# Workshop

# Mesas de Trabajo

# Metabolic Disorders
# Desordenes Metabólicos

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# Role of leptin in systemic inflammation and obesity: from bench to bedside and back

*Torres-Castro I, Martínez-Reyes C, Arroyo-Camarena UD, Gómez-Arauz GY, Escobedo G*

Unidad de Medicina Experimental, Facultad de Medicina, Universidad Nacional Autónoma de México, Hospital General de México, C.P. 06726, México, D.F. México

In obese subjects, hyperleptinemia is accompanied by increased serum levels of tumor necrosis factor alpha (TNF-α), interleukin (IL) 6, and IL-12, but reduced concentrations of IL-10. Nevertheless, it remains unclear whether leptin is capable of influencing directly the release of proinflammatory and anti-inflammatory cytokines. Monocytes/macrophages are leukocytes with the ability to produce both proinflammatory and anti-inflammatory cytokines depending on the extracellular milieu. Thus, our main goal was to evaluate the effect of leptin on the production of TNF-α, IL-6, IL-12, and IL-10 in human macrophages *in vitro*, while examining whether similar results can be observed in obese patients *in vivo*. Increasing concentrations of leptin were able to induce mRNA expression and protein synthesis of TNF-α and IL-12 but not IL-6 in primary human macrophages. On the contrary, expression and production of IL-10 was significantly reduced in human macrophages exposed to increasing levels of leptin as compared with control cells. In parallel, elevated serum levels of leptin were positively associated with increased percentage of circulating proinflammatory monocytes/macrophages in obese subjects (n=73) as compared with controls (n=71). In obese patients, increased levels of both leptin and proinflammatory monocytes/macrophages were also positively associated with serum levels of TNF-α, IL-16, and IL-12. On the other hand, serum values of IL-10 showed an inverse relationship with either leptin or circulating levels of proinflammatory monocytes/macrophages in obese patients with respect to controls. Present results suggest that leptin may directly affect production of proinflammatory and anti-inflammatory cytokines in obese patients via stimulation of monocyte/macrophages.

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# The involvement of the circadian system in the inflammatory response

*Buijs RM, Guerrero-Vargas N, Cazarez-Marquez F, Soto-Tinoco E*

Departamento de Fisiología Celular, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, México, D.F. México C.P. 04510.

Several studies have indicated the importance of time for the immune system. We have investigated the role of the suprachiasmatic nucleus (SCN) that gives time to all physiological processes in the body. We demonstrated a close interaction between the response of the immune system and the SCN; this interaction influences the intensity of the cytokine and temperature response. An increase of cytokines production after an SCN lesion suggests that the observed activation of the SCN after an LPS challenge is aimed to curb the innate immune response. Next we investigated the consequence of circadian disruption in the immune response using a rat model of shift work and identified the main factors involved in the disruption of the inflammatory response. Shift work did not change basal TNF-a levels neither in blood nor in the liver. Yet we observed that shift-work induced increased cytokines response after LPS stimulation in comparison to control rats. Also liver macrophages isolated from shift-work rats produced more TNF-a in response to *in vitro* LPS stimulation. In addition shift-work augmented the growth of subcutaneous implanted tumors, pointing to important changes in the immune defense system of shift-work rats. When shift-work rats had no access to food during the working hours the inflammatory response to LPS was prevented. These results show that dissociating behavior and food intake from the synchronizing drive of the SCN severely disturbs the immune response and promotes disease.

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# Circadian desynchrony as promoting factor for metabolic syndrome

*Escobar C*

Laboratorio de Ritmos Biológicos y Metabolismo. Departamento de Anatomia. Edificio B cuarto piso. Facultad de Medicina. Universidad Nacional Autónoma de México. México, D.F. México C.P. 04510. Tel: +52 5556232422, ext. 45062. E-mail: escocarolina@gmail.com

Adaptation to a cycling environment is necessary to exhibit right responses and with the right intensity along the day. Therefore all organisms exhibit daily changes in behavior and physiology evidencing the influence of the circadian system. In mammals the suprachiasmatic nucleus (SCN) in the hypothalamus is the clock and transmits temporal signals to the rest of the organism via humoral and autonomic pathways. The SCN is the orchestrating mechanism that keeps internal synchrony of all organs, tissues and cells with the external environment. Therefore it receives direct input from the retina providing information of the day/night cycle, however other temporal indicators (temperature cycles, activation and arousal, meal time) can provide complementary temporal information. Preferentially all temporal signals should be coherent in order to keep circadian synchrony. We have developed experimental models that mimic conditions of modern life style, where temporal signals are desynchronized and provide conflicting signals to the circadian system. We have exposed rats to forced activity during the rest phase mimicking night work, we have given food or light during the night. With our experimental models we have reported that circadian desynchrony promotes metabolic disruption and animals develop in a short term indicators of metabolic syndrome. Moreover some animals developed overweight and depressive like behavior. We conclude that circadian integrity is necessary for maintaining homeostasis.

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# Anti-inflammatory effects of organosulfur compounds derived from garlic (*Allium sativum*)

*Ortuño-Sahagún D*

Instituto de Investigación en Ciencias Biomédicas (IICB), CUCS,
Universidad de Guadalajara, Jalisco, México

The beneficial effects of garlic have been referred for centuries; however, it has not been until recently that *Allium sativum* derivatives have been postulated as promissory candidates for the maintenance of immune system homeostasis. Garlic complex biochemistry makes it possible to generate several different preparations from its processing, and slight variations produce numerous amounts and different types of compounds. Here, we present different extraction procedures, their main products, and their effects. Additionally, experimental results that demonstrate different effects of garlic compounds on the immune system and their main cells (such as macrophages, lymphocytes, Natural killer [NK] cells, eosinophils, and dendritic cells) are discussed. This is principally through mechanisms that involve modulation of cytokine secretion, immunoglobulin production, phagocytosis, and macrophage activation. Finally, because immune system dysfunction is fundamental for the disease progress in several pathologies, we analyze here the role of garlic and its derivative compounds as helpers in the co-treatment of diverse pathologies, such as metabolic syndrome, obesity, cardiovascular disorders, gastric ulcer, and even cancer. We can conclude that *A. sativum* and its derivatives modulate cytokine secretion and that such modulation explains the mechanism of action for its therapeutic effects.

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# Autoimmunity

# Autoinmunidad

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# Effects of arginine vasopressin deficiency on innate immunity in the rat

*Quintanar Stephano A[1], Viñuela-Berni V[1], Organista-Esparza A[1], Tinajero-Ruelas M[1], Huerta Carreón EP[1], Kovacs K[2] ,Berczi I[1]*

[1]Departamento de Fisiología y Farmacología. Centro de Ciencias Básicas. Laboratorio de Neuroinmunoendocrinología. Universidad Autónoma de Aguascalientes. México. [2]Department of Laboratory Medicine, Division of Pathology. St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada.

Immune and vascular endothelial cells possess arginine vasopressin (AVP) receptors. AVP is an important stimulating/regulatory hormone in acquired immunity, whereas its role on innate immunity (ININ) is not well known. Neurointermediate pituitary lobectomy (NIL) in the rat causes permanent low AVP serum levels. Here, we investigate the AVP and ININ relationship in NIL rats (3 weeks after surgeries) subject to ININ tests: Phagocytic index (PI) (peritoneal macrophages ($M_\theta$) erytrophagocytosis), and Skin Evans blue extravasation-histamine test. In the Study 1, NIL group was compared against the Intact control (IC), sham operated (SHAM) and anterior pituitary lobectomysed (AL) groups. In the study 2, NIL group was compared against IC, NIL+desmopressin (a synthetic analog of AVP) and IC+conivaptan (antagonist of V1a-V2 AVP receptors) groups. Results: Study 1 showed that as compared with the IC and AL groups, PI was significant decreased in NIL animals. In the Study 2, the Evans blue extravasation-histamine test, a significant and similar increases of skin edema histamine doses-dependent occurred in NIL and IC+conivaptan groups, whereas no significant differences in IC and NIL+desmopressin groups occurred. Conclusion: (1) AVP plays an important role regulating the phagocytic activity of the peritoneal $M_\theta$. (2) AVP participate in the stabilization of the permeability of the vascular endothelial cells during the inflammation-histamine mediated.

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# Agonista de la GnRH y su efecto neuroinmunomodulador

*Quintanar Stephano JL, Guzmán Soto I, Salinas Miralles E*

Depto. De Fisiología y Farmacología. Centro de Ciencias Básicas.
Universidad Autónoma de Aguascalientes

Recientemente se ha descrito la presencia de receptores a la hormona liberadora de gonadotropinas (GnRH) tanto en el encéfalo como en la médula espinal. La activación de estos receptores por agonistas de la GnRH, induce una recuperación neurológica de la médula espinal y por tanto de la actividad locomotora, e igualmente la modulación en la respuesta inflamatoria en el caso de la encefalomielitis experimental autoinmune (EEA), modelo de esclerosis múltiple. Particularmente se ha observado que el tratamiento con Acetato de leuprolida, agonista de la GnRH, produce una disminución en la respuesta del factor de transcripción nuclear NF-kB, así como la reducción de la expresión de citocinas proinflamatorias. También por otro lado, se ha encontrado que la administración del agonista, incrementa el número de infiltrados linfocitarios (células T reguladoras) en la médula espinal asociado a una reducción de las alteraciones motoras causadas por la EEA. Por lo anterior se puede considerar la posible aplicación de agonistas de la GnRH en la terapia de la esclerosis múltiple tanto por su potencial efecto neurorregenerador como inmunomodulador.

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# Antineural immunoreactivity in patients with fibromalgia

*De la Cruz-Aguilera DL[1], Mendieta D[2], Viadas H[1], Barrera I[2], Fernández-Valverde F[3], Becerril E[2], Hernández ME, Garcés ME[2], Martínez F[1], Rodríguez-Pérez CE, Pavón-Romero L[2], Aguirre-Cruz L[1].*

[1]Laboratorio de Neuroinmunoendocrinología, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez (INNN MVS); [2]Laboratorio de Psicoinmunología, Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz; [3]Laboratorio de Patología Experimental, INNN MVS. Laboratorio de Neuroinmunoendocrinología, Av. Insurgentes sur 3877, Col. La Fama-Talpan, C.P. 14269, México, D.F. México (55) 5606 3822 ext. 2007. E-mail: mariluci_aguirre@hotmail.com

Fibromyalgia (FM) is a chronic and idiopathic disorder characterized by generalized musculoskeletal pain that can be associated with sleep disorders, depression and cognitive alterations. Some studies suggest that this condition could be associated to autoimmune disorders. The aim of this work was to evaluate the existence of seric autoantibodies anti-neural tissue in patients with FM, in order to identify diagnostic markers and clarify the etiology of the disease. We evaluated the seric immunoreactivity revealed by the seric antibodies of 15 patients with clinical diagnosis of FM (established in base to the American College of Rheumatology criteria), without autoimmune pathology identified, in mouse cerebellum and kidney by indirect immunofluorescence test (IIFT). Three out of the fifteen patients with FM were immunoreactive to mouse cerebellum and brainstem neurons, but they were not recognized the mouse kidney. Immunoreactivity did not correlate with specific clinical characteristics. Twenty percent of FM patients had autoantibodies against nervous tissue, which could be associated to specific clinical subgroups of the disease.

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New development opportunities on neuroimmunoendocrinology

Nuevas oportunidades de desarrollo en neuroinmunoendocrinología

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# Effects of chronic sucrose intake on cognitive performance on a transgenic model of alzheimer disease

*López-Pacheco G[1], Guzmán-Ramos K[1], Bravo-Ruiseco G[1], Ayala-Guerrero L[2], Bermúdez-Rattoni F[2]*

[1]Health Sciences Department, Metropolitan University (Universidad Autónoma Metropolitana) at Lerma, Mexico, [2]Cellular Physiology Institute, National University of Mexico (Universidad Nacional Autónoma de México)

High sugar diet is among the most popular within the western societies and its consumption has produced health detriments at the central nervous level. It is known that high caloric diets and type 2 diabetes are risk factors for the development of dementias, and particularly Alzheimer's Disease (AD), which is mostly prevalent in women. The molecular and metabolic events that lead to cognitive impairments are so far not clear; we propose that astro-glial activation by a hypercaloric diet is an early event that correlates with cognitive dysfunction. Hence, we studied the effect of feeding with 20 % sucrose solution during 5 months (starting at 2 months of age) in a murine model of AD harboring three mutations (3xTg-AD) and a control wild-type strain (WT). As a consequence of the high sucrose diet administration, we found an early deterioration of cognitive performance; in particular object and spatial memories were impaired in the 3xTg-AD mice, comparable to the deterioration found in at 12 months-old 3xTg-AD mice group that had a normal diet. Additionally, the high sucrose diet induced in the WT mice a cognitive impairment in the taste recognition and spatial memories also comparable to 12 month-old 3xTg-AD mice. Metabolic and molecular dysfunctions of glucose biochemistry are also related to the cognitive performance of the affected groups; as well as astrocytes activation. This data suggest that an early exposure to high caloric food has a powerful negative impact on the acceleration of cognitive impairments.

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# Pleiotrophin function as a neuromodulator in the hippocampus

*Rojas Mayorquín AE[1], González Castillo C[2], Guzmán-Brambila-C[3], Pallas M[4], Ortuño Sahagún D[2]*

[1]Universidad de Guadalajara, Dpto. Ciencias Ambientales, Instituto de Neurociencias, CUCBA, Guadalajara, Jalisco, México. [2]Universidad de Guadalajara, Instituto de Investigación en Ciencias Biomédicas (IICB), CUCS, Guadalajara, Jalisco, México. [3]Tecnológico de Monterrey, División de Biotecnología y Salud, Escuela de Medicina, Campus Guadalajara, Jalisco, México. [4]Universidad de Barcelona, CIBERNED, IBUB, Barcelona, España

Pleiotrophin (PTN) is a secreted growth factor associated with the extracellular matrix. It is expressed in several tissues, where its signals are generally related with cell proliferation, growth, and differentiation by acting through different receptors. In Central Nervous System (CNS), PTN exerts post-developmental neurotrophic and -protective effects, and additionally has been involved in neurodegenerative diseases and neural disorders. Its expression increases after cerebral lesion or damage, and in some degenerative diseases such as in patients with Parkinson disease. Specifically in the hippocampus, recent evidence from PTN Knock-out (KO) mice involves PTN functioning in learning and memory. However, its precise role is not yet established. Thus, to obtain new insights, we analyzed the gene expression profile of 22,000 genes in the hippocampus from PTN KO mice. For the group analysis, we selected only genes that range from a median z-score over (or under) 3.0. Of these, a total of 41 identified genes (40 %) are of unknown function, which indicates that PTN deficiency elicits an unmapped response. The genes known to have increased are mainly related with neuroprotection, cell differentiation and proliferation, and transcriptional regulation. Conversely, genes that diminished PTN expression are mainly related with cytoskeleton, cell cycle regulation, neural development, ion transport, and signal transduction. The outcome of this analysis constitutes a strong starting point in the identification and study of groups of genes involved in compensatory mechanisms activated by the absence of PTN, providing a model for analyzing some aspects of neurodegenerative diseases.

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# Immunotoxicity on organophosphate pesticides through the alteration of non-neuronal cholinergic components

*Girón-Pérez MI, Toledo-Ibarra GA, Díaz-Resendiz KJG*

Universidad Autónoma de Nayarit. Laboratorio de inmunotoxicología. Cd de la Cultura s/n. Col Los fresnos, Tepic Nayarit, México. C.P. 63000. Tel: +52(311)2118800 ext 8922. E-mail: ivan_giron@hotmail.com

Organophospate pesticides (OP) are substances that inhibit the acetylcholinesterase enzyme (AChE); nevertheless, in addition to their neurotoxic effect, they have very clear immunotoxic effects. However, mechanisms through which OPs deregulate the immune system are not completely elucidated. Experiments performed in our lab, using as model organism the fish Nile tilapia (*Oreochromis niloticus*) have shown the significant increase of acetylcholine (ACh) and the decrease in the AChE activity, as well as in the concentration of muscarinic (mAChR) and nicotinic receptors (nAChR) in lymphocytes of fishes exposed to diazinon, one of the mostly used OPs in agricultural activities. On the other hand, experimental data show that cells from the immune system of fishes exposed to the pesticide, present a decrease in diverse physiological parameters, such as: proliferative capacity, phagocytic activity, calcium flow and potential of the mitochondrial membrane. This way, obtained result in our laboratory suggest that toxicity mechanisms of OPs on the immune system are not direct, but through alteration of cholinergic components belonging to lymphocytes, which apart from being vital for the cellular functioning, are phylogenetically preserved.

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# Infectious diseases

# Enfermedades infecciosas

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# Comparison patterns of 4 t1 antigens recognized by humoral immune response mediated by IgG and IgM antibodies in female and male mice with breast cancer using 2d-immnunoblots

*Ostoa-Saloma P., Hernández-Ávila R., Meneses-Ruíz DM. and Díaz-Zaragoza M.*

Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, México, D.F. México. C.P. 04510. Tel.: +52 55 56228941

E-mail: postoa@unam.mx.

Early detection of cancer is one of the most promising approaches by which to reduce the growing cancer burden. The early diagnosis in cancer is challenging, since it is the most common cancer in women worldwide. Natural immunoglobulin M (IgM) recognizes modified cell surface antigens that develop during tumorigenesis and activating complement to destroy nascent transformed cells or induce their apoptosis. Thus, IgM should be considered in developing a tool for early diagnosis before the tumor has been established. We examined tumor antigens by 2-dimensional (2D) immunoblot with antibodies in sera from male and female mice in which 4 T1 cells were injected into the mammary gland nipple. Our aim was to characterize the variability in IgM and IgG humoral immune responses in female and male mice with breast cancer at various stages of disease development and correlate antigen recognition statistically with variables that are associated with individual mice and tumor parameters. Each mouse has an individual pattern of recognition to a tumor antigenic background and a variable number of spots for IgMs. Spots variation in 2D pattern for natural IgM can be expressed as a binomial signature, which opens the way to correlate a particular pattern, in murine models, with different cancer resistance or susceptibility. The disparities in antigenic recognition by IgG or IgM during the development of cancer between female and male mice could also be attributed to the effects of sex hormones and differences in how the immune system recognizes 4 T1 antigens in both genders.

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# The contribution of the autonomous nervous system in the immunopathology of experimental pulmonary tuberculosis. Its therapeutic implications

*Hernández-Pando R[1], Islas WL[1], Revuelta-Rodríguez A[1], Mata-Espinoza D[1], Maruina B[1], Barrios-Payan J[1], Pavón-Romero L[2]*

[1]Experimental Pathology Section. Department of Pathology. National Institute of Medical Sciences and Nutrition Salvador Zubiran, Mexico City, Mexico, [2]Immunology Laboratory, National Institute of Psychiatry, Mexico City, Mexico

The brain, the endocrine glands and the immune system are the major adaptive systems of the body. During an immune response these systems constantly communicate being this process essential for maintaining homeostasis. Two major pathway systems are involved in this cross-talk: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, which is one of the autonomous nervous system (ANS) branches; the other branch of the ANS is the cholinergic system which has a significant anti-inflammatory activity. In a well characterized model of progressive pulmonary tuberculosis (TB) in BALB/c mice, it was previously showed that during the early phase of the infection (three weeks), there is high production of TNFα and IL-1β from macrophages that activate the HPA, which significantly contribute to TB pathogenesis. We now studied the contribution of the ANS in the immunopathogenesis of experimental TB. First the kinetics of noradrenaline(NA) and acetil-choline (Ach) production was studied by their measuring in the lungs by HPLC during infection.There is a progressive NA production which raised its peak at day 14, when in this model start granuloma formation that permit an efficient control of bacterial growth. Then, a progressive NA decrease was seen during late disease. Concentrations of Ach were relatively high, an early increase was observed at day 7 and 14 followed by a decrease and increasing again raising its maximal concentration during late disease at day 60 of infection, in coexistence with extensive pneumonia and high bacilli burdens. In order to study the influence of the ANS in the course of the infection, the adrenergic innervation was eliminated by the administration of 6OH-dopamine or NA receptors type 2 were stimulated by the administration of formoterol during early or late infection. The elimination of NA since day one before infection worsening the course of the disease, while the stimulation of the adrenergic system during early or late disease induced higher expression of IFNγ with a better control of bacilli growth. The pharmacological manipulation of the cholinergic system during early infection did not produced significant changes in the disease evolu-

tion, while blocking with selective drugs the nicotinic receptors β-4 and β-7 during late disease, at day 60 post-infection, induced a significant decrease of bacilli burdens in coexistence with high expression of IFNγ and TNFα. Thus, both branches of the ANS participate in the regulation of the immune system during experimental TB, during early infection the sympathetic system contributes to infection control, probably by promoting the differentiation of Th-0 to Th-1 cells by NA; while during late TB the parasympathetic system participate suppressing excessive inflammation, but at the same time favors disease progression by the well known activity of Ach producing macrophage deactivation. These experimental results have implications for enhancing immune response by immunotherapy. In fact, blocking nicotinic receptors during late disease synergized with conventional chemotherapy shortening conventional chemotherapy in animals infected with drug susceptible bacteria, while in animals infected with multi-drug resistant bacilli a significant reduction of bacilli burdens was produced after blocking nicotinic receptors. Thus, pharmacologic manipulation of ANS is a new and efficient form of treatment in experimental TB.

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# El análisis proteómico y su importancia en el estudio de los helmintos. Un enfoque hacia ténidos

*Ambrosio J*

Dpto. de Microbiología y Parasitología, Facultad de Medicina, Universidad Nacional Autónoma de México. México, D.F. México. E-mail: jrah@unam.mx

El estudio de la expresión de proteínas en un mismo instante y en su conjunto se hace mediante el análisis proteómico. Este tipo de análisis se realiza bajo diferentes estrategias entre las que se incluyen identificación de las proteínas mediante análisis de espectrometría de masas, luego de que las proteínas hayan sido separadas electroforéticamente o no. Gracias a esta tecnología se logran determinar las características de las proteínas identificadas, tales como sus modificaciones postransduccionales o la expresión de variantes de un solo tipo de proteína. Luego, cuando un conjunto de proteínas son identificadas y reconocidas en el análisis proteómico realizado, de acuerdo a sus funciones, se les busca encontrar cual es la importancia de la interacción entre ellas en el organismo y en el momento que se les está estudiando. En el caso de parásitos helmintos, se ha postulado que la proteómica forma parte del estudio de la biología básica de tales parásitos porque de ello depende el que se generen mejores pruebas de diagnóstico o se generen mejores esquemas de tratamiento quimioterapeútico y que permitan un mejor entendimiento de los mecanismos de acción y de resistencia de fármacos, así como ello influye para la toma de decisiones del control de la presencia de parásitos. Con la difusión del genoma del cestodo *Taenia solium* se abren oportunidades de profundizar en el conocimiento de la expresión de proteínas de este tipo de parásitos y con ello, se abre la posibilidad de generar más y mejores blancos farmacológicos que van a permitir el desarrollo fármacos más eficientes en el tratamiento de las enfermedades parasitarias que producen. Incluso, el conocimiento del genoma ha abierto posibilidades para postular que posibles proteínas podrían tener importancia en la relación huésped parásito, principalmente en el campo de aquellas que podrían estar expresándose en un momento dado, pero ello no es suficiente mientras no se tenga evidencia de la expresión real de estas proteínas y por ello, la proteómica ofrece una oportunidad de estudio interesante. Al momento, varios avances se tienen en el conocimiento de la proteómica de helmintos en donde se han estudiado y caracterizado principalmente la expresión de proteínas secretadas o secretadas por los parásitos en contacto con su hospedero. Lo aprendido de ello es que hay una expresión diferencial

de las proteínas dependiendo del estadio de desarrollo parasitario. En *T. solium* esto se ha podido demostrar a través de la generación de mapas proteómicos en geles bidimensionales de diferentes estadios parasitarios que se pueden obtener o mantener en el laboratorio y de ello, varias proteínas se han identificado de forma exitosa luego de su análisis mediante espectrometría de masas. Debido al conocimiento del genoma de *T. solium*, estudios de análisis proteómicos semejantes se han realizado con cisticercos de *T. crassiceps* de la cepa ORF y se ha logrado la obtención de mapas proteómicos que han permitido evaluar la expresión de sus proteínas frente al tratamiento con sustancias como las hormonas y derivados bencimidazólicos experimentales. De estos análisis se han identificado proteínas relevantes frente a los tratamiento s que de alguna forma están asociadas a los efectos que se han presentado en los parásitos, bajo los tratamientos *in vitro* llevados a cabo. Los cambios en la expresión de proteínas se han visto reflejados en cambios en los comportamientos de estructuras celulares básicas en la sobrevivencia de los parásitos como las células flama y lo cual podría tener una proyección interesante hacia el desarrollo de fármacos antiparasitarios dirigidos hacia este tipo de estructuras. Con estos avances obtenidos se ha incrementado el conocimiento de la biología y fisiología de este tipo de parásitos que seguramente tendrá una futura aplicación en el control de las enfermedades que producen, principalmente cuando las infecciones se den por el tenido de importancia médica *T. solium.*

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# El sistema inmune en la patogénesis de las enfermedades por priones

*Sánchez V.*

Universidad de Guadalajara. Carretera a Yahualica Km. 7.5, Tepatitlán de Morelos, Jalisco. México.
Tel: (378) 78 280 33 ext 56975. E-mail: victor.sanchez@cualtos.udg.mx

Las enfermedades por priones también son llamadas Encefalopatías Espongiformes Transmisibles (EET) y son un grupo de enfermedades neurodegenerativas de carácter hereditario e infeccioso que se presentan tanto en humanos como en animales y ocurren mundialmente con una incidencia de alrededor de 1 caso por 1 millón de habitantes por año. Los priones son proteínas infecciosas. En los mamíferos, los priones se reproducen reclutando proteínas priónicas celulares normales ($PrP^{C}$) y estimulando su conversión a la isoforma causante de la enfermedad ($PrP^{Sc}$). El puente neuroinmune de las enfermedades por priones se ha visto reforzado por varios estudios en los que, posterior a la inoculación intraperitoneal, se observan depósitos de priones en los órganos linfoides secundarios tales como el bazo y los nodos linfáticos; esta fase es clínicamente silente y prolongada (hasta 10 años de duración). A su vez, se han considerado como el principal tipo celular para la replicación de los priones a las células dendríticas foliculares dentro del tejido linfoide. De igual forma, las células B son un cofactor en la patogénesis periférica de los priones siendo el bazo el órgano donde ocurriría este proceso. En resumen, la patogénesis de las enfermedades por priones, y eventualmente la neuroinvasión, es dependiente de componentes del sistema inmune del huésped, siendo las células dendríticas foliculares, los linfocitos B y el bazo los principales elementos involucrados en este proceso.

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Sleep

Sueño

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# Elucidating sleep function: to maintain blood-brain barrier integrity

*Gómez González B*

Area of Neurosciences, Dept. Biology of Reproduction, CBS, Universidad Autónoma Metropolitana, Unidad Iztapalapa

Sleep function has remained elusive for decades. Since 1980s the pioneer studies showed that sleep is vital for mammals, because chronic sleep deprivation induced severe health problems and caused the death of experimental animals. More recent studies have shown that sleep loss induces several neural deficits, such as decreased neurogenesis, increased extracellular glutamate levels, and decreased hippocampal volume. Moreover, peripherally, sleep loss induces a low-grade inflammatory status, with increased levels of pro-inflammatory cytokines. A unified hypothesis that could explain all those central nervous system effects was suggested by Korth 20 years ago and not tested until 2013, when we found that chronic sleep loss alters the structure and function of the blood-brain barrier. The blood-brain barrier is a physical and chemical barrier that precludes free interchange between blood and the brain parenchyma that is located in almost all brain capillaries. After our initial report of increased blood-brain barrier permeability after chronic sleep loss, some other reports appeared showing that sleep loss leads to disruption of tight junctions between brain endothelial cells and decrease of tight junction proteins. We have shown that the changes in blood-brain barrier structure and function revert rapidly after sleep recovery and that some inflammatory mediators, such as adenosine and cytokines, are major players in regulating the blood-brain barrier function during sleep. The blood-brain barrier dysfunction during sleep loss may explain all those brain deficits induced by sleep deprivation. Therefore it seems that the sleep function is to maintain the integrity of the blood-brain barrier.

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# The frequency of absence seizures in the sleep-wake cycle

*Cortés C[1], Trujillo CA[2], Eguibar JR[1,3]*

[1]Instituto de Fisiología, [2]Escuela de Biología, [3] Dirección General de Investigación de la Vicerrectoría de Investigación y Estudios de Posgrado. Benemérita Universidad Autónoma de Puebla. Apdo. Postal 5-66. C.P. 72430. Puebla, Puebla. México.

The myelin mutant *taiep* rat showed an initial hypomyelination followed by a progressive demyelination of the central nervous system. The name is the acronym of the motor syndrome that characterized it: tremor, ataxia, immobility, epilepsy and paralysis. The phenotype is inherited as an autosomal recessive trait. This mutant developed absence seizures similar to that showed in humans. These type of epilepsy have a frequency of 6.5 Hz, it onset occurs in the frontal region spreading to the occipital cortex. The aim of this study was evaluate the prevalence of absence seizures along the circadian cycle, determine the frequency and mean duration of them along the sleep and wake brain states. The absence seizures are higher in the awake periods with respect to slow-wave sleep (SWS) or rapid eye movement sleep (REM) ($\chi^2$=16.0, *P*<0.001;followed by Tukey´s Test, *p*<0.05). The mean duration of absence seizures were higher in the awake period respect to SWS and REM sleep (H=243.2, *P*<0.001; followed by Dunn´s test *p*<0.05). In conclusion, the hyperexcitability in the thalamo-cortical circuit in *taiep* rats dependent of the time of the circadian cycle. Suggesting that the trigger neurons in the cerebral cortex differ respect to the circuit that sustain the seizures in the thalamo-cortical rhythmic pathway. The higher incidence of absence seizures during awake periods showed that light diminish the threshold. On the other hand, sleep is capable to diminish the excitability of the thalamo-cortical reverberating circuit.

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New perspectives on neuroimmunoendocrinology
Nuevas perspectivas en neuroinmunoendocriniología

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# Interleukin-6: a cytokine with a pleiotropic role in the neuroimmunoendocrine communication network

*Morales-Montor J*

Departamento de Inmunología, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, AP 70228, C.P. 04510. México D.F. México. E-mail: jmontor66@biomedicas.unam.mx

Interleukin 6 (IL-6) is a typical pleiotropic cytokine that modulates a variety of physiological events in vertebrates, including cell proliferation, differentiation, survival, and apoptosis, among other functions. IL-6 plays roles in the immune, the endocrine, the nervous, and the hematopoietic systems, in bone metabolism, regulation of blood pressure and inflammation. IL-6 exerts its effects on different tissues and organ systems. Many cell types are reported to produce IL-6: T cells, B cells, polymorphonuclear cells, eosinophils, monocyte/macrophages, mast cells, dendritic cells, chondrocytes, osteoblasts, endothelial cells, skeletal and smooth muscle cells, islet cells, thyroid cells, fibroblasts, mesangial cells, keratinocytes, microglial cells, astrocytes, oligodendrocytes, adipose tissue and certain tumour cells. Here, we review the participation of the IL-6 in the neuroimmunoendocrine network that includes all interactions across species, sexes, cells, and types of responses. The specific targeting of the IL-6 pathway can be a promising new approach for the treatment and prevention of neurodegenerative disorders in humans. Furthermore, blocking the effect of IL-6 may improve the autoinflammatory process both systemically and locally.

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# Alteraciones en la desmielinización en el sisteman nervioso central inducen resistencia a la infección con *Trichinella spiralis:* la rata taiep como modelo experimental

*Nava-Castro KE[1], Cortés MC[2], Eguibar JR[2], Río-Araiza VH[1], Morales-Montor J[1]*

[1]Departamento de Inmunología. Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México. [2]Instituto de Fisiología. Benemérita Universidad Autónoma de Puebla.

La interacción entre los sistemas neuroendócrino e inmunitario es uno de los elementos clave que intervienen para mantener la homeostasis de los vertebrados, siendo particularmente imprescindible en los mamíferos. La respuesta inmunológica, como una respuesta homeostática bajo control fisiológico, contribuye al mantenimiento de la integridad de las células corporales y de los tejidos. La comunicación eficiente de estos dos sistemas implica la existencia de vías aferentes y eferentes que constituyen un sistema complejo de retroalimentación. Cuando se producen alteraciones en esta red, se desencadenan patologías que involucran a los diferentes componentes de la misma. Para evaluar la comunicación entre el sistema nervioso central y el sistema inmune, utilizamos el modelo de ratas *Taiep*, que muestran una hipomielinización en el sistema nervioso central, pero no en el periférico. Estas ratas fueron infectadas con larvas del parásito intestinal *Trichinella spiralis* y analizamos la susceptibilidad a la infección así como la respuesta inmune a la misma. Nuestros resultados, muestran que las ratas *Taiep* tienen cargas parasitarias menores (75 %) que las ratas de la cepa silvestre (Sprague Dowley). Así mismo, encontramos que las ratas *Taiep* responden inmunológicamente de manera distinta, ya que muestran una disminución significativa en algunas subpoblaciones celulares, particularmente linfocitos T ayudadores así como linfocitos B en los ganglios linfoides mesentéricos, pero no en los del bazo. Esto sugiere que la alteración en la mielinización del sistema nervioso central afecta de manera directa la respuesta inmune local al parásito, sin alterar la respuesta inmune sistémica.

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# Effect of transcranial magnetic stimulation (TMS) in the recovery to a traumatic brain injury (TBI)

*Estrada Rojo F, Hernández Gómez E, García Espinoza A, Martínez Vargas M, Verdugo Díaz L, Hernández Chávez A, Navarro L*

Departamento de Fisiología, Facultad de Medicina, Universidad Nacional Autónoma de México.
E-mail: lnavarro@unam.mx

TBI causes a release of excitatory neurotransmitters such as glutamate, which induces a massive influx of calcium into neurons, activation of multiple enzymes, free radical production and necrosis and/or apoptosis; however, also causes activation of inhibiting systems such GABAergic and/or canabinnergic that counteract the excitotoxicity triggered by glutamate and a balance between both types of response is established. The TMS can activate or inhibit brain electrical activity and thus influences this balance. Our group is interested in the effect of TMS on the neurobehavioral and histological recovery of subjects who have suffered TBI. We have used a TBI model in rat to analyze this issue. Our results indicate that TMS favor the neurobehavioral recovery of these rats. We also have found differences in cell dispersion in hippocampal regions CA1, CA2, CA3 and dentate gyrus and we are evaluating the inflammatory process at the motor cortex, analyzing leukocyte infiltration. These last results allow us to explain how the TMS helps in neurobehavioral recovery of TBI.

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# Mental health and behavior

# Salud mental y conducta

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# The high-yawning rats showed an anxiety phenotype in different behavioral tests and different pattern of corticosterone secretion

*Eguibar Jose R, Cortes C, Trujillo A, Uribe C*

Research Office, VIEP, Institute of Physiology and Biology School. Benemerita Universidad Autonoma de Puebla. Apdo. Postal 5-66. C.P. 72430. Puebla, Puebla. México

We selectively bred two sublines from Sprague-Dawley rats, one with a high-yawning (HY) frequency with a mean of 20 yawns/h, and the low-yawning (LY) with just 2 yawns/h. HY rats ambulated more in the open-field arena (OFA) respect to LY suggesting different emotional reactivity. The aim of these studies is to analyze with detail the anxiety behavior in the OFA and in the elevated-plus maze (EPM), as well as measuring corticosterone (Cort) and adrenocorticotrophic (ACTH) hormone plasma levels using ELISA techniques.

The results showed that HY rats showed more thigmotaxis, that is ambulation close to the walls of the OFA and avoid the central square, the opposite happen in the LY rats ($p$<0.05). HY rats in the EPM showed lower number of entrances and hence time spent in the open arms respect to LY rats ($p$<0.05). ACTH levels were higher in the HY respect to LY rats ($p$<0.05) and with slower clearance of Cort peak after restriction stress. This endocrine parameters are associated with heavier adrenal glands in the HY respect to LY rats ($p$<0.05). These results support that HY animals are more anxious and has over activation of the hypothalamic-hypophysis-adrenal gland axis suggesting is an adequate animal model of anxiety with over stimulate adrenal gland activity.

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# IL-8 and IL-6 primarily mediate the inflammatory response in fibromyalgia patients

*Mendieta D[1], De la Cruz-Aguilera DL[2], Barrera-Villalpando MI[1], Becerril-Villanueva E[1], Arreola R[1], Hernández-FerreiraE[1], Pérez-Tapia SM[3], Pérez-Sánchez G[1], Garcés-Alvarez ME[1,3], Aguirre-Cruz L[2], Velasco-Velázquez MA[4] , Pavón L*[1]*

[1]National Institute of Psychiatry "Ramón de la Fuente"; [2]National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez"; [3]National Polytechnic Institute, Mexico;
[4]National Autonomous University of Mexico.

Fibromyalgia (FM) is a chronic disease that is characterized by widespread pain, tenderness, stiffness, fatigue, and sleep and mood disturbances. It affects 2 % to 5% of the world's population and is more frequent among females. The hallmark symptoms of FM are diffuse pain, lasting for more than 3 months, and pain in 11 of 18 tender points. Previous studies have linked FM symptoms to inflammatory reactions and changes in the systemic levels of proinflammatory cytokines that modulate responses in the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. In this study, we quantified the circulatory concentrations of inflammatory mediators in samples from healthy volunteers (HVs) and FM patients and correlated them with clinimetric scores. Interleukin (IL)-2, -4, -6, -8, and -10; GM-CSF; IFN-g and TNF-a were measured using a Bio-Plex system. Participants underwent clinical psychiatry tests (FIQ, BAI, and BDI). In our analysis, the serum concentrations of IL-6 and IL-8 were elevated in FM compared with HVs. Both cytokines correlated with FIQ, BAI, and BDI scores, suggesting that IL-6 and IL-8 have additive or synergistic effects in perpetuating the chronic pain that is experienced by FM patients. These findings indicate that IL-6 and IL-8 are two of the most constant inflammatory mediators in FM and that their levels correlate significantly with the severity of FM symptoms.

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# Effect of selective serotonin reuptake inhibitors and immunomodulator on cytokines in patients with major depressive disorder

*Mendieta D[1], Hernández ME [2,3], Pérez-Tapia M[4], Bojalil R[5], Estrada-Garcia I[4], Estrada-Parra S[4], Pavón-Romero L[1]*

[1]National Institute of Psychiatry "Ramón de la Fuente, [2]Department of Psychoimmunology, National Institute of Psychiatry "Ramón de la Fuente", [3]Universidad Autónoma Metropolitana, [4]Department of Immunology, National School of Biological Sciences (ENCB), National Polytechnic Institute (IPN), [5]Departamento de Inmunología, Instituto Nacional de Cardiología. México.

Major depressive disorder (MDD) is a psychiatric illness that presents as a deficit of serotonergic neurotransmission in the central nervous system. MDD patients also experience alterations in cortisol and cytokines levels. Treatment with selective serotonin reuptake inhibitors (SSRIs) is the first-line antidepressant regimen for MDD. The aim of this study was to determine the effect of a combination of SSRIs and an immunomodulator—human dialyzable leukocyte extract (hDLE)—on cytokines levels. All subjects were diagnosed by psychiatrists who applied the Mini-International Neuropsychiatric Interview, a standardized diagnostic interview that is based on DSM-IV-TR criteria. Clinical status was measured using the Hamilton Depression Scale (HDRS) and Beck Depression Inventory (BDI). Patients who met the inclusion criteria were free of antidepressants for at least 3 weeks before the study. Each subject underwent laboratory screens to rule out other medical illnesses. After receiving a detailed explanation of the study aims, all participants signed written consent forms. Patients received SSRIs or SSRIs plus hDLE. All patients were administered SSRIs (19 fluoxetine, 7 paroxetine, and 5 Sertraline) or SSRIs plus hDLEs (23 fluoxetine, 9 paroxetine, 1 sertraline, and 1 escitalopram). All patients were evaluated monthly by their psychiatrist, based on the HDRS and BDI. The proinflammatory cytokines IL-1$\beta$, IL-2, and IFN-$\gamma$; anti-inflammatory cytokines IL-13 and IL-10; were measured at weeks (W) 0, 5, 20, 36, and 52 of treatment. Reduction of anti-inflammatory cytokines and increases levels of proinflammatory cytokines in patients who were treated with SSRI plus hDLE at the study conclusion. These results suggest that the immune-stimulating activity of hDLE, in combination with SSRIs, restored the pro- and anti-inflammatory cytokine balance and cortisol levels in depressed patients versus those who were given SSRIs alone.

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