming, flashing light exposition and intermittent white noise (VASCONCELLOS et al., 2003). However its effect on dietary manipulation still has not been evaluated. On the hypothesis that lithium treatment could attenuate the stress consequences of FR, we aimed to evaluate the effects of chronic lithium treatment on anxiety-like behaviors in animals submitted to stress by FR.

MATERIAL AND METHODS

Animals

Male wistar rats (N = 31, age 7 weeks; weight 120–150 g) were housed in groups of three rats in acrylic cages (35 x 56 x 19 cm) in an environmentally controlled room (temperature 23-25 ºC; relative humidity 50-60%; light-dark cycle, 12:12 h; lights on at 3:00 pm). All experimental procedures were performed according to the NIH Guide for the Care and Use of Laboratory Animals, and all of them have been approved by the local Animal Care Committee.

Procedures

The animals were randomly divided into four groups (n = 7-8/group) according to dietary and drug manipulation: *ad libitum* (AL) with unlimited access to standard rat diet (containing: 22% of protein, 8% fiber, 4% fat, 10% minerals, 1.4% Calcium); lithium treatment (AL + Li) which received approximately 50 mg/kg animal/day of LiCl solved in water and *ad libitum* diet; FR that were fed with equivalent to 70% of total rat diet consumed by AL group, and FR + Li which received diet corresponding to FR and Li administration. Dietary manipulation was performed as previously described (HUBERT et al., 2000) to obtain a reduction on caloric intake without impair the nutritional state. Water was available freely for all groups. The lithium ingestion was estimated throw the relation of water daily intake and LiCl water concentration (100 mg/L) offered to Li treatment group. The lithium dose and treatment schedule was determined from previous works that reported pharmacological effect without toxic physiological impairs (CAPPELIEZ 1986; TEIXEIRA et al., 1995; FARIA; TEIXEIRA et al., 1993). The elevated plus-maze tests (EPM) were performed after 12 weeks of dietary manipulation and Li treatment.

The EPM apparatus consisted of four arms (50 cm long X 10 cm wide, elevated to a height of 50 cm). The two enclosed arms had 40-cm-high dark walls, whereas the two open arms had 0.5-cm-high ledges, lighting on the open arms was 1.5–2.0 lux. The experimental sessions of 5 min were recorded by a video camera set above of apparatus linked to a monitor in an adjacent room. Each rat was placed in the center of apparatus facing to a closed arm. Videotapes were later analyzed by an observer unaware of treatment conditions.

Data analyses

The parameters: total number of entries, percentage of open arm entries (100×open/total entries), percentage of time spent on the open arms (100×open/total) (CRUZ et al., 1994) and percentage of time spent on the enclosed arms (100×enclose/total) were counted min-by-min for detailed discrimination of behavior on EPM, as previously described (CAROBREZ & BERTOBLIO 2005). Data were analyzed by a Two-way analysis of variance (ANOVA) followed by the Duncan test for multiple comparisons. The level of statistical significance adopted was $P < 0.05$.

RESULTS

After 12 weeks of feed restriction, the body weight was lower in restricted groups (FR and FR + Li) compared to the control groups (AL and AL + Li) as expected according to previous studies (FERREIRA et al., 2006; HUBERT et al., 2000). There was no difference in body weigh between AL and AL + Li groups. At the EPM test, there was no difference in the total number of entries or enclosed arm entries between the groups ($F_{3,30} = 1.7795$, $P = 0.1748$; Figure 1). These data suggest that the dietary condition or drug treatment have no effect on general locomotor activity (CRUZ et al., 1994; PELLOW; FILE 1986).

Interaction between lithium treatment and feed restriction was found to percentage of open arms entries ($F_{3,30} = 4.327$, $P= 0.00459$) and percentage of time on open arms at first min ($F_{3,30} = 4.621$, $P = 0.0039$) suggesting an effect of lithium treatment of FR.

Reduction at the percentage of open arms entries was observed in FR group ($F_{3,30} = 6.0043$, $P = 0.0029$; Duncan test $P < 0.05$; Figure 2), as also the time exploring open arms ($F_{3,30} = 3.59$, $P = 0.0265$; Duncan test $P < 0.05$; Figure 2) compared to AL diet. The effect of FR on exploratory activity on EPM was more evident through min-by-min analysis, whereas time in open arms were minor

compared to AL group ($F_{3,30}$ = 4.937, P = 0.0073; Duncan test $P < 0.05$; Figure 2 and 3). This date was interpreted as an anxiogenic-like effect of FR treatment, as previously described (CRUZ et al., 1994; JAHNG et al., 2007).

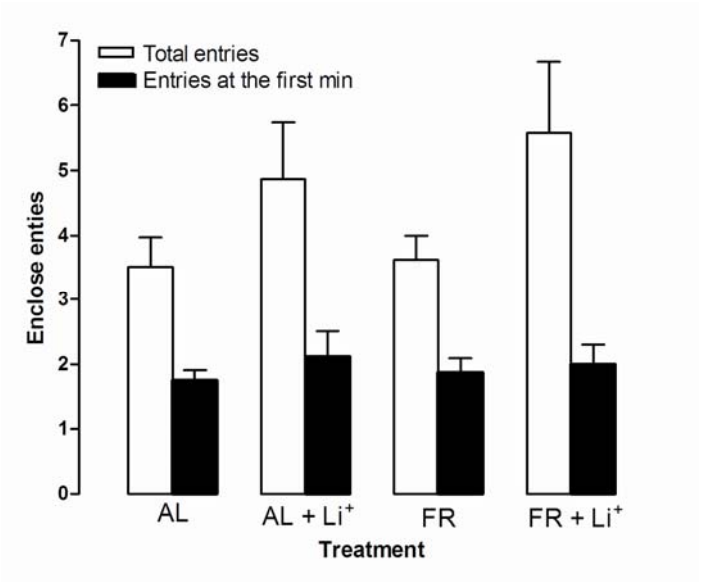

Figure 1. Effect of 12 weeks of feed restriction and lithium treatment (approximately 50 mg/kg animal/day of LiCl) on elevated plus maze (n=7-8/group). The white bars represent the means and SEM of entries in open plus enclose arms, and the black columns represent the means and SEM of entries in enclose arm. Two way ANOVA followed by the Duncan test). AL = *ad libitum*, Li^+ = Lithium, FR = feed restriction.

The effects of FR on EPM explorations were reverted by Li treatment, whereas each on of these parameters was significantly increased in FR + Li group compared to FR (Figure 2; Duncan test $P < 0.05$).

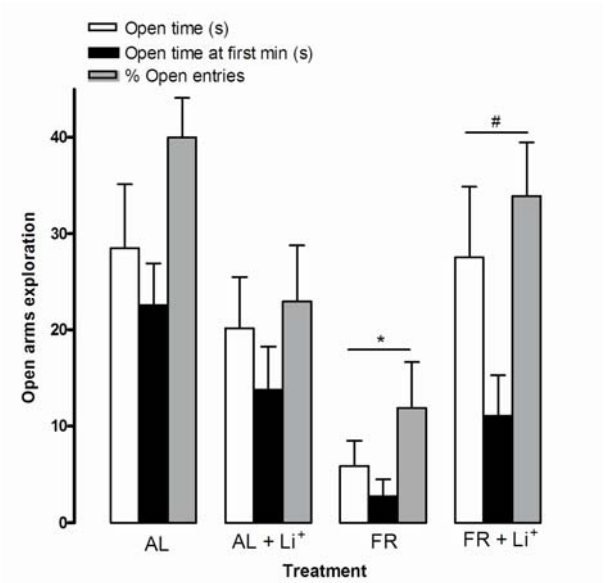

Figure 2. Effect of 12 weeks of feed restriction and lithium treatment (approximately 50 mg/kg animal/day of LiCl) on elevated plus maze (n=7-8/group). The bars represent the means and SEM. The white and hatched bars represent the open time and percentage of open entries in 5 min, respectively, and black bar represent the open time at the first min. Two way ANOVA followed by the Duncan test, $P < 0.05$). AL = *ad libitum*, Li^+ = Lithium, FR = feed restriction. * = difference compared to AL; # = difference compared to FR. Interestingly, the min-by-min analysis showed that the animals under FR + Li condition speeded less time at 3rd min on enclose arms in relation to every other groups ($F_{3,30}$ = 2.54, P = 0.07; Duncan test P<.05), moreover they spent around 73.357% of time on enclose arms at 4th min, while the AL + Li^+ and FR groups spent up to 90% ($F_{3,30}$ = 3.70, P = 0.02; Duncan test $P < 0.05$) on enclose arms (Fig. 3).

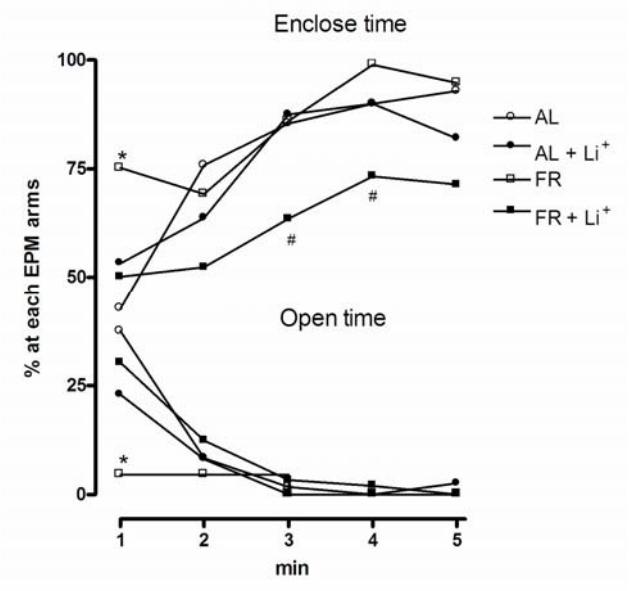

Figure 3. Effect of 12 weeks of feed restriction and lithium treatment (approximately 50 mg/kg animal/day of LiCl) on elevated plus maze (n=7-8/group). The lines represent the means of EPM exploration counted min-by-min. Two way ANOVA for repeated measures followed by the Duncan test, $P < 0.05$). AL = *ad libitum*, Li^+ = Lithium, FR = feed restriction. * = difference compared to AL; # = difference compared to FR.

DISCUSSION

The reduction of exploratory activity on open arms by animals under dietary restriction, without modify significantly the locomotor activity, suggests an anxiogenic-like effect by reduction in 70% of total food intake. These findings agreeing with previous works that found a increase of plasma corticosterone concentrations in animals under chronic moderate feed restriction (HEIDERSTADT et al., 2000; SABATINO et al., 1991), and other that found anxiogenic- and depressant-like effect associated with feed restriction (JAHNG et al., 2007). Patel and Finch (2002) suggested that FR is able to stimulate the hypothalamus-pituitary-adrenal axis (HPA) possibly due to a feeling of stress by underfeeding and energy state, leading to an increased level of circulating glucocorticoids, and consequently, behavioral response to stress condition. Thus, the anxiety-like behaviors are in agreement with feeding restriction at this level owing to glucocorticoids role on stress (form more detail see, JOCA et al., 2003; MASTORAKOS; ZAPANTI 2004; SMITH; VALE 2006).

At the present study it also was verified that the chronic treatments with lithium have effect on anxiety level of animals under FR (FR + Li^+ group). Apparently, Li^+ reduced the anxiety index in these animals, i.e. had anxiolytic effect. It was interpreted considering that the FR + Li^+ group show exploratory activity at open arms significantly higher compared to FR, and spent less time exploring enclose arms at the 3th and 4th min compared to other groups, without effect the locomotor activity on EPM. Thus, these find argument to the meaning that the Li^+ may have a protective effect on stress by dietary manipulation.

A body of molecular and behavioral evidences supports the role of lithium on stress protection. Vasconcellos and coworkers (2003) verified that lithium chronic treatment has anxiolytic-like effect by conditioned fear stress, and also was able to attenuate the memory impairments by variable chronic-stress. The chronic treatment with lithium prevents the stress-induced reduction in dendritic length in hippocampal CA3 neurons, protecting from potentially deleterious effects of chronic stress on glutamatergic activation in the hippocampus (WOOD et al., 2004). Also, there are some evidences to the involvement of lithium on the monoaminergic system both in clinical and animal studies (BAUER et al., 2003). In animals models, the hippocampal level of 5-HT was enhanced by Li^+ administration (TREISER et al., 1981). It was reported that subchronic lithium administration has additional effect on increase of extracellular serotonin concentration in the medial prefrontal cortex of rats under treatment with citalopram, a selective serotonin reuptake inhibitor (MURAKI et al., 2001). Similar effect was observes due to

combination of clorgyline, a selective monoamine oxidase inhibitor (MAO-A) with subchronic lithium. These effects were followed by a reduction of freezing behavior in conditioned fear model (KITAICHI et al., 2006). Moreover, Li^+ treatment seam to facilitate the neural protective effect mediated by neurotrophins as brain derives neurotrophic factor (BDNF) and nerve growth factor (NGF) (ANGELUCCI et al., 2003; FUKUMOTO et al., 2001).

CONCLUSION

In conclusion, our results griming with the last works those arguments to the anxiolitic/antidepressante-like effects of lithium, at least partly, probably due by modulator activity on 5-HTergic system and neurotrophins involved with neural plasticity.

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RESUMO: Restrição calórica é a principal manipulação experimental capaz de aumentar a longevidade, contudo seus efeitos sobre cognição e comportamento são pouco explorados. Por outro lado, Li^+ é uma droga re-emergente para o tratamento de distúrbios afetivos como distúrbio bipolar com efeitos antipânicos e antidepressivos. Considerando a hipótese de que o tratamento com lítio poderia atenuar os efeitos negativos do estresse sobre o Sistema Nervos Central, foi avaliado o papel do tratamento crônico com lítio no comportamento do tipo ansiedade em animais submetidos ao estresse por restrição dietária (RD). Ratos machos *wistar* foram divididos em quatro grupos (n = 7-8/grupo): (AL) com acesso *ad libitum* à dieta padrão de ratos; (AL + Li) tratados com aproximadamente 50 mg/Kg animal/dia de LiCl dissolvido em água; (RD) alimentados com o equivalente a 70% do total da dieta consumida pelos animais do grupo AL; (RD + Li) os quais receberem dieta correspondente ao grupo DR e tratamento com Li. Após 12 semanas nestas condições, o comportamento relacionado à ansiedade foi avaliada em labirinto em cruz elevada. O tratamento crônico com lítio preveniu o comportamento do tipo ansiogênico atribuído a DR (temo de exploração no braço aberto, $F_{3,30} = 3.588$; $P = 0.0265$; porcentagem de entradas no braço aberto, $F_{3,30} = 6.004$; $P = 0.00029$; e tempo utilizado no braço aberto no primeiro minuto; $F_{3,30} = 4.937$; $P = 0.0073$, Duncan test $P < 0.05$) comparado ao grupo AL. Estes resultados somam evidências para os efeitos do tipo ansiogênicos da restrição dietária moderada, além de sugerir que o tratamento crônico com lítio pode reverter estes efeitos.

PALAVRAS CHAVE: Ansiedade. Lítio. Restrição dietária.

REFERENCES

ANGELUCCI, F.; ALOE, L.; JIMENEZ-VASQUEZ, P.; MATHE, A. A. Lithium treatment alters brain concentrations of nerve growth factor, brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor in a rat model of depression. **International Journal of Neuropsychopharmacol,** Cambridge, v. 6, n. 3, p. 225-31, 2003.

BAUER, M.; ADLI, M.; BAETHGE, C.; BERGHOFER, A.; SASSE, J.; HEINZ, A.; BSCHOR, T. Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. **Canadian Journal of Psychiatry**, Ottawa, v. 48, n. 7, p. 440-8, 2003.

BELDA, X.; ONS, S.; CARRASCO, J.; ARMARIO, A. The effects of chronic food restriction on hypothalamic-pituitary-adrenal activity depend on morning versus evening availability of food. **Pharmacology, Biochemistry, and Behavior**, Phoenix, v. 81, n. 1, p. 41-6, 2005.

CAPPELIEZ, P. Comparing oral lithium carbonate and intraperitoneal lithium chloride chronic administrations on rats' activity levels. **Neuropsychobiology**, Basel, v. 16, n. 2-3, p. 103-8, 1986.

CAROBREZ, A. P.; BERTOGLIO, L. J. Ethological and temporal analyses of anxiety-like behavior: the elevated plus-maze model 20 years on. **Neuroscience Biobehavioral Reviews**, Fayetterville, v. 29, n. 8, p. 1193-205, 2005.

CONTESTABILE, A.; CIANI, E.; CONTESTABILE, A. Dietary restriction differentially protects from neurodegeneration in animal models of excitotoxicity. **Brain Research**, Amsterdam, v. 1002, n. 1-2, p. 162-6, 2004.

CHANDLER-LANEY, P. C.; CASTANEDA, E.; PRITCHETT, C. E.; SMITH, M. L.; GIDDINGS, M.; ARTIGA, A. I.; BOGGIANO M. M. A history of caloric restriction induces neurochemical and behavioral changes in rats consistent with models of depression. **Pharmacology, Biochemistry, and Behavior**, Phoenix, v. 87, n. 1, p. 162-6, 2007.

CRUZ, A. P.; FREI, F.; GRAEFF, F. G. Ethopharmacological analysis of rat behavior on the elevated plus-maze. **Pharmacology, Biochemistry, and Behavior,** Phoenix, v. 49, n. 1, p. 171-6, 1994.

DUAN, W.; LEE, J.; GUO, Z.; MATTSON, M. P. Dietary restriction stimulates BDNF production in the brain and thereby protects neurons against excitotoxic injury. **Journal of Molecular Neuroscience**, Totowa, v. 16, n. 1, p. 1-12, 2001.

FARIA, M. S.; TEIXEIRA, N. A. Reversal of learned helplessness by chronic lithium treatment at a prophylactic level. **Brazilian Journal of Medical and Biological Research**, São Paulo, v. 26, n. 11, p. 1201-12, 1993.

FERREIRA, F. R.; SPINI, V. B. M. G.; LOPES, E. J.; LOPES, R. F. F.; MOREIRA, E. A.; AMARAL, M. A. F.; CUNHA, A. L. S.; BORGES, A. P. S.; MARSON, L. B.; RIBEIRO, G. C. C. Effect of feed restriction on learning, memory and stress of rodents. **Bioscience Journal**, Uberlândia, v. 22, n. 1, p. 91-97, 2006.

FUKUMOTO, T.; MORINOBU, S.; OKAMOTO, Y.; KAGAYA, A.; YAMAWAKI, S. Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. **Psychopharmacology,** Berlin, v. 158, n. 1, p. 100-6, 2001.

GEDIK, C.M.; GRANT, G.; MORRICE, P.C.; WOOD, S.G.; COLLINS, A.R. Effects of age and dietary restriction on oxidative DNA damage, antioxidant protection and DNA repair in rats. **European Journal of Nutrition**, Darmstadt, v. 44, n. 5, p. 263-72, 2005.

GUO, Z.; MITCHELL-RAYMUNDO, F.; YANG, H.; IKENO, Y.; NELSON, J.; DIAZ, V.; RICHARDSON, A.; REDDICK, R. Dietary restriction reduces atherosclerosis and oxidative stress in the aorta of apolipoprotein E-deficient mice. **Mechanisms of Ageing and Development**, Lausanne, v. 123, n. 8, p. 1121-31, 2002.

HEIDERSTADT, K. M.; MCLAUGHLIN, R. M.; WRIGHT, D. C.; WALKER, S. E.; GOMEZ-SANCHEZ, C. E. The effect of chronic food and water restriction on open-field behaviour and serum corticosterone levels in rats. **Laboratory Animals**, New York, v. 34, n. 1, p. 20-8, 2000.

HUBERT, M. F.; LAROQUE, P.; GILLET, J. P.; KEENAN, K. P. The effects of diet, ad Libitum feeding, and moderate and severe dietary restriction on body weight, survival, clinical pathology parameters, and cause of death in control Sprague-Dawley rats. **Toxicological Science**, Orlando, v. 58, n. 1, p. 195-207, 2000.

INOUE, K.; ZORRILLA, E. P.; TABARIN, A.; VALDEZ, G. R.; IWASAKI, S.; KIRIIKE, N.; KOOB, G. F. Reduction of anxiety after restricted feeding in the rat: implication for eating disorders. **Biological Psychiatry**, New York, v. 55, n. 11, p. 1075-81, 2004.

JAHNG, J. W.; KIM, J. G.; KIM, H. J.; KIM, B. T.; KANG, D. W.; LEE, J. H. Chronic food restriction in young rats results in depression- and anxiety-like behaviors with decreased expression of serotonin reuptake transporter. **Brain Research**, Amsterdam, v. 30, n. 1550, p. 100-7, 2007.

JOCA, S. R.; PADOVAN, C. M.; GUIMARAES, F. S. Stress, depression and the hippocampus. Revista Brasileira de Psiquiatria, São Paulo, v. 25 Suppl 2, p. 46-51, 2003.

KITAICHI, Y.; INOUE, T.; NAKAGAWA, S.; IZUMI, T.; KOYAMA, T. Effect of co-administration of subchronic lithium pretreatment and acute MAO inhibitors on extracellular monoamine levels and the expression of contextual conditioned fear in rats. **European Journal of Pharmacology**, Amsterdam, v. 532, n. 3, p. 236-45, 2006.

LEE, J.; DUAN, W.; LONG, J. M.; INGRAM, D. K.; MATTSON, M. P. Dietary restriction increases the number of newly generated neural cells, and induces BDNF expression, in the dentate gyrus of rats. **Journal of Molecular Neuroscience**, Boston, v. 15, n. 2, p. 99-108, 2000.

LINDSAY, D. G. Diet and ageing: the possible relation to reactive oxygen species. **The Journal of Nutrition, Health & Aging**, Paris, v. 3, n. 2, p. 84-91, 1999.

LUCHSINGER, J. A.; TANG, M. X.; SHEA, S.; MAYEUX, R. Caloric intake and the risk of Alzheimer disease, **Archives of Neurology**, Chicago, v. 59, n. 8, p. 1258-63, 2002.

MASORO, E. J. McCay's hypothesis: undernutrition and longevity. The Proceedings of the Nutrition Society, Londom, v. 54, n. 3, p. 657-64, 1995.

MASORO, E. J.; Dietary restriction. **Experimental Gerontology**, Oxford, v. 30, n. 3-4, p. 291-8, 1995.

MASORO, E. J. Subfield history: caloric restriction, slowing aging, and extending life. **Science of Aging Knowledge Environ,**Washington, v. 26, n. 8, p. 1-7, 2003.

MASTORAKOS, G.; ZAPANTI, E. The hypothalamic-pituitary-adrenal axis in the neuroendocrine regulation of food intake and obesity: the role of corticotropin releasing hormone. **Nutritional Neuroscience**, Amsterdam, v. 7, n. 5-6, p. 271-80, 2004.

MATTSON, M. P.; DUAN, W.; CHAN, S. L.; CHENG, A.; HAUGHEY, N.; GARY, D. S.; GUO, Z.; LEE, J.; FURUKAWA, K. Neuroprotective and neurorestorative signal transduction mechanisms in brain aging: modification by genes, diet and behavior. **Neurobiology of Aging**, Fayetteville, v. 23, n. 5, p. 695-705, 2002.

McCAY, C. M.; CROWELL, M. F.; MAYNARD, L. A. The effect of retarded growth upon the length of life span and upon the ultimate body size. **Journal of Nutrition,** Burbank, v. 10, n. 1, p. 63-79, 1935.

MURAKI, I.; INOUE, T.; HASHIMOTO, S.; IZUMI, T.; ITO, K.; KOYAMA, T. Effect of subchronic lithium treatment on citalopram-induced increases in extracellular concentrations of serotonin in the medial prefrontal cortex. **Journal of Neurochemistry**, London, v. 76, n. 2, p. 490-7, 2001.

NUNOMURA, A.; CASTELLANI, R. J.; ZHU, X.; MOREIRA, P. I.; PERRY, G.; SMITH, M. A. Involvement of oxidative stress in Alzheimer disease. **Journal of Neuropathololgy and Experimental Neurology**, Baltimore, v. 65, n. 7, p. 631-41, 2006.

PATEL, N. V.; FINCH, C. E. The glucocorticoid paradox of caloric restriction in slowing brain aging. **Neurobiology of Aging**, Fayetteville, v. 23, n. 5, p. 707-17, 2002.

PELLOW, S.; FILE, S. E. Is tofisopam an atypical anxiolytic? **Neuroscice Biobehavioral Reviews**, Fayetteville, v. 10, n. 2, p. 221-7, 1986.

SABATINO, F.; MASORO, E. J.; MCMAHAN, C. A.; KUHN, R. W. Assessment of the role of the glucocorticoid system in aging processes and in the action of food restriction, **Journal of Gerontology**, Sant Louis, v. 46, n. 5, p. B171-9, 1991.

SEMBA, J.; WATANABE, H.; SUHARA, T.; AKANUMA, N., Chronic lithium chloride injection increases glucocorticoid receptor but not mineralocorticoid receptor mRNA expression in rat brain. **Neuroscice Research**, Shannon, v. 38, n. 3, p. 313-9, 2000.

SHALDUBINA, A.; AGAM, G.; BELMAKER, R. H. The mechanism of lithium action: state of the art, ten years later. **Progress in Neuropsychopharmacology and Biological Psychiatry**, Oxford, v. 25, n. 4, p. 855-66, 2001.

SMITH, S. M.; VALE, W. W. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress, **Dialogues in Clinical Neuroscience**, Neuilly-sur-Seine, v. 8, n. 4, p. 383-95, 2006.

TEIXEIRA, N. A.; PEREIRA, D. G.; HERMINI, A. H. Chronic but not acute Li+ treatment prevents behavioral depression in rats. **Brazilian Journal of Medical and Biological Research**, São Paulo, v. 28, n. 9, p. 1003-7, 1995.

TREISER, S. L.; CASCIO, C. S.; O'DONOHUE, T. L.; THOA, N. B.; JACOBOWITZ, D. M.; KELLAR, K. J. Lithium increases serotonin release and decreases serotonin receptors in the hippocampus. **Science**, Washington, v. 213, n. 4515, p. 1529-31, 1981.

VASCONCELLOS, A. P.; TABAJARA, A.S.; FERRARI, C.; ROCHA, E.; DALMAZ, C. Effect of chronic stress on spatial memory in rats is attenuated by lithium treatment, Physiology & Behavior, Oxford, v. 79, n. 2, p. 143-9, 2003.

WACHSMAN, J. T. The beneficial effects of dietary restriction: reduced oxidative damage and enhanced apoptosis. **Mutation Research**, Amsterdam,v. 350, n. 1, p. 25-34, 1996.

WEINDRUCH, R. How does dietary restriction retard diseases and aging? **Progress in Clinical and Biological Research**, New York, v. 287, n. 1, p. 97-103, 1989.

WOOD, G. E.; YOUNG, L. T.; REAGAN, L. P.; CHEN, B.; MCEWEN, B. S. Stress-induced structural remodeling in hippocampus: prevention by lithium treatment. **Proceedings of the National Academy of Sciences of the United State of America**, Washington, v. 101, n. 11, p. 3973-8, 2004.

WU, A.; SUN, X.; LIU, Y. Effects of caloric restriction on cognition and behavior in developing mice. **Neuroscice Letters**, Amsterdam, v. 339, n. 2, p. 166-8, 2003.