

14 Pharmacology: Other

14.001 Collicular auditory electrophysiological rebound as a compensatory response to the reinforcing effects of the opiate morphine. Paliarin F, Nobre MJ FFCLRP-USP – Psicobiologia

Auditory-evoked potentials (AEPs) can be modified by associative learning where the appearance of learned compensatory responses (CCRs) may result in the emergence of drug withdrawal symptoms and relapse. Although CCRs influence on later attentive and cognitive domains been extensively examined, contextual conditioned tolerance occurring in preattentive mechanisms operating at earlier stages of information processing have remained largely unexplored. To extend our knowledge on the influence of the opiate system on the early stages of auditory information we tested the ability of morphine (10 and 20 mg/kg) to elicit place preference or aversion using an ordinary two-chamber shuttle box. Changes in the motor and emotional aspects of behavior evoked by contextual cues were investigated with an electronic open field. CCRs influence on collicular AEPs was recorded with the help of a two-chamber shuttle box placed inside a Faraday cage system. The central nucleus of the IC (CIC) was chosen for AEPs recording based on its exclusive role in the conduction of auditory ascending information. Treatments were able to easily induce place preference and aversion. Behavioral analysis indicated that CCRs ensue in non-familiar contexts. Electrophysiological data revealed increases in the amplitude of collicular field potentials evoked in a non-familiar context. Our results indicate that behavioral learning responses emerge following Pavlovian conditioning even with the use of a low and regular dose of morphine on a short-term treatment. Changes in the collicular electrophysiology may indicate that the development of drug dependence occurs covertly in the early stages of sensory information processing. **License number of ethics committee:** 08.1.1547.53.3
Financial support: CNPQ; FAPESP

14.002 Obesity resistance of Thimet-oligopeptidase knockout mice. Gewehr MCF¹, Teixeira AAS², Reckziegel P¹, Santos-Eichler RA¹, Câmara NOS³, Castoldi A³, Barreto-Chaves ML⁴, Senger N⁴, Akamine EH¹, Rosa JC², Ferro ES¹ ¹ICB-USP – Farmacologia, ²ICB-USP – Biologia Celular, ³ICB-USP – Imunologia, ⁴ICB-USP – Anatomia

Introduction: Our group has shown that the proteasome and intracellular peptidases, such as thimet oligopeptidase (THOP1) and neurolysin (Nln) work together to continuously release peptides within cells. Previously, we carried out the production and phenotypic characterization of knockout animals (KO) for Nln (Nln^{-/-}), which are more tolerant to glucose and more sensitive to insulin, produce more glucose in the liver from pyruvate (gluconeogenesis), and are less tolerant to exercise. In addition, these Nln^{-/-} animals have differences in the profile of specific intracellular peptides in skeletal muscle, liver, brain and adipose tissue. Considering the structural and functional similarities between Nln and THOP1, we generated knockout animals for THOP1 (THOP1^{-/-}). In this work, our objective has been to investigate the phenotype of THOP1^{-/-} animals in relation to metabolic control. **Methods:** Animals used herein were wild-type C57BL/6 (WT) or knockout for THOP1 (THOP1^{-/-}), males and females four weeks old. All protocols were previously approved by Ethics Committee of Institute of Biomedical Sciences at the University of São Paulo (Protocol N^o138/2015). Animals were subdivided into control group, which received standard chow diet (SCD; 3.8 kcal/g, 70% carbohydrate, 20% protein, 10% fat), and obese group, which received high-fat diet (HFD; 5.4 kcal/g, 25.9% carbohydrate, 14.9% protein, 59% fat). Diet were administrated during six months, and at the end of that period animals were sacrificed and tissues removed for different analyses. **Results:** Our results suggest that male WT animals fed for 24 weeks on HFD gain nearly five times as much body mass than THOP1^{-/-} animals (14.2g x 3.8 g); WT females gained double of the weight of THOP1^{-/-} females (6.9 x 3.85 g). The chow, calories and water consumption among all groups was similar. These results are corroborated by the significant increase of the weight of internal organs such as liver, gastrocnemius and soleus muscles (only for males), retroperitoneal and inguinal fat, periepididimal (male), and ovarian (females), in WT animals fed DHF for 24 weeks compared to THOP1^{-/-}. Among the biochemical parameters evaluated, only females fed HFD showed a slight increase in the LDL cholesterol index. WT and not THOP1^{-/-} mice fed HFD for 24 weeks and submitted to the glucose tolerance test (GTT) have high plasma glucose levels and are less insulin sensitive in the insulin tolerance test (ITT). We also observed that THOP1^{-/-} animals have reduced expression of the PPAR-gamma gene and of specific intracellular peptides. Adipocytes of inguinal adipose tissue of THOP1^{-/-} animals when stimulated with isoproterenol (beta-adrenergic agonist) have higher lipolytic activity compared to WT animals. **Conclusions:** Together, these data suggest that gene silencing of THOP1 in C57BL6 mice produces animals with greater lipid metabolism efficiency. Thus, our work suggests that THOP1 is a possible pharmacological target for the treatment of obesity and disorders of lipid metabolism. **License number of ethics committee:** 138/2015 **Financial support:** Capes, Cnpq e Fapesp

14.003 Both Isoflurane and sevoflurane cause a decrease in the antioxidant capacity of plasma, but only sevoflurane promotes lipid peroxidation in anesthetized rats. Borges TF¹, Camargo GC¹, Possomato-Vieira JS¹, Rocha TLA², Dias-Junior CAC¹ ¹IBB-Unesp – Farmacologia, ²Unesp-Botucatu – Medicina

Introduction: isoflurane and sevoflurane are two inhalatory anesthetic often used in the human and veterinary clinic practice, but there are conflicting results about their capacity to cause or not lipid peroxidation, decrease antioxidant status and myeloperoxidase levels (LEE, 2015; MANATAKI, 2001; PAES, 2014). For this reason, it is very important to advance the understanding of the changes promoted by these anesthetics in such parameters. **Methods:** this project was approved by Ethics Committee: # 967/2017. To achieve our goals, we randomly separated 20 Wistar rats, with average weight of 450 grams and 22 weeks age in one of the three groups: isoflurane (Iso), n = 8; sevoflurane (Sevo), n = 4; control (CTRL), n = 7. Anesthetic induction was made with 5% of isoflurane or 9% of the sevoflurane. Maintenance of anesthesia ranged from 2 to 3% in the Iso group or from 5 to 6% in the Sevo group. After the anesthetic induction, rats were placed in dorsal decubitus position and catheter was inserted in the left carotid artery, which remained connected to a monitor that recorded heart rate, mean arterial pressure, diastolic arterial pressure and systolic arterial pressure. Temperature was measured throughout whole procedure. After approximately 120 minutes of anesthesia monitoring, rats were euthanized by isoflurane or sevoflurane overdose. Blood collected by cardiac puncture, centrifuged and plasma stored at -80° C. Rats from CTRL group were decapitated and blood collected. The lipid peroxidation was evaluated by Thiobarbituric Acid Reactive Substances assay (TBARS), the antioxidant status was evaluated by Ferric Reducing Antioxidant Power assay (FRAP) and the levels of myeloperoxidase was evaluated by Myeloperoxidase assay (MPO). ANOVA, with a 95% confidence interval, was used to compare the results of three groups. P < 0,05 were considered significant. **Results:** There were no significant differences in the TBARS levels between the CTRL group and Iso group, but there was increased lipid peroxidation in the Sevo group. When compared to the CTRL group, suggesting that isoflurane did not increase lipid peroxidation, whereas sevoflurane caused it. The FRAP concentration in the Iso and Sevo groups was significantly decreased when compared with the concentration of the CTRL group and this suggest that antioxidant status of the anesthetized rats with both anesthetics was decreased. The plasmatic levels of MPO in Iso and Sevo groups were significantly decreased, when compared with the levels of CTRL group, suggesting that both anesthetics have potential to decrease the levels of this protein. **Conclusion:** sevoflurane decreases the antioxidant status and increases lipid peroxidation, whereas isoflurane, although decreasing the antioxidant status, do not cause increased lipid peroxidation. Moreover, in both anesthetized groups, this was not related to increases in catalyzed hypochlorous acid by myeloperoxidase. Reference: MANATAKI, A. D. Surgical Endoscopy, v. 15, p. 950, 2001; PAES, E. R. C. Acta cirúrgica brasileira, v. 29, p. 280, 2014; LEE, Y. BioMed Research International, v. 2015, p. 1, 2015. **License number of ethics committee:** 967/2017

14.004 An analysis of the life medicalization in the present. Oliveira RW, Schollmeier SE, Mantuano MS, Raymundo JH, Romero GT, Machado FB, Krauser IA, Pedroso BTL, Pereira JX UFRJ – Biomedicina

Medicalization refers to the increasing use of drugs and their impact on psychosocial, economic, and cultural relations. Since 1970, when this term was proposed, the question asked is about the loss of the individual's autonomy, the ethical aspects of prescription and the modification of non-medical situations in medical problems. With this in mind, an analysis of this process, in times of globalization and large media, is relevant for possible future interventions. The present study aims to understand the current population dynamics of drug use and its relations with the various social aspects, including the doctor-patient relationship. For the study of the medicalization process, an online form with objective and discursive questions was applied, approaching the possible factors of interference in this dynamic. The questionnaires were distributed through social networks, aiming a greater collection of responses and in a randomized way. At the end of the period, 700 questionnaires were obtained in 5 days and were evaluated quantitatively and qualitatively about the following points of interest: 1) Permanent use of drugs; 2) Presence of pathologies or other comorbidities; 3) Most used drugs; 4) Impressions/feelings related to pharmacological therapy; 5) Use of non-prescription drugs. The results provided a better understanding about the increased number of prescription and nonprescription drugs use in the context of globalization, as well as a dimensioning of the interference of medicalization in other sectors, which are closely related to integral health. Regarding continuous or permanent use, 48% of those interviewed affirm that they use at least one drug in a continuous/permanent way. About pathologies and comorbidities, we can note among the reports: allergies, depression, ADHD, anxiety, allergic rhinitis, asthma, hypertension, migraine, among others. It is possible to highlight the presence of anxiolytics, antidepressants, psychostimulants and contraceptives among the drugs most used by the evaluated group. By analyzing the impressions/feelings about pharmacological therapy, 8.4% said they feel excellent considering the amount of drugs used, while 21.9% say they feel indifferent, but 21.6% report bad feelings due to pharmacological necessity. When it comes to the use of non-prescription drugs, 84.3% affirmed their previous use and 55.9% that they have already indicated it for others. There was a higher frequency of use of non-prescribed drugs weekly (17.7%), fortnightly (14.5%) and quarterly (12.9%). Therefore, it is important to understand the reception and attendance of patients' needs regarding the life medicalization process. In addition, diagnosis and individualization of care, through the approximation of the patient and a shared decision of the treatment, considering the possible advantages and disadvantages. Thus, there will be an optimization of individualized therapy, differentiating medical problems and respecting the limits of the life medicalization.

14.005 Influence of physical exercise upon advanced glycation end products in patients living with the human immunodeficiency virus. Rodrigues KL¹, Borges JP², Oliveira GL², Pereira ENGDS¹, Mediano MFF³, Farinatti PTV², Tibiriçá EV⁴, Daliry A¹ ¹Fiocruz – Investigação Cardiovascular, ²UERJ – Atividade Física e Promoção da Saúde, ³INI-Fiocruz, ⁴INC – Ensino e Pesquisa

Introduction: Combined antiretroviral therapy (cART) used to treat acquired immunodeficiency virus (HIV) induces a number of adverse effects, such as hypertension and hypercholesterolemia, which ultimately increases the cardiovascular risk. Advanced glycation end products (AGEs) have been implicated in the etiology of cardiovascular diseases, diabetes and other chronic diseases. It is known that physical exercise improves the lipid profile and reduces the risk of cardiovascular diseases. However, the impact of physical exercise on AGE levels in HIV-infected patients has not been so far investigated. Therefore, this study compared AGEs levels in people with and without HIV and verified the effect of physical training on serum AGE levels. **Methods:** Participants were initially assigned into three groups: control healthy (CTL, n=33), physically inactive HIV-infected (IPHIV, n=33) and physically active HIV-infected (APHIV, n=19). IPHIV underwent physical training for 3 months, consisting of 60-min sessions of multimodal supervised exercise (aerobic, resistance and flexibility) with moderate intensity (50-80% heart rate reserve), performed 3 times/week. AGEs were measured in serum by fluorescence spectrometry. The present study complied with recommendations of Helsinki Declaration and gained approval from the local Institutional Review Board (number CAAE 42162815.5.0000.5272). The protocol of the study was registered and made public on ClinicalTrials.gov (identifier NCT03343522). **Results:** At baseline, AGEs level was significantly higher ($P<0.001$) in IPHIV (0.95 a.u. [0.89 to 0.98]) vs. CTL (0.62 a.u. [0.59 to 0.82]) and APHIV (0.59 a.u. [0.56 to 0.61]). Triglycerides were also higher in IPHIV (182.8 ± 102 mg/dL) than CTL (132.8 ± 52.3 mg/dL; $P<0.05$), while similar values were found for body mass, fasting blood glucose, LDL, HDL, and total cholesterol. After training, AGE levels decreased among IPHIV (0.93 ± 0.07 to 0.60 ± 0.04 a.u.; $P<0.001$), no further difference being detected vs. CTL or APHIV. **Conclusion:** HIV-infected patients under cART exhibited elevated AGEs levels compared to healthy individuals. Short-term aerobic training of moderate intensity counteracted this condition. **License number of ethics committee:** CAAE 42162815.5.0000.5272 **Financial support:** This work was partially supported by grants from CNPQ (National Council of Scientific and Technological Research, Brasilia, Brazil) and FAPERJ (Research Support Foundation of the State of Rio de Janeiro, Rio de Janeiro, Brazil).

14.006 Maternal overweight and gestational weight gain associate with changes in vascular/perivascular tissue structure from human umbilical vein. Servian CP¹, Mello JPL², Said MM², Morale SO³, Costa RM⁴, Peres APS⁵, Filgueira FP⁶, Lobato NS⁶ ¹UFG – Biomedicina, ²UFG – Ciências Biológicas e da Saúde, ³UFG – Ciências Médicas, ⁴UFG – Farmacologia e Fisiologia, ⁵UFG – Ciências Morfológicas e Fisiológicas, ⁶UFG – Farmácia e Farmacologia

Introduction: Human pregnancy that courses with maternal overweight or obesity correlates with later health complications in offspring. It is known that obesity associates with abnormalities in the vascular structure in adults, however, nothing is reported on potential alterations in the fetoplacental vascular/perivascular structure in overweight and gestational weight gain conditions. The aim of this study was to determine whether maternal overweight and gestational weight gain alters vascular/perivascular tissue structure from human umbilical vein. **Methods:** Umbilical cords were collected from newborns of pregnant women (69 total of patients) divided into three groups according to the reference values from US Institute of Medicine guidelines: women exhibiting pre-pregnancy overweight (overweight group), normal weight that ended with a physiological total weight gain (control group), or supraphysiological gestational weight gain (excessive gestational weight gain group). Umbilical cords were divided into: the placental, middle and fetal portions. Specimens were fixed with 4% paraformaldehyde solution. Standard histological techniques for light microscopy were used and sections stained with Hematoxylin-eosin. Morphometric analysis was performed using the ImageJ Software. **Results:** The mean Body Mass Index (BMI) in the control group at the beginning of gestation was 21.78 and in the overweight and obese group was 28.85. Women who started pregnancy with overweight and those with increased gestational weight gain displayed significant increase in the wall thickness, lumen diameter and wall-luminal ratio of the placental, middle and fetal portions of the umbilical cord. Furthermore, perivascular tissue from the umbilical cord vein of overweight pregnant women exhibited significantly higher number of larger adipocytes compared to the control group. A significant correlation of BMI at the beginning of gestation with the total area of the medial portion vein, the total area of the placental portion and the diameter of the adipocyte fetal portion was also observed. **Conclusion:** Maternal overweight or obesity at the beginning of gestation or the excessive weight gain during the gestational period promote structural alterations in the components of the umbilical cord vein and in the perivascular tissue of these vessels. These changes might constitute important mechanisms determining changes in the fetus that may reflect complications at distinct stages of postnatal development and should be systematically addressed as a new potential target for intervention. **License number of ethics committee:** 62155316.0.0000.5083

14.007 Yerba mate (*Ilex paraguariensis*) and dimethyl fumarate can improve metabolic syndrome condition induced by high fat diet in mice. Valença HM, Lanzetti M, Valença SS UFRJ – Ciências Biomédicas

Introduction: Metabolic syndrome (MS) is a combination of clinical signs and symptoms that occur together and directly contribute to the risk of developing cardiovascular disease and diabetes. Some studies suggest that the prevalence of MS in the US is 32% of the population, while in Brazil this level reaches 23%. The criteria for the classification of MS are diverse, but according to the WHO, the presence of diabetes or reduced glucose tolerance or insulin resistance, associated with at least two of the following conditions: elevation of blood pressure, dyslipidemia and obesity are considered. MS confers a two-fold increased risk for developing cardiovascular disease, two to four times the risk of stroke, three to four times the risk of acute myocardial infarction. Our hypothesis is that toasted yerba mate and dimethyl fumarate have a therapeutic effect on the metabolic syndrome in mice.

Methods: Metabolic syndrome was induced by hyperlipidic diet (60% of total calorie) in C57BL / 6 mice for 12 weeks, and treatment was performed concomitantly with yerba mate (2 mg / g) and dimethyl fumarate (0.24 mg / g) diluted in water, to which the animals had free access. The groups were separated as follows: control group (standard diet and water), HFD group (hyperlipid diet and water), HFD + Mate group (hyperlipid diet and mat herb tea) and HFD + DMF group (hyperlipid diet and dimethyl fumarate). **Results:** It was observed that the HFD + Mate group obtained an increase in body mass in the same way as the HFD group, also increasing triglyceride levels, but maintained normal HDL levels. The HFD + DMF group, however, remained with body mass equal to the control group, maintaining normal levels of HDL and triglycerides. Both the HFD + Mate group and the HFD + DMF group remained at optimal glycemic levels, including glucose tolerance and insulin resistance tests. Histological analysis of the liver showed hepatic steatosis in the HFD group, but not in the HFD + Mate and HFD + DMF groups. **Conclusion:** It can be stated that the yerba mate was able to promote a partial improvement in the MS, as it was not able to avoid the weight gain, as well as the increase of the levels of triglycerides, although it presented cardioprotective effect by preserving the HDL. Dimethyl fumarate was able to protect against MS, since the results of the tests used in its diagnosis remained normal. Regarding the control of the blood pressure of the mice, the data could not be collected, but it is worth noting that of the five criteria used for the diagnosis of MS, only this one was not tested. The diagnosis of MS is conclusive when a minimum of three of the parameters involved is reached. **License number of ethics committee:** CEUA/CCS/UFRJ 042/2016

14.008 Lung expression of acetylserotonin methyltransferase correlates with light exposure.

Ribeiro-Paz ED¹, Cordoba-Moreno MO², Silva-Sousa E¹, Muxel SM², Fernandes PA², Markus RP¹
¹IB-USP – Chronopharmacology, ²IB-USP – Neuroimmunoendocrinology

Introduction: Melatonin, the hormone of darkness, is now known to be synthesized by extra-pineal sources. In the presence of the enzyme aralkylamine N-acetyltransferase (AANAT), serotonin is converted to N-acetylserotonin (NAS), which is converted to melatonin by the enzyme acetylserotonin methyltransferase (ASMT), which is the rate limiting enzyme in melatonin biosynthesis (Liu, J. Pineal Res. 3: 91,2015). This multifaceted molecule which, besides acting as a biomarker of darkness, modulates immune responses via GPCRs melatonin receptors (MT1 and MT2) (Markus, Brit. J. Pharmacol. 0.1111/bph.14083. 2017). Extra-pineal melatonin is synthesized on demand by macrophages or microglia in injured areas, and constitutively synthesized in the guts, which is continuously exposed to the external ambient. The use of melatonin receptors ligands in the clinics results in erratic outputs, as the sources and role of endogenous extra-pineal melatonin is, till now, not well understood. The fact that the lungs are in direct contact with the environment could represent a constant aggression, requiring a constitutive presence of melatonin. On the other hand, this could reduce the daily signaling of darkness, provided by pineal melatonin. Here we explored the possibility that the lung expresses the rate-limiting enzyme ASMT and whether the amount of this enzyme varies along the day. **Methods:** Wistar male rats, 3-4 months old from the animal facility of the Department Physiology, IBUSP, maintained under 12/12 h light–dark cycle (lights on at ZT0 and off at ZT12) were decapitated at ZT05, ZT12L (just before lights off) and ZT18. Lungs and pineal glands (ZT18) were immediately removed to liquid nitrogen. The relative expression of Asmt mRNA was detected by PCR. GAPDH and beta-Actin were used as house keepers. The expression of the protein ASMT was measured by Western Blot, using the beta3-tubulin as normalizer. **Results:** Both lung and pineal gland expressed ASMT gene and the protein. The percentual expression of ASMT in relation β 3-tubulin was 121 ± 9.00 ; 40 ± 1.2 and not detectable at ZT05, ZT12L and ZT18, respectively. The linear regression ($y = -8.62 h - 1.07$) was statistically significant ($F = 64.58$; $P < 0.0001$, $n = 3$ rats per point) indicating that the expression of ASMT in the lung varies along the day. **Conclusion:** Our results showed that the lung synthesizes the rate limiting enzyme of melatonergic biosynthetic pathway in a rhythmic manner, being higher during the light phase than during the dark phase. Does melatonin protect the lung independent of the hour of the day, and therefore it is necessary a proper compensation during daytime? This result, indeed, opens a new and unexpected perspective for clarifying the role of extra-pineal melatonin in physiological conditions. **License number of ethics committee:** Animal Research Ethical Committee license # 198/2014 CEUA IBUSP **Financial support:** FAPESP: 2013/13691-1; EDR-P, ES-S and MOC-M are CAPES graduation fellows

14.009 Locally-produced melatonin powers liver mitochondrial activity and systemic metabolism. da Silveira Cruz-Machado S¹, Kakimoto P², Caldeira C², Trevizan I¹, Santos-Pardinho A¹, Kowaltowski A², Markus RP¹ ¹USP – Fisiologia, ²USP – Bioquímica

Melatonin, classically produced by the pineal gland at night, orchestrates rhythmic functions of the body and has exquisite roles in regulating metabolism and immune responses (Markus et al., 2017). Acute fat intake triggers pineal gland inflammation, resulting in increased microglia activation, reduced arylalkylamine N-acetyltransferase expression and loss of melatonin rhythm, parallel to body weight gain and adiposity (da Silveira Cruz-Machado et al., 2017). In addition, increased weight and inflammation are linked to the long-lasting decrease in melatonin rhythm, both in rodents and humans (Cano et al., 2008). The present study addressed whether inflammation induces extra-pineal production of melatonin and the impact of blocking melatonin receptors to energy homeostasis and immune quiescence. Adult Wistar rats received *ad libitum* access to low-fat (LFD) or high-fat diet (HFD) along 7 days. Melatonergic regulation of inflammatory mediators, mitochondrial activity, and metabolism were accessed by blocking melatonin receptor (DH97, 170 ng/mL, a selective antagonist of MT2) administered along 7 days in the drinking water. Average water intake was 25-30 mL per day. HFD rapidly increased food intake, body weight gain and fat depots. In addition, increased melatonin content was detected in the liver of animals fed a HFD (Chow: 18.8 ± 2.4 versus HFD: 567.4 ± 53.9 pg/mg of protein). Indeed, increased protein expression of acetylserotonin O-methyltransferase (ASMT), the limiting enzyme for producing melatonin, was significantly increased in the liver of animals fed a HFD (chow: 100 ± 6.88 versus HFD: 126.6 ± 6.66, P<0.05, n=4, % relative to chow). Blocking MT2 potentiates HFD-induced weight gain, fat accumulation, and liver steatosis and increased mitochondrial-derived hydrogen peroxide formation. In addition, blocking MT2 prevented the increase in state 3 and state 4 oxygen consumption promoted by HFD, assessed by high-resolution respirometry in isolated liver mitochondria. Systemically, blocking MT2 reduced IL-4 and IL-12p70 anti-inflammatory cytokine levels, induced hyperphagia, hyperglycemia, and adiposity. Altogether, our findings uncover a protective mechanism mediated by local production of melatonin in the liver, which improves the metabolism and avoids fat accumulation in hepatocytes. We also determined novel roles for MT2 in the regulation of anti-inflammatory cytokines and suggest that melatonin is instrumental for regulation of metabolism and immune responses. **References:** Cano P, et al., *Endocrine*, 33(2): 118, 2008. da Silveira Cruz-Machado S, et al., Abstract 13.001. In: *Anais do 49º Congresso Brasileiro da Sociedade Brasileira de Farmacologia e Terapêutica Experimental*, 2017, Ribeirão Preto, Brasil. Markus RP, et al., *Br J Pharmacol*, no prelo, 2017. doi: 10.1111/bph.14083. **License number of ethics committee:** CEUA license number 194/2014 **Financial support:** FAPESP 2013/13691-1 (RPM), 2015/04557-5 (SSCM) and 2015/25862-0 (AK), CAPES and CNPq.\$-\$360