

Setor 07. Endócrino e Gastrintestinal/ Endocrine and Gastrointestinal

07.001

Effect of chronic treatment with rosiglitazone on the testosterone production in normal rats. Couto, JA¹, Barros CD¹, Mariano, AFS², Udrisar DP³, Lima MCA¹, Galdino SL¹, Pitta IR¹, Wanderley MI³ ¹UFPE - Antibióticos, ²UFRPE - Morfologia e Fisiologia Animal, ³UFPE - Fisiologia e Farmacologia

Introduction: Rosiglitazone is a thiazolidinedione hypoglycemic drug used in the treatment of type 2 diabetes mellitus. This therapeutic agent and exert their effects through the peroxisome proliferator-activated receptor (PPAR)- γ , which facilitates the expression of genes responsible for glucose and lipid metabolism. The PPAR- γ is a member of the nuclear hormone receptor superfamily that is involved in several physiological processes, such as glucose homeostasis, cellular differentiation, regulation of lipid and lipoprotein metabolism, as well as in pathological states, including atherosclerosis, inflammation, cancer and infertility (Inan, M. et al., Clin Exp Pharm and Phys 34: 457, 2007). It was hypothesized by Carruthers M. et al. (Cardiovasc Diabet 7:30, 2008) that rosiglitazone induces androgenic deficiencies in patients with type 2 diabetes mellitus. The aim of the present study was to test this hypothesis in normal animal models. Thus, it was evaluated the effect of chronic treatment with rosiglitazone on plasma levels of testosterone (*in vivo* model) and on the testis production of this hormone (“ex-vivo” model), using normal adult male rats.

Methods: Six adult male Wistar-albino rats weighing 250-300 g, were treated with rosiglitazone (5mg/kg) administered by gavage for 15 days. Six control animals were treated with the vehicle. After the treatment, the animals were sacrificed and their blood was collected for dosage of testosterone by radioimmunoassay (RIA). The testes were removed for the obtaition and purification of the Leydig cells by Percoll gradient. $0,35 \times 10^6$ cells/0,5 mL were incubated for 3 hours with 199 medium (basal testosterone), with the activators of PKA, hCG (1 mUII/mL) and dbcAMP (1mM), and with the steroidogenic precursors 22(R)-hydroxy-cholesterol (10 μ M) and pregnenolone (1 μ M) (induced testosterone). Testosterone was determined in medium of incubation by RIA. The experimental protocol of the study was approved by the local ethics committee (23076.024603/2008-84). **Results and Discussion:** The treatment with rosiglitazone did not change the plasma levels of testosterone (control: $25,01 \pm 3,5$; rosiglitazone: $38,4 \pm 7,0$ ng/mL). The results of the testosterone production in the “ex-vivo” model were expressed as $\Delta\%$ of the stimulated minus basal and showed that the rosiglitazone inhibited by $51,6 \pm 1,7$ % and $45,8 \pm 0,9$ % the stimulated testosterone production with the hCG e dbcAMP, respectively, and by $59,8 \pm 5,1$ % the testosterone induced with the 22(R)-hydroxy-cholesterol, but did not influenced the secretion of the hormone induced with the pregnenolone. These results show that the chronic treatment with the rosiglitazone inhibits the testosterone production by Leydig cells and indicate that this inhibition may be due to the inhibition of the P450 scc enzyme function.

Financial support: UFPE, CNPq

07.002

Study of pharmacological mechanisms involved in the gastroprotective effect of esculetin (6,7-dihydroxycoumarin) in mice. Rios ERV¹, Venâncio ET¹, Rocha NFM¹, Linhares MI¹, Moura BA¹, Feitosa ML¹, Cerqueira, GS¹, Silva AH², Leal LKAM², Fonteles MMF³ ¹UFC- Fisiologia e Farmacologia, ²UFC - Farmácia, ³UFC- Farmácia, Fisiologia e Farmacologia

Introduction: Esculetin (6,7-dihydroxycoumarin) is a coumarin derived that generated a considerable interest by its diverse bioactivity. Previous studies showed its anti-inflammatory effect that encouraged us to evaluate the gastroprotective action of esculetin on ethanol-induced ulcer models in mice and further investigate the pharmacological mechanisms involved in this action. **Methods:** We utilized mice of the lineage swiss, weighing 25-35g. The esculetin (25 and 50 mg/kg, p.o.) was administered and one hour before the injury was induced with ethanol absolute, 0.2 ml/animal p.o. The L-NAME (10 mg/kg, i.p.), a nitric oxide synthesis inhibitor, glibenclamide (10 mg/kg, i.p.), a K_{ATP} channel blocker, and indomethacin (10 mg/kg, p.o.), a prostaglandins synthesis inhibitor, were administered 15 minutes, for L-NAME and glibenclamide, or 2 hours, for indomethacin, before of the coumarin derived (25 mg/kg, p.o.), and one hour after of the esculetin administration the injury was induced with ethanol. The study was approved by ethics committee for Animal Experiment, Department of Physiology and Pharmacology, Faculty of Medicine, Federal University of Ceará, Brazil, with protocol number, 40/09. **Results and Discussion:** Esculetin in all doses was able to protect the gastric mucosa from ethanol in 71,8% and 72,6%, respectively, with $p < 0,001$. The gastroprotective mechanism of esculetin was analyzed at the dose of 25 mg/kg. The animals pretreated with the antagonists were able to revert, significantly, the gastroprotection promoted by esculetin. In conclusion, gastroprotective effect on ethanol-induced ulcer promoted by esculetin may be associated with stimulation of endogenous prostaglandins, nitric oxide synthesis and K_{ATP} channels. **Financial support:** CAPES and CNPq

07.003

Gastroprotection effect of the umbelliferone (7-hydroxycoumarin) in mice and possible mechanisms. Silva AH¹, Rios ERV², Venâncio ET², Rocha NFM², Linhares MI², Moura BA², Feitosa ML², Cerqueira, GS², Leal LKAM¹, Fonteles MMF³ ¹UFC - Farmácia, ²UFC - Fisiologia e Farmacologia, ³UFC- Farmácia, Fisiologia e Farmacologia

Introduction: Umbelliferone (7-hydroxycoumarin) is a coumarin derived that has taken a considerable interest due to its diverse bioactivity. The aim of this work was to evaluate the gastroprotective action of umbelliferone on ethanol-induced ulcer model in mice in order to investigate the pharmacological mechanisms involved. The study was submitted to Ethic Committee in animal research of UFC (protocol number: 40/09). **Methods:** Swiss mice, weighing 25-35g, were administered with coumarin (25 and 50 mg/kg, p.o) and after induced ulcer using ethanol, 0.2 mL/animal, p.o. The gastroprotective mechanism was analyzed at to dose of 25 mg/kg pretreated with L-NAME (10 mg/kg i.p.), a nitric oxide synthesis inhibitor, glibenclamide (10 mg/kg i.p.), a K_{ATP} channel blocker, or indomethacin (10 mg/kg p.o.), a prostaglandins synthesis inhibitor. **Results and Discussion:** The oral administration of coumarin in both doses was able to protect the gastric mucosa from ethanol in 69,8 and 68,4%, respectively, with p<0,001. The gastroprotective effect of the umbelliferone was significantly antagonized, suggesting a role for nitric oxide and demonstrating a likely activation of K_{ATP} channels in its gastroprotection, besides, may also be associated with stimulation of endogenous prostaglandins. **Financial support:** CAPES and CNPq

07.004

Study of the esculetin (6,7-dihydroxycoumarin) on ulcer-induced models in mice: gastroprotective effect? Silva AH¹, Rios ERV², Venâncio ET², Rocha NFM², Linhares MI², Moura BA², Feitosa ML², Cerqueira, GS², Leal LKAM², Fonteles MMF³ ¹UFC - Farmácia, ²UFC - Fisiologia e Farmacologia, ³UFC- Farmácia, Fisiologia e Farmacologia

Introduction: Coumarin compounds from natural origin have been utilized as therapeutic agents in humans presenting different bioactivities. Particularly, esculetin, 6,7-dihydroxycoumarin, a coumarin derived, has been investigated as antiinflammatory. This way, the objective of our work was to evaluate, for the first time, the gastroprotection activity of esculetin in animals. Methods: We used the model of gastric injury promoted by absolute ethanol (0.2 mL/animal) and by indomethacin (20mg/kg) in Swiss mice, as described in the project submitted to ethic committee in animal research of UFC (protocol number: n° 40/09). In the model with absolute ethanol, the injury was measured, in the glandular face, utilizing the program ImageJ and expressed in percentage of the total gastric area. Results and Discussion: Esculetin, (25 and 50 mg/kg, p.o) reduced, significantly $p < 0.001$, the injury in 71.8 and 72.6%, respectively, in the similar way to reduction observed with cyproheptadine (10mg/kg, p.o.), a serotonergic and histaminergic not selective antagonist (77.6%; $p < 0.001$). In the model of ulcer induced by indomethacin, the injury was measured using a scale of arbitrary points. Esculetin, in both doses, also reduced, significantly, the injury (52.7 and 40.4%, respectively; $p < 0.001$), similarly observed with ranitidine, an antagonist histaminergic H₂, in this experiment (28.4%; $p < 0.05$). In conclusion, according to our findings, results suggests a gastroprotective effect of esculetin, in both doses analyzed, against the gastric injury caused by ethanol and by indomethacin in mice. Financial support: CNPq and CAPES

07.005

Umbelliferone (7-hidroxicoumarin) promoted gastroprotection in models of gastric injury in mice. Rios ERV¹, Venâncio ET¹, Rocha NFM¹, Linhares MI¹, Feitosa ML¹, Moura BA¹, Silva AH², Cerqueira, GS¹, Leal LKAM², Fonteles MMF³ ¹UFC - Fisiologia e Farmacologia, ²UFC - Farmácia, ³UFC- Farmácia, Fisiologia e farmacologia

Introduction: Umbelliferone (7-hidroxicoumarin) is a coumarin derived that has been investigated as potential therapeutic agent in humans. In this context, we aimed to study its action as gastroprotector in animal models of gastric injury, using the ethanol-induced and indomethacin-induced ulcer model. **Methods:** We used Swiss mice, 25-35g, administered with umbelliferone in the doses of 25 and 50 mg/kg, p.o. In the model with absolute ethanol (0.2 mL/animal), the injury was measured, in the glandular face, utilizing the program ImageJ and represented by percentage of the total gastric area. In the model of ulcer induced by indomethacin (20mg/kg), the injury was measured using a scale of arbitrary points. The study was approved by ethics committee for Animal Experiment, Department of Physiology and Pharmacology, Faculty of Medicine, Federal University of Ceará, Ceará, Brazil, with protocol number, 40/09. **Results and Discussion:** In this experiment umbelliferone, in both doses, reduced significantly, $p < 0.001$, the injury caused by ethanol in 69.83 and 68.4%, respectively. Similar effect was observed with cyproheptadine 10mg/kg p.o, a serotonergic and histaminergic not selective antagonist (77.6%; $p < 0.001$). Umbelliferone, in this test, also reduced, significantly $p < 0.05$, the injury in 31.6 and 23.2%, in both doses, similarly to the protector effects demonstrated by ranitidine, an antagonist histaminergic H₂ (percentage of gastroprotection = 28.4%; $p < 0.05$). In conclusion, the results obtained suggest a gastroprotector effect of umbelliferone, in both doses studied, in the gastric injury model caused by ethanol and indomethacin in mice. **Financial support:** CAPES and CNPq

07.006

Comparative effect of mammalian (bovine) phospholipase A₂ (PLA₂) versus snake venom secretory sPLA₂ in the development of an experimental model of pancreatitis in the rat. Silva CI¹, Camargo E², Teixeira SA¹, Muscará MN¹, Costa SKP¹ ¹ICB-USP - Farmacologia, ²UFS – Fisiologia

Introduction: previously, members of our group showed that snake venom secretory phospholipases (sPLA₂) produced a model of acute pancreatitis in the rat, and the catalytic activity is not essential to induce the local effects in the pancreas¹. By comparison, it has been shown that high levels of PLA₂ are found in patients with acute pancreatitis². We have now attempted to model and compare the signs and possible mechanisms seen previously in the pancreatitis model using a different PLA₂ isolated from mammalian (bovine) pancreas. **Methods:** male Wistar rats (250-300g) were used, and all experimental protocols were performed under approval of the CEEA/USP (n^o 055 pg 44 book 2). Briefly, animals were anaesthetized with isoflurane in oxygen (2:3), and either the injection of bovine PLA₂ (300 mg/kg) or sPLA₂ from *Crotallus durissus terrificus* (Cdt; 300 mg/kg) venom was carried out in the rat common bile duct. Following 4 hours period interval, the rats were killed and some pancreatitis biomarkers such as pancreatic oedema (plasma protein extravasation), histopathological changes, myeloperoxidase (MPO) activity and serum amylase levels were evaluated. The intensity of mechanical hyperalgesia in the upper abdominal region was also determined prior and at 4 h post PLA₂ injection using a modified (electronic) von Frey device. **Results:** as seen with the snake Cdt venom sPLA₂, the injection of bovine PLA₂ evoked a significant increase of serum amylase activity (440 ± 66 U/L; n=7) compared with control group injected with saline (177 ± 25 U/L; n=8). In contrast to data produced by snake Cdt venom sPLA₂, there was no statistical difference in the plasma extravasation seen in the pancreas of rats injected with bovine PLA₂ as compared to control group (data not shown; n=5-6), but a marked increase of oedema index (dry weight/wet weight) was observed in the pancreas of rats injected with bovine PLA₂ (6.1 ± 0.1 mg; n=5) compared with saline group (4.7 ± 0.1 mg; n=6). Furthermore, increased MPO activity (4.2 ± 1.1 UMPO/mg; n=5) in association with intense pancreatic tissue neutrophilia was observed in the group of rats treated with bovine PLA₂ when compared with saline group (2.1 ± 0.7 UMPO/mg; n=6). Both the snake sPLA₂- and the bovine PLA₂-induced pancreatic inflammatory signs were accompanied by early abdominal hyperalgesia as compared with saline-injected group (not shown; n=5). **Conclusions:** bovine PLA₂, similar to Cdt venom sPLA₂, produces pain associated with inflammatory signs of acute pancreatitis in the rat. Thus, the current model of pancreatitis evoked by mammalian PLA₂ offers a new tool in the investigation of pain associated with inflammatory signs commonly seen in pancreatitis. **Acknowledgments:** FAPESP, CNPq e CAPES. **References:** 1. Camargo EA et al. *Toxicon*. 2005 Dec 15;46(8):921-6. 2. Formela LJ et al. *Br J Forme Surg*. 1995 Jan 82(1):6-13.

07.007

Irinotecan (CPT-11)- induced mucositis delays gastric emptying of liquids in awake mice. Filho Belarmino JN, Vale J, Botelho KP, Nunes NG, Silva LR, Miranda SP, Soares PMG, Medeiros J-VR, Lima-Júnior RCP, Ribeiro RA, Souza MHLP UFC - Fisiologia e Farmacologia

Introduction: Intestinal mucositis (IM) is a common side-effect of Irinotecan (CPT-11), a topoisomerase I inhibitor used to colorectal cancer treatment. During chemotherapeutic treatment, 70% of oncological patients present IM, with severe diarrhea (grades 3-4) in 15-25%. Data recently published (Soares et al. Cancer Chemother Pharmacol., 63(1):91-8, 2008) report a delay in gastric emptying during 5-fluorouracil- induced mucositis. However, there is not any study concerning the effect of CPT-11 on gastrointestinal motility **Aims:** To study the gastric emptying of liquid in CPT-11- induced mucositis in mice. **Methods:** Swiss mice (n=36) received saline (5 mL/kg, i.p) or CPT11 (75 mg/kg, i.p.) for 4 days. On the seventh day later the first injection, the animals, had diarrhea assessed. Then, phenol red (PR, 0.75 mg/mL, 300 μ L) by gavage was administrated and mice were sacrificed by cervical dislocation 10, 20 e 30 min later. The stomach and intestinal portions were collected, processed with NaOH 0.1N to the measurement of PR concentrations and determination of gastric emptying (retention fraction %) by spectofotometry (540 nm). Statistical analysis was performed with t-Student or Kruskal Wallis/Dunn as appropriate. Statistical significance was set at $p < 0.05$. (CEPA: Protocol 63/09). **Results:** CPT-11 induced significantly ($p < 0.05$) diarrhea (median= 3[2-3]) compared with saline group (median= 0 [0-0]). In all of post- prandial intervals, CPT-11 increased significantly ($p < 0.05$) the gastric retention (10 min= $67.26 \pm 3.39\%$; 20 min= $77.89 \pm 1.27\%$; 30 min= $66.67 \pm 5.43\%$) compared with saline treated group (10 min= $46.08 \pm 3.60\%$; 20 min= $36.82 \pm 5.15\%$; 36.82%; 30 min= $33.44 \pm 4.99\%$). **Conclusions:** CPT-11 induced significant functional alterations on the gastrointestinal tract seen through diarrhea associated with delay in gastric emptying. These findings merit further investigations and additionally provide perspectives on the development of future studies concerning the mechanisms involved in such dysfunction. **Financial support:** CAPES/CNPq.

07.008

Efeito cicatrizante do extrato etanólico bruto e fase clorofórmica de *Praxelis clematidea* sobre úlcera gástrica crônica. Falcão HS, Mendes JM, Barbosa Filho JM, Batista LM UFPB - Ciências Farmacêuticas

Introdução: A úlcera gástrica é uma doença crônica de causa multifatorial que se apresenta na forma de lesão necrotizante na mucosa podendo acometer camadas teciduais profundas como a musculatura externa. Estas lesões normalmente cicatrizam-se devido à capacidade de renovação celular do estômago, no entanto falhas neste processo poderão contribuir na reincidência da doença. *Praxelis clematidea* (Griseb.) R. M. King & H. Rob. (Asteraceae) é uma espécie vegetal nativa da América do Sul bastante confundida com espécies do gênero *Ageratum*, as quais são indicadas para tratamento de inflamações pela população, e foi selecionada para o presente estudo por critério quimiotaxonômico, ou seja, presença de flavonóides que são metabólitos com potencial antioxidante, antiinflamatório e antiulcerogênico. Portanto, o objetivo deste trabalho foi investigar a atividade antiulcerogênica de *P. clematidea*, quanto ao efeito cicatrizante sobre úlcera gástrica crônica. **Métodos:** Foram utilizados o extrato etanólico bruto (EEtOH) e a fase clorofórmica (FCHCl₃) obtidos das partes aéreas de *P. clematidea*, administrados oralmente nas doses de 500 e 125 mg/kg, respectivamente, a ratos Wistar machos (n=7) ulcerados com ácido acético 30 % (Takagi et al., JPN J Pharmac, 19, 418, 1969). O efeito cicatrizante foi avaliado após 14 dias de tratamento com as amostras vegetais, cimetidina 100 mg/kg (controle positivo) e solução tween 80 a 12% (controle negativo). A área de lesão ulcerativa (ALU) dos estômagos de cada grupo avaliado foi determinada e expressa como média ± d.p. após ANOVA seguida do pós-teste Dunnett ($p < 0,05$). Este protocolo experimental faz parte de um projeto aprovado pelo Comitê de Ética em Pesquisa Animal – CEPALTF/UFPB sob o registro de nº. 0209/06. **Resultados e Discussão:** Observou-se que o EEtOH, a FCHCl₃ e cimetidina reduziram significativamente a área de lesão ulcerativa ($21,49 \pm 8,64^{***}$; $28,70 \pm 10,42^{***}$; $26,41 \pm 9,09^{***}$) quando comparados, respectivamente, ao grupo controle negativo ($61,89 \pm 14,79$). Assim, tanto o EEtOH quanto a FCHCl₃ de *P. clematidea* apresentam efeito cicatrizante sobre úlcera gástrica crônica possivelmente por estimular fatores protetores a mucosa gástrica, como acelerar a renovação tecidual, estimular a produção de muco e agir como antioxidante, uma vez que ambas as amostras dependem de compostos sulfidrilicos para promover citoproteção e a FCHCl₃ aumenta a quantidade de muco aderido a mucosa gástrica (Falcão et al., Simponature, análs em cd, 2007). **Agradecimentos:** FAPESQ, CAPES e LTF.

07.009

Investigação da participação do óxido nítrico e grupamentos sulfidrílicos na gastroproteção promovida pela fase acetática de *Praxelis clematidea*. Falcão HS, Mendes JM, Barbosa Filho JM, Batista LM UFPB - Ciências Farmacêuticas

Introdução: A úlcera gástrica é uma doença crônica recorrente caracterizada por lesões inflamatórias e necrotizantes na mucosa do estômago devido ao desequilíbrio entre fatores protetores (muco, bicarbonato, fluxo sanguíneo, prostaglandina, sistema antioxidante endógeno, renovação celular) e agressores endógenos/exógenos (ácido clorídrico estomacal, pepsina, ácidos biliares, antiinflamatórios, estresse e *Helicobacter pylori*). *Praxelis clematidea* (Griseb.) R. M. King & H. Rob. (Asteraceae) é uma espécie vegetal nativa da América do Sul muito confundida com espécies do gênero *Ageratum*, as quais são indicadas para tratamento de inflamações pela população, e foi selecionada para o presente estudo por critério quimiotaxonômico, ou seja, presença de flavonóides que são metabólitos com potencial antioxidante, antiinflamatório e antiulcerogênico. Portanto, o objetivo deste trabalho foi investigar a participação do óxido nítrico e de grupamentos sulfidrílicos na gastroproteção promovida pela fase acetática obtida de *P. clematidea*. **Métodos:** A fase acetática (FAcOEt) obtida das partes aéreas de *P. clematidea* na dose de 62,5 mg/kg foi administrada oralmente a ratos Wistar machos (n=7) após o tratamento intraperitoneal com salina 0,9%, o inibidor da enzima sintase de óxido nítrico (L-NAME 70 mg/kg) ou o bloqueador de grupos sulfidrílicos (N-etilmaleimida 10 mg/kg). A ulceração gástrica foi induzida com etanol absoluto (4 mL/kg, v.o.) (Sikiric et al., Eur J Pharmacol, 332, 23, 1997; Matsuda et al., Eur J Pharmacol, 373, 63, 1999). O índice de lesão ulcerativa (ILU) para os grupos das amostras vegetais, carbenoxolona 100 mg/kg (controle positivo) e solução tween 80 a 12% (controle negativo) foi determinado e expresso como média \pm d.p. após ANOVA seguida dos pós-testes Dunnett e Tukey ($p < 0,05$). Este protocolo experimental faz parte de um projeto aprovado pelo Comitê de Ética em Pesquisa Animal – CEPALTF/UFPB sob o registro de nº. 0209/06. **Resultados e Discussão:** Nos grupos tratados previamente com salina 0,9%, observou-se que a FAcOEt e carbenoxolona reduziram significativamente o ILU ($94 \pm 35^{**}$; $80 \pm 21^{**}$) quando comparados, respectivamente, ao grupo controle negativo (170 ± 43). Nos grupos tratados previamente com L-NAME ou N-etilmaleimida, a FAcOEt e carbenoxolona reduziram significativamente o ILU ($147 \pm 35^{**}$; $134 \pm 46^{**}$ ou $203 \pm 38^{**}$; $206 \pm 14^{**}$) quando comparados, respectivamente, ao grupo controle negativo (238 ± 56 ou 277 ± 24). Estes ao serem comparados àqueles grupos tratados previamente com salina 0,9% demonstraram que não houve diferença significativa na proteção gástrica quando a síntese de NO foi inibida, no entanto houve uma perda ($p < 0,001$) na proteção quando os grupos sulfidrílicos foram bloqueados. Assim, a gastroproteção apresentada pela FAcOEt de *P. clematidea* provavelmente depende de mecanismos envolvendo os grupamentos sulfidrílicos e não o óxido nítrico. **Agradecimentos:** FAPESQ, CAPES e LTF.

07.010

A influência dos esteróides anabolizantes sobre a vocalização de ratos treinados fisicamente. Bittencourt MFQP¹, Dong KE¹, Caetano AL¹, Andrada e Silva MA², Buck HS¹ ¹FCMSCSP - Ciências Fisiológicas, ²FCMSCSP - Distúrbio da Comunicação Humana

Introdução: Os esteróides anabolizantes são derivados sintéticos da testosterona (hormônio sexual masculino). Ela é responsável pelas mudanças e crescimento do sistema reprodutivo e características sexuais secundárias do homem. Os efeitos anabólicos da testosterona envolvem, entre outros, aumento da laringe e das pregas vocais (PPVV), aumento de massa e da força dos músculos esqueléticos. Efeitos semelhantes foram observados também em ratos, inclusive alterações morfológicas e histológicas da laringe. O objetivo desse estudo foi determinar a influência do uso de esteróides anabolizantes associados a prática de exercício físico sobre a vocalização de ratos. **Métodos e Resultados:** Para avaliar o efeito dessas substâncias na funcionalidade das pregas vocais, 32 animais foram divididos em quatro grupos (o grupo sedentário (controle)- GS, grupo treinado- GT, e sedentário anabolizado- GSA e grupo treinado anabolizado- GTA). Esse trabalho foi submetido ao Comitê de Ética em Pesquisa Animal da Faculdade de Ciências Médicas da Santa de São Paulo sendo aprovado sob o número 180. Os grupos GT e GTA foram submetidos a um treinamento físico moderado em esteira. Os animais dos grupos GTA e GSA, receberam doses semanais de esteróide anabolizante (por onze semanas). Para este experimento, as vocalizações dos animais foram registradas quinzenalmente (Avisoft-Lab Pró e Avisoft Recorder). Os dados obtidos foram comparados com os respectivos controles. Para os valores de frequência máxima (a maior frequência que o animal atingiu no total de sua produção), frequência mínima (menor valor obtido no total da vocalização do animal) e frequência fundamental não foram observadas diferenças na comparação entre os grupos. Porém observou-se diferença significativa ($P < 0,05$) para os valores de duração média da vocalização, os animais treinados e anabolizados apresentaram vocalizações mais curtas em relação ao grupo controle. **Conclusão:-** Esse dado sugere que por apresentarem possível aumento de massa nas PPVV, os animais não conseguiram manter o mesmo tempo fonatório quando comparados aos controles, esse estudo, indica a necessidade de uma análise morfométrica das PPVV dos animais tratados e controles. Podemos ainda inferir que os animais que não conseguiram manter o mesmo tempo fonatório, não tiveram nenhum tipo de mudança nas frequências atingidas. Mostrando assim a importância, para que haja comunicação, em manter as mesmas frequências que os animais do grupo controle. Apoio financeiro: FAP- FCMSCSP e CAPES- PROSUP

07.011

Involvement of nitric oxide and potassium channels in the mechanism of the gastroprotection action of 1,4-cineole in animal models of gastric ulcer. Feitosa ML, Gomes, PB, Venâncio ET, Rios ERV, Moura BA, De Sousa DP, Sousa FCF UFC - Fisiologia e Farmacologia

Introduction: 1,4-Cineole is a monoterpene ether, widely distributed, which is one of the flavor constituents of lime juice. The aim of this study was to evaluate the mechanism of the gastroprotection effect of 1,4-cineol in animal models of gastric injury. This work was submitted to Ethic Committee in animal research of UFC (protocol number: 64/09). **Methods:** Swiss mice, weighing 25-35g were administered with 1,4-cineole in ulcer model using ethanol, 0.2 mL/animal, p.o. The injury was measured, in the glandular face, utilizing the program ImageJ and represented by percentage of the total gastric area. The gastroprotective mechanism of 1,4-cineole was analyzed at the dose of 200 mg/kg. Before 1, 4- cineole administration, the animals were pretreated with L-NAME (10 mg/kg i.p.), an oxide nitric synthesis inhibitor, and, in other group, with glibenclamide (10 mg/kg i.p.), a K_{ATP} channel blocker. **Results and discussion:** 1,4-cineole significantly protect the gastric ulcer induced by ethanol (3.46 ± 0.89 , $p < 0.001$) when compared with control (20.73 ± 2.60), however this effect wasn't antagonized by L-NAME (1.88 ± 0.63 , $p < 0.001$) or glibenclamide (2.48 ± 1.39 , $p < 0.001$), suggesting that the mechanism of 1,4-cineole isn't involved with nitric oxide synthesis or with the K_{ATP} channels. Other experiments will be performed to clarify its mechanism. **Financial support:** CNPq and FUNCAP

07.012

Evaluation of the gastroprotection activity of 1,4-cineole in animal model of gastric ulcer. Feitosa ML, Gomes, PB, Rios ERV, Venâncio ET, Moura BA, De Sousa DP, Sousa FCF UFC - Fisiologia e Farmacologia

Introduction: 1,4-Cineole, an analog of 1,8-cineole, is a natural monoterpene ether present in lime juice. The aim of this work was to evaluate the gastroprotective action of 1,4-cineole on ethanol-induced ulcer model in mice in order to investigate the pharmacological mechanism involved. The study was submitted to Ethic Committee in animal research of UFC (protocol number: 64/09). **Methods:** Swiss mice, weighing 25-35g, were pre-treated with 1,4-cineole (100 and 200 mg/kg, p.o.). Sixty minutes after that, ethanol were administered (0.2 ml/animal, p.o.). Thirty minutes later, the animals were sacrificed; the stomachs were removed, opened by the great curvature, washed with 0.9% saline and the gastric ulceration were analyzed. The total areas and the areas of injured stomachs (glandular face) were determined by planimetry. The injured area is expressed as a percentage on the total area of the gastric body. **Results and Discussion:** The oral administration of 1,4-cineole at dose of 200 mg/kg was able to protect the gastric mucosa from ethanol in 76.09%, with $p < 0.001$, compared to control. Similar effect was observed with cyproheptadine 10mg/kg p.o, a serotonergic and histaminergic not selective antagonist (77.6%; $p < 0.001$). The results obtained suggest a gastroprotector effect of 1,4-cineole, however more studies has to be done to identify its mechanism. **Financial support:** CNPq, FUNCAP

07.013

Efeito da infecção por *Helicobacter pylori* na resposta imune de animais ulcerados por ácido acético. Souza MC, Beserra AMSS, Silva RM, Martins DTO UFMT - Ciências Básicas em Saúde

Introdução: O *Helicobacter pylori* (*H. pylori*) é o principal agente etiológico da úlcera péptica, sozinho ele causa pequeno ou nenhum efeito na mucosa gástrica intacta de ratos, porém é capaz de retardar a cicatrização de úlceras pré-existentes. A infecção por *H. pylori* desencadeia um processo inflamatório o qual pode ser avaliado através da dosagem das citocinas inflamatórias presentes neste quadro, onde ocorre o aumento de múltiplas citocinas na mucosa gástrica, no entanto induz também a produção de citocinas imunoreguladoras que atuam em limitar a resposta inflamatória. O objetivo deste trabalho foi avaliar o efeito da infecção por *H. pylori* na expressão das citocinas IL-1 β , IL-10, TNF- α e VEGF em animais ulcerados com ácido acético.

Métodos: O Projeto de Pesquisa foi aprovado pelo Comitê de Ética em Pesquisa Animal (CEPA/UFMT), de acordo com os Princípios Éticos na Experimentação Animal adotados pelo Colégio Brasileiro de Experimentação Animal (COBEA), protocolo nº 23108.002841/08-4. Os animais foram ulcerados com administração de 30 μ L de ácido acético a 20% na camada subserosa da parede anterior da porção glandular do estômago, após 24h foi inoculado *Helicobacter pylori* ATCC 43504 9×10^8 por 7 dias. As citocinas IL-1 β , IL-10, TNF- α e VEGF foram determinados no plasma dos animais, sendo o procedimento realizado pela empresa Gênese, utilizando o Kit plex de citocinas e quimiocinas de ratos (cat. RCYTO-80K), equipamento Luminex.

Resultados: Nos animais ulcerados por ácido acético sem *H. pylori* a expressão das citocinas IL-1 β , IL-10, TNF- α e VEGF foram de $0,218 \pm 0,16$; $9,25 \pm 3,36$; 0 e 0, enquanto no grupo ulcerado por ácido acético e inoculados com *H. pylori*, os níveis foram de $0,620 \pm 0,25$; $20,02 \pm 7,90$; 0 e 0, respectivamente. **Discussão:** Os níveis das citocinas IL-1 β , TNF- α e VEGF não diferiram entre os dois grupos analisados, no entanto, os níveis da citocina IL-10 estavam elevados no grupo com úlcera gástrica inoculados com *H. pylori*, mostrando que havia um processo de cronificação da úlcera gástrica, o que levou a um retardo na cicatrização da úlcera induzida por ácido acético. Embora a secreção de IL-10 na infecção por *H. pylori* seja protetora por inibir a resposta imune mediada por células, a limitação do dano tecidual causado pela inflamação pode contribuir com a falha da resposta imune em eliminar este microorganismo. FAPEMAT; CPP; CAPES; FIOCRUZ; SES-MT.

07.014

Hydrogen sulphide (H₂S) accelerates gastric emptying of liquid in awake mice: role of K_{ATP} channels and TRPV1 receptors. Bezerra VH¹, Medeiros J-VR², Soares PMG³, Lucetti LT¹, Barbosa ALR², Souza MHLP¹, Cunha FQ⁴ ¹UFC - Fisiologia e Farmacologia, ²UFC/UFPI - Fisiologia e Farmacologia/Biologia, ³UFC - Morfologia, ⁴FMRP-USP

Introduction/Aim: H₂S is formed in mammalian cells by the activity of two enzymes: cystathionine γ -lyase (CSE) and cystathionine β -synthetase (CBS) (Moore *et al.*, 2003). Similarly to other gaseous mediators (nitric oxide and carbon monoxide), H₂S has effects in the contractility of gastrointestinal muscles (Teague B *et al.*, Br J Pharmacol. 2002 Sep;137(2):139-45). The aim of this study was to evaluate the mechanism for which the H₂S increases the gastric emptying of liquids in awake mice. **Methods:** Swiss mice, (20-30g), previously fasted for 24h, were treated with: saline (control), and NaHS (H₂S donor, 5, 15 e 50 μ mol/kg, i.p). For other experiments, mice were pre-treated with glibenclamide (K_{ATP} channels blocker) or capsazepine (TRPV1 antagonist). Afterwards, mice received NaHS (50 μ mol/kg, i.p). After 30 minutes, mice were gavage-fed (1.5ml) with the test meal (5% glucose solution with 0.05g/ml phenol red). Twenty minutes later, mice were sacrificed and the gastric dye recovery was measured by spectrophotometry. Data were analyzed using One-Way ANOVA and Newman-Keuls test. All animal treatments and surgical procedures were approved by the local ethics committee (protocol No 63/07). **Results:** Treatment with H₂S donor significantly ($p < 0.05$) decreased the gastric retention (NaHS 50 μ mol/kg = $27.75 \pm 3.75\%$, N=6) as compared to vehicle-treatment (saline = 46.7 ± 1.73 , N= 12). Glibenclamide ($45.04 \pm 3.27\%$, N=6) and capsazepine ($42.98 \pm 2.56\%$, N=6) reversed the NaHS ($27.75 \pm 3.75\%$, N=6) effect in the gastric retention. **Discussion:** Hydrogen sulphide (H₂S) accelerates gastric emptying of liquids in awake mice by activation of K_{ATP} channels and TRPV1 receptors. **Financial Support:** CNPq, FUNCAP.

07.015

Involvement of prostaglandin in the mechanism of the gastroprotection promoted by 1,4-cineole in animal models of gastric ulcer. Siqueira RMP¹, Feitosa ML¹, Gomes PB¹, Venâncio ET¹, Moura BA¹, Rios ERV¹, De Sousa DP², Sousa FCF¹ ¹UFC - Fisiologia e Farmacologia, ²UFS - Departamento de Fisiologia

Introduction: 1,4-Cineole is a monoterpene ether, widely distributed in the vegetal kingdom, which is one of the flavor constituents of lemon juice. The aim of this study was to evaluate the possible involvement of prostaglandin of the gastroprotection effect of 1,4-cineol in animal models of gastric injury with ethanol absolute. This work was submitted to Ethic Committee in animal research of UFC (protocol number: 64/09).

Methods: Swiss mice, weighing 25-35g were administered with 1,4-cineole in ulcer model using ethanol, 0.2 mL/animal, p.o. The injury was measured, in the glandular face, utilizing the program ImageJ and represented by percentage of the total gastric area. The gastroprotective mechanism of 1,4-cineole was analyzed at the dose of 200 mg/kg, before 1,4- cineole administration, the animals were pretreated with Indomethacin (10 mg/kg i.p.), COX inhibitor. **Results and discussion:** The gastroprotective effect of 1,4-cineole was significantly reverted by the pre-treatment with indomethacin (Control: 18,59±0,93; Cineole 200: 4,45±1,065; Indomethacin+Cineole 200: 14,29±1,283), suggesting that the mechanism of 1,4-cineole is involved with prostaglandin synthesis. Other experiments will be performed to clarify its mechanism. Financial support: CNPq and CAPES

07.016

Spectrometry for *nondestructive* assessment to characterize the femur mineral contents on androgen deficient and chronic ethanol consuming rats. Lodi KB¹, Soares LES², Santo AME², Rocha RF da¹ ¹FOSJC-UNESP - Biociências e Diagnostico Bucal, ²UNIVAP

Introduction Ethanol abuse is correlated with decreased bone mass, increase of fracture risks and, should a fracture occur, may impair bone healing. Overall, fractures in alcoholics are associated with longer hospitalization and increased mortality. Up to 50% of ambulatory chronic alcoholics demonstrate evidence of bone loss. Although ethanol affects various biochemical processes such as neurotransmitter release, enzyme function, and ion channel kinetics, we are only beginning to understand the specific action on ions and the consequence in their functions. The aim of this study was to investigate the effect of these two variables, androgen deficient and chronic ethanol consuming, on femur mineral contents. **Methods** Wistar rat (n=54) were divided in orchietomy (ORQ) or SHAM-operated and subdivided in 6 groups by diet: ethanol/ORQ, free-diet/ORQ, pair-feed/ORQ, ethanol/SHAM, free-diet/SHAM and pair-feed/SHAM. They were daily fed with a Lieber–DeCarli diet model for 8 weeks long. The controls groups were free-diet and pair-fed. Ca and P were analyzed by μ X-ray fluorescence (μ EDX) and FT-Raman on the same femur area. This study was approved by the FOSJC-UNESP Research Ethics Committee (n° 0 37/2007-PA/CEP). **Results** Spectrometry μ EDX indicated a decrease in bone Ca content in ORQ groups, mainly for ethanol groups. Phosphorus content and Ca/P molar ratio, otherwise, doesn't diverge in all 6 groups. Ethanol consumption impaired Ca and P homeostasis in ORQ rat more than SHAM. The results showed lower intensities for the ν_4 PO₄³⁻ vibrations (580 cm⁻¹ and its shoulder at 610 cm⁻¹) in specimens of ethanol/ORQ and ethanol/SHAM than the other groups. The amide I peak intensity at 1660 cm⁻¹ was more intense in ethanol/ORQ and free-diet/ORQ groups. Changes in bone mineral contents also can correspond to changes in tissue organization, the cross-linking of the collagen component and the amount of collagen. These disturb of mineral contents and the increase in amide I (one of the bone matrix band markers for the collagen backbone), has important role in the bone quality. The present study also demonstrates, by μ ED-XRF spectrometry, that P value increases with ethanol consume in ORQ animals (11.67±1.96) and SHAM group (12.01±0.62). By comparing Ca values, we observed a decrease in ethanol/ORQ (17.99±2.95) when compared to free-diet/ORQ (22.61±1.71) and no significant increase in ethanol/SHAM (20.30±2.32) group when compared to free-diet/SHAM (19.41±5.90) and pair-feed/SHAM (17.79±3.64). **Discussion** Osteoporosis in men is usually underdiagnosed and the consequences of the fracture can be more severe. The relationships among ethanol consume and androgen deficit support the hypothesis that ethanol affects the mineral-regulating hormones and may mediate some effects on bone. These findings demonstrate that ethanol seemed to interfere with the normal compensatory response to these Ca and P levels, and is more significant in androgen deficiency rats. Recent observations seem to confirm our results that ethanol can lead to a decrease estrogen in the liver, studies with male rats and high alcohol consumption have seen changes also in the aromatization of androgens hormones, reduce in testosterone and an increase of estradiol resulting in BMD loss. This work was supported by FAPESP and CNPq.

07.017

Avaliação funcional do sulfeto de hidrogênio (H₂S) em camundongos. Medeiros J-VR¹, Bezerra VH², Barbosa ALR³, Lucetti LT², Magalhães PJC², Soares PMG⁴, Cunha FQ⁵, Souza MHL², ¹UFPI - Biologia, ²UFC - Fisiologia e Farmacologia, ³UFPI - Fisioterapia, ⁴UFC - Morfologia, ⁵FMRP-USP

Introdução: O H₂S é hoje considerado uma molécula importante para a regulação do calibre dos vasos sanguíneos, além de atuar como gasomediador em diversos órgãos, principalmente no sistema nervoso e no trato gastrointestinal. Recentemente, o H₂S também foi considerado como modulador chave nos processos imunes e inflamatórios. Contudo, vários aspectos da fisiologia do H₂S permanecem desconhecidos. O objetivo deste estudo foi avaliar o efeito do NaHS, um doador de H₂S, na contratilidade gástrica normal e na capacidade secretora da mucosa gástrica. **Métodos:** Camundongos (Swiss) machos foram manipulados de acordo com os princípios éticos que regem o uso de animais de experimentação e foram aprovados pelo comitê de ética local (protocolo N° 63/07). Foi usado imunohistoquímica para detectar as enzimas produtoras de H₂S (cistationina γ-liase (CSE) e cistationina β-sintase (CBS)). Para avaliação contrátil, tiras longitudinais do fundo do estômago com aproximadamente 1 cm foram retiradas e montadas em uma câmara muscular contendo solução fisiológica de Tyrode (pH 7.4, a 37°C e aerados com 95% de O₂ / 5% de CO₂). As medidas de contratilidade foram obtidas através de um transdutor de força isométrica acoplado a um sistema de aquisição de dados (Chart 4.2). Como protocolo experimental, utilizou-se inicialmente uma solução contraturante de KCl (controle, contração correspondente a 100%), após lavagem com a solução Tyrode, foi adicionado cumulativamente NaHS na concentração de 1 até 1000 μM. Para estudo da atividade secretora utilizou-se o método descrito por Vissher et al., (1954), onde conteúdo gástrico foi acumulado durante 4 horas e avaliado em termos de volume secretado, pH e acidez total. **Resultados:** Observou-se intensa imunomarcagem para as enzimas CSE e CBS nas células zimogênicas. O NaHS foi capaz de induzir um aumento no tônus basal que se iniciou na concentração de 30 μM (19,51 ± 11,99%), continuando aumentado na concentração de 100 μM (27,21 ± 13,54%), sendo máximo na concentração de 300 μM de NaHS (50,63 ± 15,14%) em relação à contração controle de KCl (100%; 0,53 ± 0,08g). Contudo, em concentração maiores (1000 μM) o NaHS apresentou efeito relaxante que foi eficaz em restaurar o tônus basal espontâneo. O NaHS não interferiu no volume total de secreção gástrica, pH ou acidez total. **Discussão:** Esse estudo confirma que CSE e CBS são produzidos na mucosa gástrica normal e sugere que o H₂S apresenta um efeito bifásico no músculo liso do fundo gástrico de camundongos.

07.018

Evaluation of ileal reactivity of *mdx* (dystrophic) mice submitted to long-term moderate exercise. Alves GA¹, Rosa EF¹, Aboulafia J¹, Souccar C², Nouailhetas VLA¹ - ¹UNIFESP - Biofísica, ²UNIFESP - Farmacologia

Introduction: Duchenne's muscular dystrophy (DMD) is an X-linked pathology that can be characterized by the lack of the protein dystrophin (427 kDa isoform) that links cytoskeleton to sarcolemma, which avoids cell membrane disruption during skeletal muscle contraction. Moreover, there is clinical evidence that dystrophies may cause intestinal pseudoobstruction. We investigated an animal model that reproduces some features of the disease, the *mdx* mice that was originated after a spontaneous mutation in C57Bl/10 strain. Recent findings from our group have shown that ileum reactivity relative to muscular layer thickness is abnormally increased in *mdx* mice (data not published). As physical exercise has been investigated as a possible contributor to the well being of DMD patients, we now investigated whether *mdx* mice submitted to a long-term moderate exercise program could avoid the intestinal functional changes caused by the dystrophic condition. **Methods:** Animals were divided in four groups (n = 6 in each group): control C57Bl/10 sedentary (CT SED), control exercised (CT EX), *mdx* sedentary (MDX SED) and *mdx* exercised (MDX EX). Exercise protocol consists of a 30-min treadmill running session, three times a week at 50% of the maximal velocity for six months (from 3 to 9 months old). Maximal velocity for each animal was previously determined by the performance of a maximal incremental test. Sedentary animal groups were only submitted to the corresponding environmental stress. Intestinal contractility was assessed by building-up ileum isometric-contraction-concentration curves through a force transducer connected to a digital 'acquisition & analysis' system in response to KCl-induced electromechanical and carbachol-induced pharmacomechanical signalings. E_{max} (maximum contraction, measured in grams) and EC_{50} (the concentration of drug that elicits half of the maximum response,) parameters were obtained. The statistical analysis was performed by Two-way ANOVA, and a significance level (p) less than 0.05 was considered significant difference. **Results:** No significant differences in EC_{50} between exercised animal groups (CT EX and MDX EX) and sedentary animal groups (CT SED and MDX SED) for KCl and carbachol stimulations were observed. But there was a significant decrease of 12,1% and 18,0% on the E_{max} parameter, in both KCl and CCh-induced contractions, respectively, in exercised groups CT EX and MDX EX in comparison with their corresponding sedentary ones (CT SED and MDX SED). **Discussion and Conclusion:** According to the present findings, a long-term and moderate exercise program seems not to affect the intestinal reactivity caused by the dystrophic condition. However, a final conclusion must await the normalization of the present data relative to muscular layer thickness, which has been shown to be a critical parameter. In addition, moderate exercise protocol reduced intestinal reactivity, causing similar decreases in both electromechanical and pharmacomechanical efficacies also in C57Bl/10 mice, dystrophic or not, thus corroborating our previous results in C57Bl/6 mice. CEP/UNIFESP 0097/2008 **Supported by:** FAPESP

07.019

Rat gastric fundus motility is enhanced after 4 weeks of treadmill training. Bau FR¹, Priviero FBM¹, Gómez-Campos RA², Valgas da Silva CP¹, Antunes E¹, Zanesco A²
¹UNICAMP - Farmacologia, ²UNESP - Educação Física

Background: The impact of physical activity on the gastrointestinal tract is an area of emerging interest. In recent years, interest has focused on the potential benefits of physical activity on the gastrointestinal tract. Data on the effect of exercise on gastrointestinal motility are scarce and mostly indirectly obtained and limited to acute exercise. Thus, this study aimed to investigate the motility of the isolated gastric fundus in rats submitted to 4 weeks of treadmill training. Methods: Male Wistar rats were trained in a treadmill with an intensity of 70- 80% of maximal oxygen consumption, in sessions of 60 minutes, 5 days a week. Animals were anesthetized with urethane and exsanguinated. The gastric fundus was removed and placed in 10 ml organ baths containing warmed Krebs solution and coupled to an isometric transducer. Concentration-response curves were obtained for carbachol (CCh), serotonin (5-HT), sodium nitroprusside (SNP). Electrical field stimulation (EFS) was delivered at supramaximal voltage with train duration of 10 s in the presence or in the absence of L-NAME (100 μ M). Results: Experimental procedures were approved by the Animal Care and Use Committee of the State University of Campinas (Protocol # 1307-1). The potency (pEC_{50}) of CCh was significantly increased after 4 weeks of exercise compared with sedentary rats (6.87 ± 0.03 vs 6.56 ± 0.03 ; $p < 0.001$) while both pEC_{50} and maximal response (E_{MAX}) to 5-HT were enhanced after physical training compared with sedentary group ($pEC_{50} - 7.92 \pm 0.03$ vs 6.15 ± 0.23 ; $p < 0.001$; $E_{MAX} - 65.82 \pm 7.38\%$ vs $24.06 \pm 4.02\%$; $p < 0.05$). In concentration response curves to SNP the pEC_{50} was significantly increased in trained rats comparing to sedentary rats (6.02 ± 0.03 vs 5.23 ± 0.21 ; $p < 0.05$) without affecting the E_{MAX} . Furthermore, EFS produced frequency dependent contractions without any difference between the groups. The treatment with L-NAME did not change EFS-induced contraction in sedentary group but in trained group, there was a significant increase of the contraction at 4 and 8 Hz. Contractile responses to EFS at 4 Hz and 8 Hz before and after the treatment with L-NAME in trained rats were respectively: 4 Hz- $11.82 \pm 2.10\%$ vs $52.90 \pm 9.36\%$, $p < 0.05$; 8 Hz - $31.08 \pm 8.70\%$ vs $75.43 \pm 9.11\%$, $p < 0.05$. Discussion: Four weeks of moderate physical exercise increased contractile responses induced by the muscarinic agonist CCh and 5-HT, although EFS-induced contraction was not changed. Furthermore, EFS-induced contraction was increased after the treatment with L-NAME at small frequencies whereas the potency of SNP was enhanced in trained groups. These results suggest that physical exercise modulates muscarinic, serotonergic and nitrergic signaling pathways in gastric fundus. **Financial Support:** FAPESP