08. Respiratory, Urinary and Reproductive Pharmacology

08.001

Ipriflavone in a self-emulsifying drug delivery system (SEDDS) improves female sexual function in young and menopausal senescent hyepertensive rats. Martins TA, Mendes JC, Mosqueira VCF, Grabe-Guimarães A, Rodovalho GV, Leite R CiPharma-UFOP

Introduction: Female sexual dysfunction (FSD) is a condition in which there are alterations in the processes involved in the female sexual response cycle. A major subcategory of FSD is female sexual arousal disorder (FSAD) that results in a series of vasocongestive and lubricative events resulting primarily from increased blood flow to clitoral, labial, and vaginal tissue. A decline in serum estrogen, which occurs in menopause, results in a significant decrease in the clitoral intracavernosal, vaginal, and urethral blood flow, thinning of vaginal mucosal epithelium and atrophy of vaginal wall smooth muscle. The influence of estrogen is related to the local action of nitric oxide (NO) in genital tissues. Experimental findings from our laboratory and from others have demonstrated the close association of neuronal nitric oxide synthase expression (nNOS) and estrogen and ipriflavone treatment. The phytoestrogen ipriflavone has been used lately to prevent and treat osteoporosis, a common comorbidity associated with menopause. However, the effect of ipriflavone chronic treatment on FSAD is still unknown. The aim of this study was to investigate the potential of ipriflavone administered orally in a self-emulsifying drug delivery system (SEDDS) in the treatment of FSAD. **Methods**: All experiments were approved by the Ethics Committee on Animal Use of UFOP (protocol number: 2013/15). Young (4-5 months) and senescent (18-19 months) female spontaneously hypertensive rats (SHR) were treated via oral gavage with vehicle, 10 and 30 mg/kg of Ipriflavone in a SEDDS during 30 days (n = 8, for all experimental groups). Under xilazine/ketamine anesthesia physiological parameters such as vaginal lubrication, temperature and intravaginal pressure were measured before and during pelvic nerve stimulation in both vehicle and iprifavone treated rats. Tail cuff blood pressure was measured before and after vehicle or ipriflavone treatment. **Results:** Intravaginal temperature significantly increased at the dose of 10 mg/kg in the senescent SHR group ($p<0.05$, ANOVA followed by Bonferroni post- test). The vaginal lubrication was improved after treatment with ipriflavone 30 mg/kg in the young and in the senescent rats ($p<0.05$, ANOVA followed by Bonferroni post-test). Intravaginal pressure was significantly higher in both young and senescent groups treated with both 10 and 30 mg/kg of ipriflavone ($p<0.05$, ANOVA followed by Bonferroni post- test). **Discussion:** Our results demonstrate that ipriflavone treatment using a SEDDS improves some physiological conditions that are important for female sexual function. These data suggest a potential for the phytoestrogen ipriflavone, administered in a formulation that improves absorption and bioavailability, to prevent the sexual discomfort during intercourse observed in women in a condition of natural hipoestrogenism observed during menopause. **Financial Agencies:** CNPq, Capes, FAPEMIG and UFOP.

08.002

Ipriflavone chronic treatment improves apomorphine induced genital vasocongestive arousal in ovariectomized and senescent hypertensive female rats. Mendes JC, Lopes IM, Martins TA, Mosqueira VCF, Grabe-Guimaraes A, Rodovalho GV, Leite R CiPharma-UFOP

Introduction: Apomorphine, a central acting nonselective dopamine receptor agonist, improves genital blood flow (clitoral and vaginal engorgement) by increasing clitoral intracavernosal and vaginal wall blood arterial inflow. In a state of estrogen deficiency, vaginal wall becomes thinner and drier, thus more susceptible to trauma, which can lead to pain during intercourse, anxiety and lack of sexual satisfaction. There is evidence that isoflavones, a natural phytoestrogen, prevents postmenopausal bone loss, reduces the intensity and frequency of vasomotor symptoms in menopausal women, improves lipid profile, promotes coronary vasodilation and ameliorates female sexual function. Ipriflavone (7-isopropoxy-isoflavone) is a semisynthetic isoflavone derivative from daidzein that has been prescribed to prevent and treat osteoporosis in postmenopausal women. In this study we tested the hypothesis that the phytoestrogen ipriflavone would have a beneficial effect on sexual function of female rats. **Methods:** All experiments were approved by the Ethics Committee on Animal Use of UFOP (protocol numbers: 2010/54 and 2013/15). To evaluate sexual function, the genital vasocongestive arousal (GVA) was counted from conscious adult (4-5 months) female ovariectomized Wistar (n=6-9) and from senescent (18-19 months) spontaneously hypertensive rats (SHR, n=6-9) that received via subcutaneous injection either vehicle (1% ascorbic acid in saline) or apomorphine (80 µg/kg). The rats were submitted to a 6 days estradiol (38 µg/kg, intramuscular), 30 days ipriflavone in a self-emulsifying drug delivery system (SEDDS) (10 or 30 mg/kg, oral gavage) or respective vehicle control treatment. **Results:** The apomorphine induced GVA (number of responses/30 min) was significantly reduced in ovariectomized Wistar rats and in senescent SHR, compared to respective controls ($p<0.05$, ANOVA followed by Bonferroni post- test). Either sort term estradiol or long term ipriflavone (administered in a SEDDS) treatment significantly improved sexual response in both groups of ovariectomized Wistar rats and in senescent SHR, compared to respective controls ($p<0.05$, ANOVA followed by Bonferroni post-test). **Discussion:** Long term treatment with the phytoestrogen ipriflanove in a SEDDS have shown the same improvement in sexual function observed with estrogen replacement in two different rat models: a model of induced hypoestrogenism after total ovariectomy and a model of natural hypoestrogenism associated with senescence and spontaneous hypertension. Our results indicate that ipriflavone could be used as a safer alternative for hormone replacement therapy to ameliorate sexual function. **Financial Support:** CNPq, Capes, FAPEMIG and UFOP.

08.003

Relaxant activity of new pde4 inhibitors on guinea pig airway smooth muscle. Martins IRR[1], Nunes IKC[2], Lima LM[2], Barreiro EJ[2], Silva BA[1] [1]DCF-UFPB, [2]LASSBio-UFRJ

Introduction: asthma is an inflammatory chronic disorder on airways with bronchial hyper-reactivity leading to airflow blockade (BATEMAN, *Eur Respir J*, v. 31, p. 143, 2008). Currently, in the asthma therapy are used β-adrenergics and corticoids (HOLGATE, *J Allergy Clin Immunol Pract*, v. 128, p. 495, 2011), besides antihistaminics, anticholinergics, antileukotrienes and phosphodiesterases (PDEs) inhibitors that cause airway relaxation. Despite these therapeutic possibilities, there are patients that present difficulties in responding to treatment (HEANEY, Thorax, v. 65, p. 787, 2010). Through rational planning of new PDE4 inhibitors designed from rolipram, a PDE4 inhibitor prototype, the LASSBio® (Laboratório de Avaliação e Síntese de Substâncias Bioativas/UFRJ) aimed to contribute in development of new drugs to treat asthma symptoms in an efficient manner and with milder side effects. Thus, we assessed a possible bronchodilator activity of a new PDE4 inhibitors series (LASSBio-1846, LASSBio-1847, LASSBio-1848, LASSBio-1849 and LASSBio-1851) on guinea pig airway smooth muscle. **Methods:** from guinea pigs (300-500 g) was obtained the trachea. Then, it was cleaned of connective tissue, cut into rings and suspended in organ baths on appropriated conditions. Before experiments, epithelium integrity was verified using arachidonic acid 10^{-4} M (TSCHIRHART, *J Pharmacol Exp Ther*, v. 243, p. 310, 1987). All experimental protocols were previously approved by Ethical Committee on Animal Use of CBiotec/UFPB (Protocol 0203/11). **Results:** the derivatives (LASSBio-1846, LASSBio-1847, LASSBio-1848, LASSBio-1849 and LASSBio-1851) showed a concentration-dependent relaxant effect on guinea pig trachea pre-contracted by carbachol 10^{-6} M (n = 5), both in the epithelium presence (pD_2 = 5.34 ± 0.04; 4.80 ± 0.03; 4.51 ± 0.03; 4.20 ± 0.08 and pD_2 = 4.70 ± 0.06, respectively) and in absence (pD_2 = 5.15 ± 0.08; 4.61 ± 0.01; 4.44 ± 0.03; 4.10 ± 0.07 and 4.85 ± 0.08, respectively). Based on these values, LASSBio-1846 was the most potent derivative. All compounds showed maximum effect (E_{max}) values equal to 100%, except LASSBio-1849 (E_{max} = 70.93 ± 3.34% in epithelium presence and E_{max} = 97.97 ± 1.26% in epithelium absence). **Discussion:** the cAMP pathway is the most important relaxant signal transduction pathway in airway smooth muscle (KNOX, Thorax, v. 50, p. 894, 1995) and it is regulated by PDEs that hydrolyze the cyclic nucleotides and interrupt the signal (LUGNIER, Pharmacol Ther, v. 109, p. 366, 2006). So, in the searching for new therapeutic agents that inhibit selectively PDE isozymes, PDE4 inhibitors were designed by LASSBio®. Previously, Nunes (Thesis, UFRJ, 2013) showed that the compounds inhibited human PDE4 isoforms, but none experiments were carried out on tissue level. On guinea pig trachea, all tested compounds presented concentration-dependent relaxant activity and according to pD_2 and E_{max} values, LASSBio-1846 showed to be the more promising derivative. In a next step, will be evaluated the relaxant effect of these new PDE4 inhibitors on guinea pig asthma model, as well as their action mechanism, to assign a possible role as antiasthmatic drugs. **Support:** CNPq, Capes, PPgPNSB/CCS/UFPB.

08.004

Administration of ketamine reduced depressive-like behavior induced by ovariectomy in rats. Oliveira C[1,3,4], Moreira SFS[3,4,5], Scarabelot VL[2,3,4], Marques PR[1,3,4], Medeiros LF[2,3,4], Nunes EA[2,3,4], Kuo J[3,4], Macedo IC[2,3,4], Muchale AV[3,4], Caumo W[1,3], Torres ILS[1,2,3,4] [1]UFRGS – Medicine, [2]UFRGS – Physiology, [3]UFRGS – Pharmacology [4]HCPA – Animal Experimentation [5]ICS-FM–UFPA.

Introduction: Menopause is a physiological process characterized by the loss of ovarian follicular activity and may be a relatively plastic event that happens between the ages 40 to 55. As currently women have an increase on life expectancy, they spend a significant part of their lives in postmenopausal state. Estrogen deficiency is associated to the onset of depressive and anxiety symptoms, cognitive impairment, among others. It is important to use animal models to study the pathophysiology of cognitive impairment, depressive and anxiety disorders associated with estrogen decline. The present investigation aims to explore depressive-like and anxiety-like behaviors and cognitive impairment in ovariectomized and aged rats. **Methods:** 28 female Wistar adult rats (60 days old) were housed four per cage and maintained with food and water available ad libitum on a 12-h light/dark cycle in a temperature-controlled environment (22 ± 2°C). Initially they were distributed into two groups: ovariectomized (OVX) and false surgery (SHAM). Hormonal status was verified by vaginal cytology and then the rats were subjected to the forced swimming (FS), object recognition (OR), elevated plus maze (EPM), and open field (OF) tests. The rats of the OVX group entered the menopause process with 90 days and the rats of SHAM group at 180 days. After natural menopause in SHAM group, each group was subdivided into two more groups that received ketamine (10 mg/kg, i.p) or vehicle and the FS test was repeated. All data are presented as mean ± S.E.M. Student's t test was used to evaluate differences between groups. All experiments and procedures were approved by the Institutional Animal Care and Use Committee (GPPG-HCPA protocol No. 110586). **Results:** OVX rats and natural menopause SHAM rats showed depressive-like behavior probably related to hypoestrogenism and this behavior was reversed by ketamine. Moreover, OVX group exhibited anxiety-like behavior in the EPM test and worse performance in OR test. OVX group showed worse performance of long-term memory in OR test. Groups showed no difference in OF test. **Conclusion:** This is consistent with the scientific evidence about neuromodulatory effect of estrogen on mood and cognition. In conclusion, this study corroborates scientific evidences about neuromodulatory effect of estrogen on mood and cognition, and shows the ketamine's acute action on depressive-like behavior on a model of menopause. Furthermore, SHAM group showed signs of hypoestrogenism at six months of age, as verified by vaginal smears. The precocity of the ovarian failure was an unexpected finding, for, in general, female rats only show aciclicty when they reach about twelve months. We suggest a new animal model of menopause, similar to natural evolution, induced by ovarian and fallopian tubes exposition. **Financial Support:** FIPE/GPPG,CNPq,Capes.

08.005

Resveratrol prevents the reproductive damage induced by sodium valproate on male rats. Dalenogare JF, Ourique GM, Saccol EMH, Pês TS, Glanzner WG, Pavanato MA, Barreto KP UFSM – Fisiologia e Farmacologia

Introduction: Sodium valproate (VPA) is the most widely prescribed antiepileptic drug in the world due to its broad therapeutic spectrum. However, its use has been associated with adverse effects on male reproductive system. Moreover, oxidative stress is appointed as one of the main mechanisms responsible for the toxicity of VPA in the reproductive system. Natural antioxidant compounds like resveratrol (RSV) have been described as capable of preventing damage to male fertility induced by different inducers of oxidative stress and may be an alternative to minimize the reproductive damage caused by continuous use of VPA. Thus, this study aimed to investigate the effect of RSV on reproductive function of male rats treated with VPA. **Methods:** Adult male Wistar rats (70-90 days) were divided in four experimental groups with eight animals each: (C) control; (RSV) treated with 10 mg/kg of RSV; (VPA) treated with 400 mg/kg of VPA; and (VPA + RSV) treated with 400 mg/kg of VPA and 10 mg/kg of RSV. The VPA was administered by gavage and RSV intraperitoneally for 28 days. At the end of the experimental period animals were euthanized for the removal of their epididymis and testes. Analysis of concentration and motility of spermatozoa from epididymal tail was performed. The testes were homogenized for measurement of lipid hydroperoxides (LOOH) by the methodology of xylenol orange (JIANG ZY. Lipids, v.26, p.853, 1991) and analysis of the total reactive antioxidant potential (TRAP) (EVELSON P. *Arch Biochem Biophys,* v.338, p.261, 2001). The results were analyzed using a two-way analysis of variance (ANOVA) followed by Duncan's test. The level of statistical significance was set at $P<0.05$. All animal procedures were approved by the Animal Ethics Committee of the UFSM (process 076/2013). **Results:** The sperm concentration did not show a significant difference among the experimental groups. The sperm motility was lower in VPA than in Control ($P<0.05$). In addition, VPA + RSV animals presented sperm motility higher than VPA ($P<0.05$). In the testes, LOOH levels were higher in VPA than in Control animals, whereas VPA + RSV presented lower LOOH than VPA animals. In VPA group, TRAP was lower than in Control. RSV prevented this decrease, and VPA + RSV animals presented higher TRAP than VPA animals. **Discussion:** Oxidative stress is a major cause of the loss of male fertility and has been identified as one of the main mechanisms responsible for the toxicity of VPA on male reproductive system. Our results demonstrated that VPA treatment lead to a decrease on sperm motility. This decrease may have been induced by the oxidative stress, since the animals treated with VPA showed an increase on the LOOH levels and a decrease on TRAP on the testes when compared to the control animals. RSV has been reported to have several beneficial effects on reproductive health related to its antioxidant effect. The results of the present study demonstrated that RSV decreased the oxidative damage and prevented the decrease on antioxidant potential induced by VPA treatment in adult rat testes, preventing the loss of sperm motility. **Financial** Agencies CNPq and Capes **Acknowledgments:** Authors are grateful to CNPq, Capes and graduate program in pharmacology-UFSM

08.006

Relaxing effects of the new nitric oxide donor in isolated trachea from rats with experimental asthma. Castro PFS[1,2], Batista AC[3], Silva RS[4], Rocha ML[1] [1]FF-UFG, [2]Universo, [3]FO-UFG, [4]FCFRP-USP

Introduction: Airway smooth muscle tone is maintained by equilibrium between bronchoconstriction and bronchodilation. Endogenous nitric oxide (NO) is produced mainly by nerves and epithelial cells and it has been demonstrated to be the primary agent in relaxing airways. However, its relaxing effect is impaired in the asthma[1]. In this work, we investigated the effects of a new NO donor $[Ru(terpy)(bdq)NO^{+}]^{3+}$ (TERPY) in isolated trachea of control or asthmatic rats (induced by ovalbumin) contracted with carbachol (0.5μM) in an isolated organ bath. **Methods:** We verified the relaxing effect, the contribution of prostanoids (using COX inhibitor sodium diclofenac, 10μM), leukotriene receptor (using antagonist montelukast, 10μM) and the importance of superperoxide anions (O_2^{-}) (using superoxide scavenger TIRON, 1 mM) for the relaxing response induced by TERPY or standard drug sodium nitroprusside (SNP) (both 10nM to 100μM). These protocols were approved by the Animal Research Ethics Committee of the UFG under protocol 029/2013. **Results:** The histological analysis has confirmed intense inflammation and cell migration into the tracheal tissue of the asthmatic rats. The SNP led to relaxation of isolated pre-contracted rat trachea in a dependent-concentration way, producing maximum effect (Emax) higher in control (68.3 ± 3.1%;n=9) than asthmatic rats(48.3 ± 2.7%;n=5). The sodium diclofenac treatment altered significantly ($P<0.001$) the Emax to SNP in asthmatic rats (73.6 ± 4.0%;n=5) as well as montelukast (85.6 ± 7.1%;n=5) and TIRON (77,9 ± 7.0%;n=5). The TERPY led to relaxation of isolated pre-contracted rat trachea in a dependent-concentration way, producing Emax similar in control (111.8 ± 6.9%;n=4) or asthmatic rats (105.5 ± 2.0%;n=5). The sodium diclofenac treatment did not alter the relaxation to TERPY in control (102.9 ± 9.6%;n=5) or asthmatic rats (115.2 ± 4.1%;n=5). However, TERPY-induced relaxation was increased significantly ($P<0.01$) by montelukast (124.1 ± 3.6%;n=5) and TIRON (118.8 ± 2.2%;n=5) in asthmatic rats. **Discussion:** The new NO donor TERPY was more effective than SNP in induce relaxation of airway smooth muscle both in control or asthmatic rats. These results have shown that TERPY and SNP have increased their effects in asthmatic rats after treatment with montelukast or TIRON, highlighting the involvement of the leukotriene and superoxide anion in the asthma. **Financial support:** FAPEG/CNPq. [1]Arnold, W.P. *et al. Anesthes* 61, 254, 1984.

08.007

Effect of subcutaneous serotonin injection on male rat sexual behavior *in vivo.* Barbosa EC, Lumbard B, Linder AE UFSC – Farmacologia

Introduction: The drugs used for the treatment of depression are often associated with sexual dysfunction and the relation between antidepressant and erectile function is somewhat controversial[3, 6]. The incidence of sexual dysfunction during antidepressant treatment appears to differ among antidepressants with different mechanisms of action[5]. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine delay ejaculation in humans[4] and in rats[2]. Studies have shown that injection of imipramine, a tricyclic antidepressant (serotonin and norepinephrine reuptake inhibitor) directly into the corpus cavernosum of humans causes erections[1]. Unpublished data from our laboratory and also observed by Millan and Perrin – Monneyron (1997) showed that fluoxetine induces erection in rats. Knowing that fluoxetine is an SSRI, the hypothesis of this study is to evaluate whether the administration of serotonin (5-hydroxytryptamine, 5-HT) induces erection in rats *in vivo*. **Methods:** Male Wistar rats (270- 380g) were placed, on the test day, individually in observation boxes for videotaping over a period of 60 minutes after receiving 5-HT (3.0, 5.0, or 7.5 mg/kg) or vehicle (1 ml/kg) subcutaneously (s.c.). All animals spent 30 minutes in the observation boxes before the injections for acclimatization. A camera was placed under the transparent cages to facilitate observation of the animals. The recording took place in a quiet environment. During recording, the number of erections was quantified based on behavioral alterations. An erection is the typical time that rats rely on their hind legs while curving towards the penis with their front legs, holding and licking the member for more than 5 seconds. Data were expressed as mean values ± standard error of erections obtained from n experiments. Data were compared by analysis of variance, $p<0.05$ represents significant difference compared with the group that received the vehicle. All experimental procedures were performed according to the protocol approved by the institutional ethics committee (PP00706). **Results and discussion:** The group receiving vehicle showed 1.8 ± 0.20 erections (n = 5), which is normal, since rats can present spontaneous erections. The 5-HT dose of 3.0 mg/kg triggered 2.5 ± 1.28 erections (n = 6), while the doses of 5.0 and 7.5 mg/kg triggered 8.8 ± 1 5 erections (n = 6, $p<0.05$), and 6.3 ± 2.09 erections (n = 6), respectively, during the filming time. **Conclusion:** Our results indicate that 5-HT stimulates penile erection in rats. Knowing that there are several subtypes of 5-HT receptors, additional studies are needed to investigate which receptor subtype is involved in inducing erections in male rats. The results from these experiments may be used to provide more information about the effect of 5-HT and antidepressants on sexual function. **References:** 1-Brindley G *Br J Pharmacol*; *87*:495 – 500 (1986). 2-Cantor, J. M.; Binik, Y. M.; Pfaus, J. G.. *Psychopharmacology*, [s.i.], v. 144, n. 4, p.355-362, jun. 1999. 3-Clayton, A. H., *et al.*. *J Clin Psychiatry*, v.63, p.357–366, 2002. 4-Kara, H., *et al.*. *J Urol*, V.156, p.1631–1632; 1996. 5-K.U. Lee, Y.M. Lee, J.M. Nam, H.K. Lee, Y.S. Kweon, C.T. Lee *et al. Psychiatry Invest*, 7, pp. 55–59(2010); 6-Millan, M. J., and S. Perrin-Monneyron. *European Journal of Pharmacology* 321.3 (1997). **Suporte Financeiro:** CNPq/FAPESC, PPG-FMC-UFSC.

08.008

Strength training changes trachea rectivity by modulating prostanoids pathway on rat Wistar. Brito AF[1], Silva AS[2], Souza AA[2], Ferreira PB[1], Felix GS[2], Sampaio RS[1], Tavares RL[2], Souza ILL[1], Pereira RA[2], Araujo LCC[3], Miranda Neto M[2], Miranda Neto M[2], Silva BA[4] – [1]UFPB – Produtos Naturais e Sintéticos Bioativos, [2]UFPB – Treinamento Físico Aplicado ao Desempenho e à Saude, [3]UFPB – Biologia Celular e Molecular, [4]UFPB – Ciências Farmacêuticas

Introduction: current research shows that regular practice of strength training promotes strengthening of respiratory muscles (SILVA, Cochrane Database Syst. Rev., v. 8, p. 9, 2013) and improves lung capacity (LATORRE-ROMÁN, J. Asthma., v. 25, p. 1, 2014), nevertheless, no data demonstrating the direct influence of strength training on the respiratory smooth muscle. Thus, this study aimed to evaluate the relaxant and contractile reactivity in rat trachea by means of concentration-response curves after eight weeks of strength training and to investigate about the physiological mechanisms involved. **Methods**: after a week of adaptation to strength training, rats (250-300 g, n = 10), were undergone for 8 weeks of progressive strength training (STG) (MARCHETT, *Am J Sports Med*, v. 34, p. 1274, 2006). The control group CG (n = 10) was only acclimatized (non-exercised). 48 hours after exercise, rats were euthanized and the trachea removed and suspended in organ baths with Krebs solution, under rest tension of 1 g at 37 ˚C and bubbled with carbogen mixture. After a stabilization period of 45 min isometric contractions were recorded. All experimental protocols were previously approved by Ethical Committee on Animal Use of CBiotec/UFPB (Protocol 1101/11). **Results:** all experimental groups exhibited maximum effect (E_{max}) of relaxation equal to 100%. The trained animals presented an increased relaxant potency for lower concentrations of aminophylline (AMF) on trachea with epithelium compared to CG, which is observed by pD_2 = 4.5 ± 0.12 and 5.8 ± 0.12 for CG and STG, respectively. Without epithelium, this phenomenon was reduced when compared with control group, which is shown by pD_2 values of 3.3 ± 0.05 and 4.1 ± 0.04 for CG and STG respectively. The trained animals presented contractile potency reduced to CCh in epithelium presence compared with CG, which is demonstrated by 5.5 ± 0.04 and 5.1 ± 0.3 for CG and STG, respectively. In epithelium absence, these differences were abolished, which is shown by pD_2 = 6.2 ± 0.13 and 5.9 ± 0.06 for CG and STG, respectively. Indometacin increased the contractile potency to CCh in STG compared with CG, in epithelium presence, pD_2 = 5.5 ± 0.03 *vs*. 5.7 ± 0.08 for CG and 5.1 ± 0.03 *vs*. 5.6 ± 0.06 for ST. **Discussion:** this study reveals for the first time the influence of strength training on trachea reactivity of rat. It was observed that this type of exercise promotes a decrease in contractile reactivity and in turn an increase in reactivity relaxing. Although the literature on exercise physiology demonstrate that an exercise program does not promote changes in respiratory capacity (McArdle; Katch, 6ª edition Ed. Guanabara, 2008), these pharmacological data support that strength training has a direct beneficial effect on respiratory smooth muscle, indicating that future guidelines for exercise prescription can indicating strength training as a new alternative for individuals with respiratory problems. **Financial support:** CNPq, Capes, PPgPNSB/UFPB.

08.009

JME-173, non-anesthetic analogue of mexiletine, exerts spasmolytic action at least in part by inhibiting calcium influx in the airway smooth muscle. Carvalho KIM[1], Santos-Filho OA[1], Joca HC[2], Cruz JS[2], Silva ET[3], Costa JCS[3], Silva PMR[1], Martins MA[1] [1]IOC-Fiocruz, [2]LAMEX-UFMG, [3]Farmanguinhos-Fiocruz

Introduction: Prior studies showed that analogues of the local anesthetics (LA) lidocaine, screened for reduced inhibitory activity upon sodium channels, exhibited better antispasmodic, anti-inflammatory and safety properties as compared to the prototype. Since the low oral bioavailability is a pivotal limitation of this class of agents, this study was undertaken in order to access the drug likeness and antispasmodic profile of JME-173, a novel non-anesthetic analogue derived from the LA mexiletine, used in the clinic for oral treatment of cardiac arrhythmia and neuropathic pain. **Methods:** *In silico* druglikeness analysis and computational ligand-docking simulation were employed to access drugability as well as the probable binding mode of interactions of JME-173 with a L-type calcium channel model, respectively. Rat trachea rings were mounted in tissue baths filled with Krebs' solution, and the contractile response to distinct stimuli was measured in the presence or absence of JME-173. Complementary assays, using epithelium-denuded trachea or co-treatments with specific inhibitors, were employed to clarify the putative mode of action. The effect of JME-173 on voltage-dependent calcium channels was investigated using isolated mice cardiomyocytes and patch clamp technique. All animal experiments were under the CEUA Fiocruz license number LW-23/10. **Results**: Our *in silico* findings showed that JME-173 has a drug likeness profile better than that exhibited by mexiletine (see Table). In addition, both mexiletine and JME-173 interact at the same channel-binding sites that a major class of L-type calcium channel blockers (benzothiazepine) does. In functional assays, JME-173 and mexiletine inhibited tracheal contraction induced by either allergen (IC_{50s}= 8.3 μM and 440.2 μM, respectively), carbachol (IC_{50s}= 32.0 μM and 395.2 μM, respectively) or extracellular Ca2+ under high K+ depolarization (IC_{50s}= 10.0 μM and 380.8 μM, respectively). Notably, the relaxing effect of JME-173 remained unaltered following epithelium removal or co-treatment with either nitric-oxide synthase inhibitor N -nitro- L-arginine methyl ester (L-NAME 100 μM), beta adrenergic receptor antagonist (propranolol 1 μM) or adenylate cyclase inhibitor (SQ22,536 100 μM). In another setting of experiments, JME173 blocked L-type Ca2+ channels expressed in cardiomyocytes (IC_{50}= 30 μM). **Conclusion:** These results show that JME-173 has marked anti-spasmodic properties in respiratory smooth muscle. The effect is unrelated to either epithelium, nitric oxide, cyclic AMP or β2 receptor, and seem to be, at least in part, accounted for by blockade of voltage-dependent Ca2+ channels. **Financial support:** PDTIS, Faperj and CNPq.

Molecule	Mutagenic	Tumorigenic	Irritant	Reproductive effective	CLogP	Solubility	Molweight	TPSA	Druglikeness	Drug-Score
JME-173	No	No	No	No	2.44	-3.40	257	35.25	-4.56	0.43
Mexiletine	No	No	Yes	Moderated	1.72	-2.54	179	35.25	-0.44	0.31

Table. Drug likeness profile of mexiletine and the analogue JME-173.

08.010

Effects of chronic administration of tamsulosin and tadalafil, alone or in combination, in rats with bladder outlet obstruction induced by chronic nitric oxide deficiency.

Santos LCO, Sales LC, Sousa PRR, Silva BGB, Pamplona TL, Marinho LB, Santos JMS, Segundo SAS, Silva Júnior JVM, Cerqueira JBG, Maia RR, Gonzaga-Silva LF, Regadas RP
UFC – Cirurgia e Fisiologia e Farmacologia

Introduction: The aim of this study was to define if tadalafil cause detrusor muscle impairment and to observe the effect of combination of tadalafil with tamsulosin on the lower urinary tract of rats with bladder outlet obstruction (BOO) induced by chronic nitric oxide deficiency. **Methods:** Thirty-one male rats were randomized to following groups: 1 – control; 2 – L-Nitroarginine methyl ester (L-NAME); 3 – Tamsulosin + L-NAME, 4 – Tadalafil + L-NAME; and 5 – Tamsulosin + Tadalafil + L-NAME. At the end of the treatment period (30 days), all animals were submitted to urodynamic study. The Ethics Committee on Animal Research of the UFC approved the animal protocol (Protocol n° 54/2011). **Results and discussions**: The administration of L-NAME increased the number of non-voiding contractions (NVC) (1.04 ± 0.22), volume threshold (VT) (1.86 ± 0.35), and micturition cycle (MC) (1.34 ± 0.11) compared with control (0.52 ± 0.06, 0.62 ± 0.06, and 0.67 ± 0.30), respectively. The administration of tamsulosin reduced the number of NVC (0.57 ± 0.42) and VT (0.76 ± 0.24) compared with L-NAME group. Co-treatment with tadalafil decreased the number of VT (0.85 ± 0.53) and MC (0.76 ± 0.22) compared with L-NAME group. The combination of tamsulosin with tadalafil improved the number of NVC (0.56 ± 0.18), VT (0.97 ± 0.52) and MC (0.68 ± 0.30) compared with L-NAME group. Rats with BOO induced by chronic nitric oxide deficiency, tadalafil did not cause impairment in detrusor muscle and seems to have an addictive effect to tamsulosin because the combination decreased non-voiding contractions as well the number of micturition cycles. **Financial support:** CNPq