Abstract/Resumen: Objective: To improve prescriptive behavior in medical professionals of a Social Security Institute in Corrientes. A quasi-experimental study was conducted, without a control group. All application forms for extended treatment plans in a Social Service Institute of Corrientes were analyzed during a period of six months before and after an educational intervention during the year 2018-2019. The variables analyzed were: gender, age, diagnoses, prescribed medications, medication errors. To describe the types of errors the taxonomy of Otero Lopez was used. Were analyzed 600 application forms and 293 (49 %) prescription errors were observed during the prescription phase. Seventy seven percent (n= 150) of the patients were male, average age 52 years (range 5-91 years). The most frequent error detected before the intervention was prescription of erroneous medication (99 %) grouped as follows: a) inappropriate medications: meloxicam + glucosamine (5), ranitidine + domperidone (7), ergotamine + ibuprofen + caffeine (6), bromazepam + clebopride + simethicone (2), trimebutin + pancreatin + simethicone (7), denosumab (3), fexubostat (2); omega 3 (10), deproteinized extract of calf blood (2), donepecil (4), memantine (3); b) unnecessary medication: aspirin (15), rosuvastatin (9), omeprazole (8). Post-intervention results: only 4 errors were observed in the 600 application forms: inappropriate medications meloxicam + glucosamine (1), memantine (1), pancreatin + simethicone + trimebutin (1); unnecessary medication: aspirin (2). Through educational intervention an improvement in the prescriptive behavior was observed, especially those medications considered inappropriate, improving patient safety and quality of care.

0612 - CLASSIC HISTAMINE H1 RECEPTOR INVERSE AGONISTS ACTIVATE ERK1/2 PATHWAY AND MODULATE THE TRANSCRIPTION OF INFLAMMATORY GENES

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Abstract/Resumen: Recently, we showed that widely used histamine H1 receptor (H1R) ligands that exert therapeutic actions by blocking the effects of histamine (HA), display positive efficacy concerning receptor desensitization and/or internalization. Now we aimed to investigate whether these processes affect the modulation of pro-inflammatory genes and its relationship with the activation of other signaling pathways independent from G protein. While 3 h (long term) exposure to anihistamines decreased expression of pro-inflamatory genes, when we exposed A549 cells to HA, chlorpheniramine (CHLOR) or diphenhydramine (DIPH) for 10 min (short term) and ligands were removed, ciclooxigenase 2 (COX-2) and interleukin 8 (IL-8) mRNA levels were increased after 2h 50 min (among 40 and 100 % for all ligands, $p<0.05$). Consistently, ERK1/2 phosphorylation levels were increased by HA (373 ± 102 %), CHLOR (95 ± 30 %) and DIPH (56 ± 16 %), $p<0.05$, indicating that they display positive efficacy towards this signaling pathway that has been described to be involved in regulation of both genes. When A549 cells were pre-exposed for 3 h with these ligands and after 1 h recovery, were stimulated with HA for 10 min, we found lower COX-2 mRNA levels compared to those observed without pretreatment (HA 29.5 ± 0.5 %, CHLOR 40.5 ± 16.5 and DIPH 34 ± 8.8 % of reduction, $p<0.05$). We also found lower IL-8 mRNA levels in CHLOR and DIPH pretreated samples (both around 20 % of reduction, $p<0.05$) although no differences were observed in HA pretreated cells. Thus, although short term exposure to antihistamines increase pro-inflammatory genes expression, a prolonged exposure with these ligands diminished it and impaired the increase induced by HA indicating that their anti-inflammatory effects continue despite the ligands being removed. In all, these findings reinforce the biased nature of these ligands and claim for a correct classification, providing evidence for a more rational and safe use of antihistamines.

0630 - THE ANTIALLODYNIC EFFECTS OF INTRATHECALLY APPLIED IMT504 ARE RELATED TO MODULATION OF GLIAL/MICROGLIAL RESPONSES AND OF THE EXPRESSION OF INFLAMMATORY FACTORS IN RATS WITH HINDPAW INFLAMMATION

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Abstract/Resumen: Chronic immune diseases, pathogenic infection, or tissue injury are common medical conditions, often leading to the development of chronic inflammatory pain which is unfortunately difficult to treat and often unresponsive to conventional therapies. We recently showed that the oligodeoxynucleotide IMT504 has remarkable antiallodynic and anti-inflammatory effects upon systemic administration in rats undergoing unilateral hindpaw chronic inflammation. In this study, we addressed if IMT504 intrathecal (i.t.) delivery is capable of modulating mechanical allodynia and its underlying mechanisms of action in the spinal cord. Male Sprague-Dawley rats with complete Freund´s adjuvant (CFA)-induced unilateral hindpaw inflammation, received an acute i.t. injection of IMT504 (2 µg/µl; 10 µl). C-reflex, wind-up and mechanical hyperalgesia were recorded during 72 h after injection. Spinal cords were processed for immunofluorescence or western blot analysis for markers of activated glia and microglia such as fibrillary acidic protein (GFAP) and integrin αM (OX42), toll-like receptor 4 (TLR-4) and NF-B p65 subunit. Intrathecal IMT504 induced a clear reduction in mechanical hyperalgesia starting 1 h and lasting 48 h after administration, in association with parallel progressive reductions in C-reflex and wind-up responses. Furthermore, IMT504 significantly downregulated the expression of GFAP, OX42, TLR4 and NF-B. Altogether, we show that i.t. IMT504 efficiently eliminates inflammatory mechanical hyperalgesia for at least 24 h, in association with a depression in spinal sensitization and reductions in the activation of glia, microglia, and the NF-B and TLR-4 pathways. The exact mechanisms, by which these different events relate to explain the antihyperalgesic effects of IMT504, remain to be demonstrated. However, it could be hypothesized that the net effect of IMT504 are reductions in the synthesis of spinal pro-inflammatory mediators.

0670 - DUAL MODULATION OF GLUCOCORTICOID RECEPTOR ACTIVITY BY HISTAMINE H2 RECEPTOR SIGNALING. INVOLVEMENT OF RAP, ERK AND CAMP.

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Abstract/Resumen: There are reports describing the interaction between membrane G-protein coupled receptor signaling and glucocorticoid receptor (GR) transcriptional activity. We have already reported that the signaling of the G alpha s-coupled histamine H2 receptor (H2r) increased GR transcriptional activity. The aim of the present work was to study the molecular mechanisms of this effect. HEK293 cells were transfected with plasmids coding to H2r, GR and a GR-driven reporter gene TAT3-Luc. While pretreatment with 10 µM amthamine, an H2r agonist which augments cAMP levels, increased dexamethasone (dex)-induced GR activity in a 50 % ($p<0.05$), raising cAMP levels with

25 µM forskolin reduced dex-induced GR activity in a 30 % ($p<0.05$). This discrepancy indicates that H2r regulation of GR activity is not strictly mediated by cAMP pathway, suggesting the involvement of other signaling partners. It has been described that H2r activation with amthamine also triggers ERK1/2 phosphorylation. In fact, treatment with the MEK inhibitor UO126 prevented amthamine potentiation of GR activity, pointing to ERK as a relevant player in the potentiation effect. Moreover, pretreatment with 10 µM of the H2r inverse agonists, famotidine and ranitidine, both of which decrease cAMP levels and increase ERK phosphorylation, boosted dex-induced GR activity to almost the quadruple. Trying to elucidate the role of other signaling proteins, cells were transfected with Rap-GAP, an inactivator of the small G-protein Rap. In this system, amthamine also lost its potentiating effect. The whole of our results points to a dual parallel regulation of the GR transcriptional activity: an inhibitory effect mediated by cAMP and an enhancing effect mediated by Rap and ERK proteins. Considering the co-expression of H2r and GR in several physiological systems and the widespread use of their ligands, the interaction described herein could have an impact on glucocorticoid based therapy and grants further research.

0810 - TREATMENT OF IRRADIATED MICE WITH ORAL RADIOPROTECTOR ATTENUATES INSULT.

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Abstract/Resumen: Ionizing radiation directly affects DNA structure by inducing primarily DNA double strand breaks (DSBs), and secondarily production of reactive oxygen species (ROS) that oxidize proteins, lipids, and also induce several different damages to DNA, like generation of abasic sites and single strand breaks (SSB). Consequently, all these changes induce cell death and mitotic failure. The important use of IR in X ray exams and in radiotherapy and its undesirable effects took us to validate a murine model in order to evaluate DNA damage of X Rays and characterize natural and food supplements compounds with radio mitigation properties. Essiac Genuine tea has been used widely in the homeopathy market as a popular anticancer and antioxidant tonic. Due to the reported ROS scavenging properties of Essiac formula, we evaluate DNA damaged mitigation in 50 male Balb/c mice under 25-100m Sv-Gy, which is an average effective dose received by most X Ray exams during a year of radioimaging services by its personnel. The tea formula resulted in a significant reduction of DNA damaged of mice under the formula evidenced by Comet Assay ($p<0.01$) and acridine orange assay for micronuclei and DNA fragmentation evaluation ($p<0.02$) as well as in a normalization of the complete blood count (CBC). The tea did not show any cytotoxicity at the used doses, glucose and animal weight was similar between treatments. We not only demonstrated that Essiac tea is not toxic and acts as a radioprotector of IR X rays at doses to which are exposed the X ray personnel though we also optimized a murine model for further analysis of other natural compounds and supplements (e.g. Ascorbic Acid).

0819 - ESSENTIAL OILS AS SOURCES OF POTENTIAL ANTHELMINTIC COMPOUNDS TESTED ON THE MODEL ORGANISM CAENORHABDITIS ELEGANS

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Abstract/Resumen: Parasitic nematodes are of major significance as human pathogens and have important economic impact worldwide due to considerable losses in livestock and food crops. Drug treatment of nematode infections are the pillar of worm control in human and veterinary medicine. Due to the appearance of drug resistant nematodes, there is a need of developing novel drugs. As parasitic nematodes are not ideal laboratory animals, the non-parasitic nematode Caenorhabditis elegans, has emerged as a model organism for drug discovery. Essential oils (EOs) are natural products produced by aromatic plants. EOs are complex mixtures that usually contain two or three major phytochemicals, which can be terpenes and/or aromatic compounds. We used paralysis assays of wild-type and mutant C. elegans strain and electrophysiological recordings to identify EO with potential anthelmintic activities, reveal the active components, the target sites and mechanisms of action. We found that EOs belonging to six different orders produced rapid paralysis of C. elegans and we establish the half maximal effective concentration values between 0.02-1.2 percent of EOs. We also found that all EOs inhibit egg hatching. Thus, EOs can mediate both rapid and long-term anthelmintic effects. We determined that trans-cinnamaldehyde (TC), a major component of C. verum EO, produces both paralysis and egg-hatching inhibition. By testing mutant worms, we identified that muscle L-AChR and GABA receptors are EO and TC targets in vivo. Electrophysiological studies from C. elegans cultured muscle cells identified the mechanism underlying the antiparasitic effect. Thus, by modulating two receptors with key roles in worm motility, these EO emerge as novel sources of anthelmintic compounds.

0864 - UNRAVELING THE MOLECULAR MECHANISM OF DII, A NEW ANTHELMINTIC DRUG

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Abstract/Resumen: Nematode parasites cause substantial morbidity to billions of people and considerable losses in livestock and food crops. The repertoire of effective anthelmintic compounds is very limited, as drug development has been delayed for decades. By using C. elegans as a model for parasitic nematodes, we previously identified a new imidazole derivative, diisopropylphenyl-imidazole (DII), as a promising candidate for anthelmintic agent. DII lethal effects rely on a previously unidentified muscle nicotinic receptor (AChR), different from the classical levamisole-sensitive AChR. This novel AChR is composed by UNC-29 (a non-alpha subunit incapable of forming homomeric receptors) and other unidentified subunits. To elucidate its stoichiometry, we performed an initial screening of strains containing null mutations in different AChR subunits. By exposing these animals to DII (600 µm), we found a null mutant in acr-23 (an alpha nicotinic subunit) that is even more resistant to DII than UNC-29 null mutants. Since the mutants used in the initial screening had not been outcrossed to the wild-type (wt), we performed this outcross four times, selecting (by genotyping) those animals that contain the deletion in acr-23. Surprisingly, these outcrossed animals are as sensitive to DII as the wt. Moreover, when we outcrossed the original mutant strain to the wt selecting by their resistance to DII, we obtained animals that contain wild-type acr-23 alleles. This strongly suggests that another mutation, different from acr-23 deletion, causes the DII resistance. The drug resistance of these mutants appears to be DII-specific, as it is as sensitive to the classic anthelmintic levamisole as the wt. We are now focused on determining the gene that underlies this DII resistant phenotype. Parasite resistance to traditional nematocidal drugs has become a global concern. Therefore, the identification of new anthelmintics with novel targets, as DII, is mandatory to circumvent this growing problem.

0955 - NEBIVOLOL AND N-ACETYLCYSTEINE IN A MODEL OF GENETIC HYPERTENSION.