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IN NEUROFARMACOLOGIA

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IL PROMETEO

Bollettino di Dottorato

Direttore: Prof. Filippo Drago

La luce della scienza cerco e 'l beneficio

LUX SCIENTIAE

DOTTORATO
INTERNAZIONALE
DI
NEUROFARMACOLOGIA

Università degli Studi di Catania

Dipartimento di Biomedicina Clinica e Molecolare
Sezione di Farmacologia e Biochimica

Viale Andrea Doria, 6 - Catania

Tel.: +39 095 7384237
Tel.: +39 095.7384238

il_prometeo@email.it
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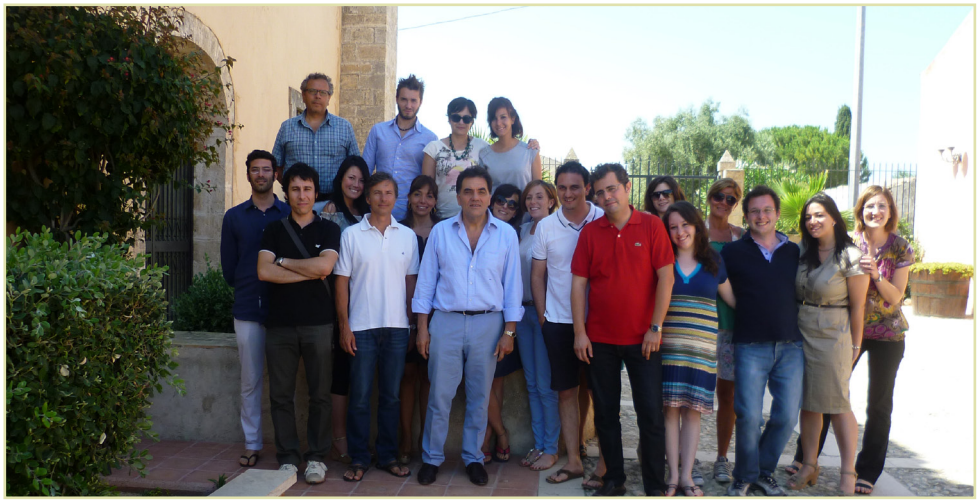
Retreat - Edizione 2012



Come di consueto il 24 giugno di quest'anno, nella stupenda cornice di Villa Giulia sita in Contrada S. Lorenzo a Noto, si è svolto il "retreat" dei dottorandi della scuola di Dottorato in Neurofarmacologia, diretta dal Prof. Filippo Drago. L'obiettivo primario di questo incontro è quello di condividere i risultati ottenuti durante l' attività di ricerca in un contesto informale e conviviale.

Hanno partecipato all'edizione 2012 del "retreat" gli studenti del primo anno (XXVII ciclo), Barbara Di Marco, Giuseppe Grosso, Giulia Malaguarnera e Soraya Scuderi.

Barbara di Marco si è occupata lavoro relativo alla formazione di granuli di stress e sopravvivenza cellulare in Astrociti WT e Fmr1 KO sotto condizioni di stress, nel contesto del progetto di ricerca, sulla Sindrome dell' X-fragile.

Giuseppe Grosso ha presentato una revisione critica delle evidenze scientifiche sull'associazione tra recettori dopaminergici (in particolare i D3) e lo sviluppo di addiction e dipendenza.

Giulia Malaguarnera ha invece presentato un progetto che la vede impegnata nel reclutamen-

to di 165 pazienti diabetici con retinopatia diabetica proliferativa e non da cui verranno dosati i livelli di omocisteina, folati, vitamina B12 e vitamina B6.

Anche la studentessa *Soraya Scuderi* si è occupata di retinopatia diabetica, presentando i risultati preliminari riguardo la capacità dei peptidi PACAP e VIP di ridurre i danni nella barriera emato-retinica indotti dall' iperglicemia e da citochine infiammatorie (e.g. IL-1ß).

Gli studenti del XXVI ciclo di dottorato hanno presentato i risultati ottenuti in questi due anni di corso.

Elisabetta Aloisi, ha presentato un progetto sulla sindrome X-Fragile occupandosi del trafficking di superficie dei recettori mGlu5 nel modello animale della Sindrome del Cromosoma X-Fragile.

Graziana D'Amico ha presentato il suo lavoro su PACAP e VIP, noti per la loro azione protettiva in diversi tipi cellulari sottoposti a stress, incluso le cellule di glioma; il suo lavoro sperimentale consiste nel valutare l'effetto di tali peptidi in cellule coltivate in condizioni normali e deprivate del siero.

Michele Malaguarnera ha esposto il suo lavoro di ricerca riguardo il trattamento dell'encefalopatia epatica con L-acetilcarnitina. Chiara Platania ha presentato i risultati di uno studio di tipo computazionale sulla selettività di ligandi nei confronti dei diversi sottotipi recettoriali del sistema dopaminergico.
Gli studenti del dell'ultimo anno di corso che hanno presentato il proprio lavoro al "retreat" sono *Giovanni Camillieri, Valentina Cicirata, Flora Tomasello e Giulia Treccani.*

Giovanni Camillieri ha presentato i risultati di un progetto che valuta gli effetti dell'antagonismo sul recettore dopaminergico D3 e "gene-delation" dello stesso recettore sull'assunzione di alcol in un modello animale.

Valentina Cicirata ha presentato un lavoro volto a delucidare il meccanismo molecolare correlato al ruolo citoprotettivo del cloruro di litio.

Flora Tomasello ha presentato i risultati di un progetto riguardante il ruolo fisiologico di monomeri di b-amiloide.

Infine *Giulia Treccani* ha parlato dell'effetto indotto da stress acuto e del corticosterone sulla popolazione di vescicole presinaptiche a pronto rilascio in corteccia frontale e prefrontale di ratto.

Vincenzo Urso, medico specializzando in Farmacologia Medica, ha presentato i risultati riguardo all'effetto di ligandi dopaminergici sul tono vascolare, tali risultati sono stati ottenuti utilizzando arterie femorali e mesenteriche di ratti sprague dawley montate su miografo a filo.

ABSTRACT

The role of neutrophils in corneal wound healing in ho-2 null mice

Giuseppina Marrazzo[1, 2], Lars Bellner[1] , Adna Halilovic[1], Giovanni Li Volti[2] , Filippo Drago[3], Michael W. Dunn[1] and Michal Laniado Schwartzman[1*]*

[1]Department of Pharmacology and Ophthalmology, New York Medical College, Valhalla, New York
[2]Department of Drug Sciences Section of Biochemistry, University of Catania, Catania, Italy
[3]Department of Experimental and Clinical Pharmacology, University of Catania, Catania, Italy
[*]Corresponding Authors: Giuseppina Marrazzo and Michal Laniado Schwartzman, Department of Pharmacology, New York Medical College, Valhalla, NY 10595; TEL (914) 594-3560 (GM), or (914) 594-4153 (MLS); FAX (914) 594-4273; E-mail: giuseppina_marrazzo@nymc.edu ; michal_schwartzman@nymc.edu

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ABSTRACT
Our studies demonstrated that Heme oxygenase (HO), in particular, the constitutive HO-2, is critical for a self-resolving inflammatory and repair response in the cornea. Epithelial injury in HO-2 null mice leads to impaired wound closure and chronic inflammation in the cornea. This study was undertaken to examine the possible relationship between HO-2 and the recruitment of neutrophils following a corneal surface injury in wild type (WT) and HO-2 knockout (HO-2-/-) mice treated with Gr-1 monoclonal antibody to deplete peripheral neutrophils. Epithelial injury was performed by removing the entire corneal epithelium. Infiltration of inflammatory cell into the cornea in response to injury was higher in HO-2-/- than in WT. However, the rate of corneal wound closure following neutrophil depletion was markedly inhibited in both WT and HO-2-/- mice by 60% and 85%, respectively. Neutropenia induced HO-1 expression in WT but not in HO-2-/- mice. Moreover, endothelial cells lacking HO-2 expressed higher levels of the Midkine and VE-cadherin and displayed strong adhesion to neutrophils suggesting that perturbation in endothelial cell function caused by HO-2 depletion underlies the increased infiltration of neutrophils into the HO-2-/- cornea. Moreover, the fact that neutropenia worsened epithelial healing of the injured cornea in both WT and HO-2-/- mice suggest that cells other than neutrophils contribute to the exaggerated inflammation and impaired wound healing seen in the HO-2 null cornea.

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Note

Un poster sul seguente studio è stato presentato al Congresso Internazionale ARVO (Association for Research and Visual Science) che si è tenuto a Fort Lauderdale, FL, USA dall'1 al 6 Maggio 2011.

Tin chloride enhances parvalbumin-positive interneuron survival by modulating heme metabolism in a model of cerebral ischemia.

Li Volti G, Zappalà A, Leggio GM, Mazzola C, Drago F, La Delia F, Serapide MF, Pellitteri R, Giannone I, Spatuzza M, Cicirata V, Cicirata F.

Department of Drug Sciences, Section of Biochemistry, University of Catania, Viale A. Doria 6, 95125 Catania, Italy.

ABSTRACT

SnCl(2) has been reported to increase the expression of heme-oxygenase 1 (HO-1), a major antioxidant enzyme, and to decrease ischemic injury, in non-nervous tissues. This study examined the neuroprotective effect of SnCl(2) in the hippocampus of rats submitted to cerebral ischemia. SnCl(2) was administered 18 h before bilateral carotids obstruction. Changes in HO-1 expression and activity, heme content, inducible nitric oxide synthase (iNOS) expression and parvalbumin positive interneuron survival were studied. Thereafter both behavior and memory recovery were tested. The administration of SnCl(2) increased the expression of HO-1 protein and HO activity in the hippocampus and concomitantly decreased heme content at both mitochondrial and nuclear level. Furthermore, ischemized animals showed a strong increase in iNOS expression in the hippocampus, where a loss of parvalbumin positive interneurons also occurred. Pre-treatment with SnCl(2), decreased both iNOS expression in ischemized rats and increased cell survival. The beneficial effects of SnCl(2) were prevented by concomitant treatment with SnMP, a strong inhibitor of HO activity. SnCl(2) also caused an improvement in short term memory recovery. Our results showed that following SnCl(2) administration, HO-1 is strongly induced in the hippocampus and modulate iNOS expression, resulting in a strong neuroprotective effect.

Behavioural and neurochemical changes induced by stress-related conditions are counteracted by the neurokinin-2 receptor antagonist saredutant.

Tamburella A, Leggio GM, Micale V, Navarria A, Bucolo C, Cicirata V, Drago F, Salomone S.

Department of Clinical and Molecular Biomedicine, Section of Pharmacology and Biochemistry, Catania University, Catania, Italy.

ABSTRACT

These experiments were undertaken to assess the mechanisms underlying the antidepressant-like effects of the neurokinin-2 (NK2) receptor antagonist saredutant (SR48968) in rats tested in the forced swim test (FST), by analysing hippocampal brain-derived neurotrophic factor (BDNF) and plasma corticosterone [as index of hypothalamic-pituitary-adrenal (HPA) axis activity]. Male Wistar rats received three intraperitoneal injections over 24 h of vehicle, saredutant (5 mg/kg), citalopram (15 mg/kg), clomipramine (50 mg/kg). Rats were subjected to restraint stress (4 h) 24 h prior to the FST procedure. This stress procedure increased immobility and decreased swimming behaviour in the FST; furthermore, it lowered hippocampal BDNF protein expression and increased plasma corticosterone levels. Saredutant and clomipramine or citalopram, used here as positive controls, reduced the immobility time in the FST both under basal conditions and after stress exposure. This effect was not attributable to changes in locomotion, because locomotor activity was unchanged when assessed in the open field test. Pretreatment with para-cholorophenylalanine (150 mg/kg, 72 h and 48 h prior to FST) abolished the effect of citalopram and saredutant on immobility time. At neurochemical level, saredutant attenuated activation of HPA axis in stressed animals more than clomipramine or citalopram. The behavioural effects of saredutant support the hypothesis that NK2 receptor activity is involved in stress-related disorders. These effects of saredutant may be related to normalization of the HPA axis. Moreover, saredutant increases BDNF expression in the hippocampus, confirming the role of NK2 receptor blockade in BDNF activation following stressor application.

Safety profile assessment of buflomedil: an overview of adverse reactions between 1975 and 2011.

Bucolo C, Longo L, Camillieri G, Drago F, Salomone S.

Department of Clinical and Molecular Biomedicine, Section of Pharmacology and Biochemistry, University of Catania, Italy.

ABSTRACT

PURPOSE:

Review all the individualized cases of adverse drug reaction (ADR) potentially related to buflomedil, a vasodilator with the indication for peripheral arterial disease (PAD), marketed in Europe since the 1970s but recently suspended by the European Medicines Agency.

METHODS:

A review of all available individualised case safety data relating to oral buflomedil from the buflomedil global safety database (provided by the manufacturer of buflomedil), the worldwide published medical literature, toxicology/poison centres and regulatory authorities.

RESULTS:

The main ADRs reported were in the cardiovascular (CVS) and nervous systems (NS), grouped under four (MedDRA) System Organ Classes (SOCs): (i) Cardiac disorders; (ii) Vascular disorders; (iii) Investigations; (iv) NS disorders. From an initial cumulative number of 1054 case reports, there were 401 cases of intentional overdose (IOD) of which 63 were fatal, and 137 cases of accidental overdose, with two fatalities, and 516 case reports of ADRs under normal conditions of use of the product at normal therapeutic dosage with 11 fatalities. Overdosage (intentional or accidental) represented 50.9% of cases, with 47.6% of patients <40 years of age. The indications for which these young patients were prescribed buflomedil were not reported in most cases.

CONCLUSIONS:

The main indication of buflomedil is PAD; however, because most cases of IOD occurred in people <40 years of age, where PAD is unlikely, it is possible that buflomedil was prescribed for other indications and/or that it was not directly prescribed to the end user, who rather gained access to the medication prescribed to family members or friends.

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