Universidad de Granada

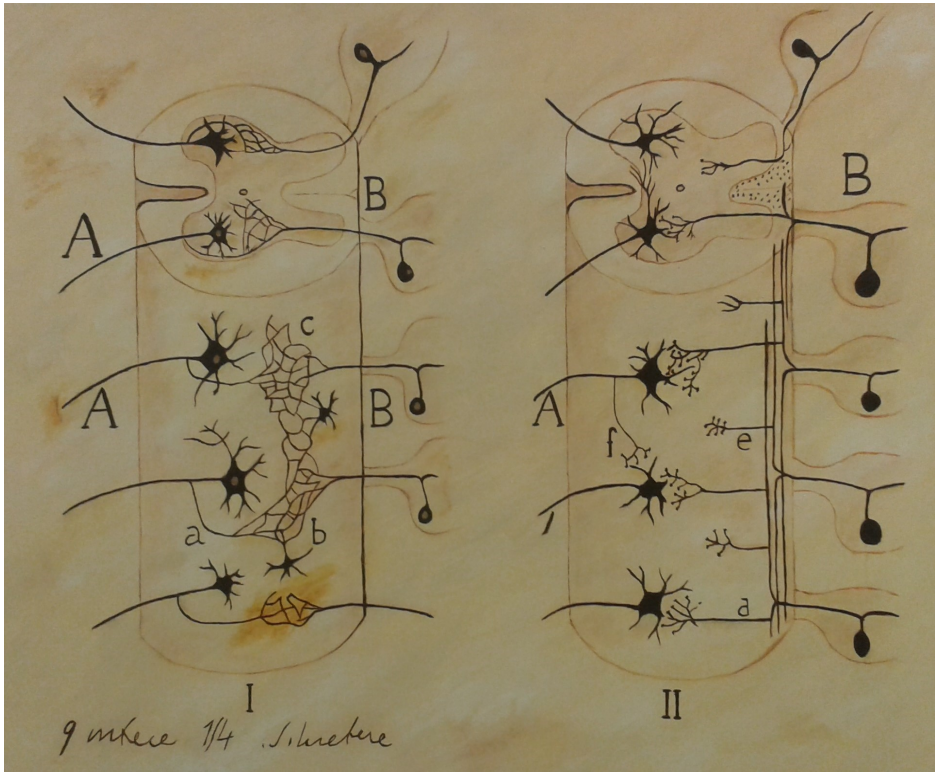
XX

ANIVERSARIO

DEL

PREMIO A JÓVENES INVESTIGADORES EN NEUROCIENCIAS

Instituto de Neurociencias
Universidad de Granada



Reproducción de una lámina de Cajal

cedida por el profesor F. Javier Cañizares García

El “Instituto Universitario de Investigación de Neurociencias Federico Olóriz” es el decano de los Institutos de investigación de la Universidad de Granada y el segundo en antigüedad entre los Institutos de España. Fue creado por O. M. de 30 de diciembre de 1955 (B.O.E. nº 34, pg. 81, 3-2-1956) con ocasión de la celebración del centenario del nacimiento de dicho catedrático. Inicialmente estuvo muy vinculado a las investigaciones en el campo de la Anatomía, de la Técnica Anatómica y de los Estudios Antropológicos dentro de la Facultad de Medicina.

En la Junta General de la Real Academia de Medicina y Cirugía de Granada del día 13 de diciembre de 1966 acordaron por el entonces Director del Instituto, D. Miguel Guirao Pérez, y la Academia la concesión del *Premio Federico Olóriz*. A dicho premio podían aspirar solamente estudiantes de Medicina con un trabajo de investigación de tema libre versado en la *“Iniciación a la investigación en relación con la Anatomía”*. Dicho premio se les entregaría al terminar sus estudios de licenciatura. El 30 de mayo de 1972, el Instituto “Federico Olóriz” comunicó a la Academia que daba carácter definitivo al premio.

La relación de los premios hasta 1990 puede consultarse en la siguiente tabla:

AÑO	TEMA	AUTOR
1967	Estudio de la cúpula pleural y de su aparato suspensor.	D. Juan Aréchaga Martínez
1972	Restos humanos eneolítico con incisiones de la provincia de Granada.	D. Miguel Botella López
1972	Estudio anatómico de la organización neuroglica de la médula espinal.	D. Jesús Vaquero Crespo
1973	Estudio de los huesecillos del oído en inhumados de la necrópolis argárica de la "Cuesta del Negro" de Purullena (Granada).	D. Carlos Gustavo de Linares
1973	Modificaciones estructurales en el páncreas endocrino de hámster por la administración de anovu-latorios orales.	D. José María Campos Gutiérrez
1974	Iniciación a la investigación en relación con la anatomía. Lema Granada.	D. Fernando Escobar Jiménez
1975	Estudio de una Momia Filipina.	D. Guillermo Medina Rossino
1976	Evolución.	Dª María del Mar Morales Illescas
1977	Aportaciones al estudio de las lesiones hipóxicas cerebrales perinatales.	D. Miguel Guirao Piñeyro
1978		D. Cristobal Zaragoza Fernández
1979	Aportación al estudio roentgeno anatomométrico de los senos paranasales.	D. Rafael Olóriz Sáez
1980	Bases anatómicas de los síndromes del Túnel Carpiano y del Túnel de Guyón.	D. Jesús Tercedor Sánchez
1981	Cronología del desarrollo fetal.	Dª María del Mar Morales Hevia
1982		Desierto
1983	Estudio biométrico cráneo-encefálico en el pollo recién nacido.	D. Rafael Gallardo López D. Santiago Oliver Chamorro
1984	Estudio biométrico cráneo-encefálico en el recién nacido como base para su estudio estereotáxico.	D. Rafael Gallardo López D. JoséAntonio Contreras D. Juan Emilio Fernández
1985	Regeneración cartílago-auricular. Alteraciones morfofuncionales huesos carpianos.	D. Eduardo Fernández Segura D. Juan Aliaga Gómez
1986	Coroides en el embrión de pollo. Morfología suelo cuarto ventrículo.	D. Antonio J. Gutiérrez Martín D. J García Gallardo
1987	Morfología núcleos nervios craneales.	D. Gonzalo Piédrola Maroto
1988		Desierto
1989		Desierto

En 1990 se jubiló su director fundador, y la actividad del Instituto, que había estado centrada fundamentalmente en estudios anatómicos y antropológicos, se reorienta hacia el estudio multidisciplinar de la Neurociencia. Entre dicho año y 1995 fue una época de transición en la que se fueron modelando y asentando las nuevas bases y orientación del Instituto con la incorporación de profesores afines a otras ramas del conocimiento pero con interés en la Neurociencia. Durante muchos años el Instituto de Neurociencias "Federico Olóriz" fue el único Instituto de Investigación en Neurociencias en la Comunidad Andaluza, y uno los escasos Institutos de Neurociencias existentes en nuestro país durante las últimas décadas. Por ello, la relación de premios entre 1988 y 1996 aparece en suspenso.

Por fin, en 1996 se retomó la concesión del Premio y la formación de procedencia de los participantes al premio se amplió a otros tipos de estudios y áreas diferentes a la Anatomía y además se les exigió estar en posesión del título de doctor.

En la siguiente tabla se exponen todos los premios recientemente concedidos, motivo de la celebración del XX Aniversario.

AÑO	TEMA	AUTOR
1997	Properties of the nociceptive neurons of the leech segmental ganglion	D. Jesús Pastor Gómez, D. Bernat Soria, D. Carlos Belmonte
1998	Effects of botulinum neurotoxin type A on the expression of gephyrin in cat abducens motoneurons	D. Bernardo Moreno López, D. A. M. Pastor, D. R. R. de la Cruz, D. J. M. Delgado García, D. F. J. Álvarez
1999	Mature intrastriatal striatal grafts reverts the changes in the expression of pallidal and thalamic alpha 1, alpha 2 and beta 2/3 GABAA receptor subunit induced by ibotenic acid lesions in the rat striatum.	D. H. J. Caruncho, D. J. Rodríguez Pallares, D. M. G. Guerra, D. J. L. Labandeira García
2000		Desierto
2001	The subthalamic nucleus in Parkinson's disease: somatotopic organization and physiological characteristics.	Dª. Mª Cruz Rodríguez Oroz
2002	Two populations of kainate receptors with separate signaling mechanisms in hippocampal interneurons.	D. Antonio Rodríguez Moreno
2003	Differential regulation of steroid 5alpha-reductase isozymes expression by androgens in the adult rat brain.	D. Jesús Torres Pinedo
2004	The generation of dopaminergic neurons by human neural stem cells is enhanced by Bcl-XL, both in vitro and in vivo?"	Dª. Elisa García García
2005	Localization of the GLYT1 glycine transporter at glutamatergic synapses in the rat brain.	Dª. Beatriz Cubelos
2006	Cooperative glutamatergic and cholinergic mechanism generate short-term modifications of synaptic effectiveness in prepositus hypoglossi neurons.	D. Juan de Dios Navarro López
2007	Irreversible blockade of sigma-1 receptors by haloperidol and its metabolites in guinea pig brain and SH-SY5Y human neuroblastoma cells.	D. Enrique José Cobos del Moral
2008	Stargazin attenuates intracellular polyamine block of calcium-permeable AMPA receptors.	D. David Soto del Cerro
2009	The distribution of chandelier cell axon terminals that express the GABA plasma membrane transporter GAT-1 in the human neocortex.	Dª. María del Carmen Inda
2010	Histone H1 poly[ADP]-ribosylation regulates the chromatin alterations required for learning consolidation.	Dª. Ángela del Carmen Fontán Lozano
2011	- Alpha-Synucleinopathy in the human olfactory system in Parkinson's disease: involvement of calcium-binding protein- and substance P-positive cells. - Nerve growth factor regulates the firing patterns and synaptic composition of motoneurons. (ver fe erratas)	Dª. Isabel María Úbeda Bañón María América Davis López de Carrizosa
2012	Topographic distribution, frequency, and intensity dependence of stimulus-specific adaptation in the inferior colliculus of the rat.	D. Daniel Duque Doncos
2013	Cyclin-dependent kinase inhibitor p21 controls adult neural stem cell expansion by regulating Sox2 gene expression.	Dª. María de los Ángeles Marqués Torrejón
2014 Básica	Zic2-Dependent Axon Midline Avoidance Controls the Formation of Major Ipsilateral Tracts in the CNS.	D. Augusto Escalante Rodríguez
2014 Clínica	Functional Conectivity Bias in the Prefrontal Cortex of Psychopaths.	Dª. Oren Contreras Rodríguez
2015	Mitofusin 2 in POMC Neurons Connects ER Stress with Leptin Resistance and Energy Imbalance.	D. Marc Schneeberger Pané
2016	A fast pathway for fear in human amygdala.	D. Constantino Méndez Bértolo

AÑO 1997

PREMIADO: **D. Jesús Pastor Gómez**

TÍTULO: **Properties of the nociceptive neurons of the leech segmental ganglion.**

REFERENCIA: **J Neurophysiol. 1996 Jun;75(6):2268-79.**

AUTORES: **Pastor J, Soria B, Belmonte C.**

Abstract:

1. The electrical responses of nociceptive (N) lateral and N medial neurons of the leech segmental ganglion to mechanical, chemical, and thermal stimulation of the skin were studied in a superfused ganglion-body wall preparation. 2. Mechanical indentation of the skin > 10 mN evoked in both types of cells a sustained discharge of impulses; afterdischarge was often observed with suprathreshold stimulations. 3. Application to the cutaneous receptive area of 10-100 mM acetic acid or of NaCl crystals and solutions also elicited a firing response in N medial and N lateral cells. In contrast, capsaicin applied to the skin (3.3 x 10(-5) to 3.3 x 10(-2) M) excited N lateral but not N medial neurons. Likewise, impulse discharges were obtained when capsaicin was applied to the cell bodies of N lateral but not of N medial neurons. 4. In both types of N neurons, heating of the skin above 39 degrees C evoked a discharge of impulses whose frequency was roughly proportional to temperature values. 5. Application of repeated suprathreshold heating cycles at 10-min intervals enhanced the impulse frequency of the response (sensitization). Shorter time intervals between heating cycles depressed the response to heat. Sensitization could not be obtained by equivalent soma depolarizations obtained by intracellular current injection. 6. Impulse discharges evoked by irritant agents were also augmented by previous application of noxious heat. 7. N lateral neurons fired in response to low-pH solutions and capsaicin directly applied onto the ganglion. N medial neurons responded inconsistently to acid and were insensitive to capsaicin. Action potentials evoked in N lateral cells by capsaicin had a slow rise, a prominent hump, and a prolonged afterhyperpolarization. 8. It is concluded that N neurons of the leech segmental ganglion respond to different modalities of noxious stimuli applied to their peripheral receptive fields and develop sensitization after repeated noxious stimulation. These properties are typical of mammalian polymodal nociceptors; thus N neurons may be a simple model for analysis of membrane mechanisms associated with polymodality of nociceptive neurons.

AÑO 1998

PREMIADO: **Bernardo Moreno López**

TÍTULO: **Effects of botulinum neurotoxin type A on the expression of gephyrin in cat abducens motoneurons.**

AUTORES: **Moreno-López B, De la Cruz RR, Pastor AM, Delgado-García JM, Alvarez FJ.**

REFERENCIA: **J. Comp Neurol. 1998 Oct 12;400(1):1-17.**

Abstract:

In this study, we investigated the effects of long-term synaptic blockade on postsynaptic receptor clustering at central inhibitory glycinergic synapses. High doses of botulinum neurotoxin type A injected in the lateral rectus muscle completely abolishes inhibitory postsynaptic potentials onto abducens motoneurons within 2 days postinjection, and transmission remains blocked for at least 2 months. Using this model, we analyzed the expression of gephyrin, a glycine receptor clustering protein, on the membrane of motoneuron somata after botulinum neurotoxin type A injection in their target muscle. Immunofluorescence or electron microscopy immunohistochemistry revealed gephyrin-immunoreactive clusters (most < 0.5 microm in diameter) densely covering the surface of control abducens motoneurons. Ultrastructurally, presynaptic terminals containing flattened synaptic vesicles (F terminals) were found associated with multiple gephyrin-immunoreactive postsynaptic densities (average 1.24 gephyrin clusters/ F+ profile). No significant changes in gephyrin-immunoreactive clusters were observed at 5 days postinjection, but we found significant reductions (25-40%) in the density of gephyrin clusters 19 and 35 days postinjection. Hence, the physiological alterations reported in this model precede structural changes on postsynaptic receptor cluster density. The decrease in gephyrin-immunoreactive clusters was paralleled by reductions in synaptic covering (F+ terminals per 100 microm of membrane). Presumed inactive F+ terminals that remained attached to the motoneuron surface displayed normal gephyrin-immunoreactive clusters; however, the pre- and postsynaptic membranes in between synaptic active zones frequently appeared separated by enlarged extracellular spaces. We concluded that postsynaptic receptor cluster dissolution seemed more directly related to terminal retraction than to inactivity alone.

AÑO 1999

PREMIADA: **Janette Rodríguez Pallarés**

TÍTULO: **Mature intrastriatal striatal grafts revert the changes in the expression of pallidal and thalamic alpha 1, alpha 2 and beta 2/3 GABAA receptor subunit induced by ibotenic acid lesions in the rat striatum.**

REFERENCIA: **Brain Res Mol Brain Res. 1998 Jun 15;57(2):301-9.**

AUTORES: **Caruncho HJ[1], Rodríguez-Pallares J, Guerra MJ, Labandeira-García JL.**

Abstract:

A between-side comparison of GABAA receptor subunit expression levels in the globus pallidus and anterior-pole motor thalamic nuclei of rats with an ibotenate lesion of the striatum, and rats receiving a fetal striatal graft in the lesioned area was made by using immunocytochemistry with subunit-specific antibodies, at different times post-lesion or different times post-grafting. At 10 days post-lesion, there was already an increase in the labeling of the alpha 1- and beta 2/3-subunits in the globus pallidus, entopeduncular nucleus and ventrolateral nucleus ipsilateral to the lesion when compared with the contralateral side, while there were no significant changes at the level of the ventromedial nucleus. Labeling of the alpha 2-subunit showed a clear increase in the entopeduncular nucleus compared with the contralateral side at 10 days post-lesion. Similar changes were also observed for the different subunits studied at 30 and 120 days after lesioning. Rats with 20-day old transplants of fetal striatal neurons that were implanted in the ibotenate lesioned striatum at 10 days post-lesioning, continued to show changes in the expression of GABAA receptor subunits, albeit at a lower level than those of ibotenate lesioned rats at similar age post-lesion. However, when examining rats with 70-day old transplants, the ibotenate-lesion induced between-side changes were almost completely compensated. These findings suggest a correlation between the maturation of the grafts and their capability to function in reestablishing neuronal circuits as shown by the reduction of changes in GABAergic transmission induced by ibotenate lesions, as indicated by the reversal of changes in GABAA receptor subunit in several areas of the basal ganglia circuit.

AÑO 2000

PREMIO: **Desierto**
TÍTULO:
REFERENCIA:
AUTORES:

Abstract:

AÑO 2001

PREMIADA: **María de la Cruz Rodríguez Oroz**
REFERENCIA: **Brain. 2001 Sep;124(Pt 9):1777-90.**
TÍTULO: **The subthalamic nucleus In Parkinson's disease: somatotopic organization and physiological characteristics.**
AUTORES: **Rodriguez-Oroz MC, Rodriguez M, Guridi J, Mewes K, Chockkman V, Vitek J, DeLong MR, Obeso JA.**

Abstract:

Single-cell recording of the subthalamic nucleus (STN) was undertaken in 14 patients with Parkinson's disease submitted to surgery. Three hundred and fifty neurones were recorded and assessed for their response to passive and active movements. Thirty-two per cent were activated by passive and active movement of the limbs, oromandibular region and abdominal wall. All neurones with sensorimotor responses were in the dorsolateral region of the STN. Arm-related neurones were lateral (> or =14 mm plane) to leg-related neurones, which were found more medially (< or =12 mm). Representation of the oromandibular musculature was in the middle of the sensorimotor region (approximately 13 mm plane) and ventral to the arm and leg. Two hundred neurones were adequately isolated for 'off-line' analysis. The mean frequency of discharge was 33 +/- 17 Hz (13-117 Hz). Three types of neuronal discharges were distinguished: irregular (60.5%), tonic (24%) and oscillatory (15.5 %). They were statistically differentiated on the basis of their mean firing frequency and the coefficient of variation of the interspike interval. Neurones responding to movement were of the irregular or tonic type, and were found in the dorsolateral region of the STN. Neurones with oscillatory and low frequency activity did not respond to movement and were in the ventral one-third of the nucleus. Thirty-eight tremor-related neurones were recorded. The majority (84%) of these were sensitive to movement and were located in the dorsolateral region of the STN. Cross power analysis (n = 16) between the rhythmic neuronal activity and tremor in the limbs showed a peak frequency of 5 Hz (4-8 Hz). Neuronal activity of the substantia nigra pars reticulata was recorded 0.5-3 mm below the STN. Eighty neurones were recorded 'on-line' and 27 were isolated for 'off-line' analysis. A tonic pattern of discharge characterized by a mean firing rate of 71 +/- 28 Hz (35-122 Hz) with a mean coefficient of variation of the interspike interval of 0.85 +/- 0.29 ms was found. In only three neurones (11%) was there a response to sensorimotor stimulation. The findings of this study indicate that the somatotopic arrangement and electrophysiological features of the STN in Parkinson's disease patients are similar to those found in monkeys.

AÑO 2002

PREMIADO: **Antonio Rodríguez Moreno**
REFERENCIA: **Proc Natl Acad Sci U S A. 2000 Feb 1;97(3):1293-8.**
TÍTULO: **Two populations of kainate receptors with separate signaling mechanisms in hippocampal interneurons.**
AUTORES: **Rodriguez-Oroz MC[1], Rodriguez M, Guridi J, Mewes K, Chockkman V, Vitek J, DeLong MR, Obeso JA.**

Abstract:

Consistent with the epileptogenic and deleterious effects of the potent neurotoxin kainate, the activation of kainate receptors reduces the synaptic inhibition induced by the amino acid gamma-aminobutyric acid (GABA). Extrapolating from these data led to the conclusion that kainate receptors are located presynaptically. However, kainate directly depolarizes the inhibitory interneurons, causing them to fire repeatedly. This effect might indirectly decrease the size of inhibitory postsynaptic currents recorded from pyramidal cells and places in doubt the presynaptic location for kainate receptors. Here we show that both effects, membrane depolarization and the reduction of inhibitory potentials, can be dissociated by several means, particularly by the natural agonist of kainate receptors, glutamate. Indeed, when applied at low concentrations, glutamate inhibited GABA release without affecting the firing rate of GABA interneurons. These results indicate that CA1 interneurons contain two populations of kainate receptors, each with different agonist sensitivity and coupled to distinct signaling pathways.

AÑO 2003

PREMIADO: **Jesús María Torres de Pinedo**
TÍTULO: **Differential regulation of steroid 5alpha-reductase isozymes expression by androgens in the adult rat brain.**
REFERENCIA: **FASEB J. 2003 Aug;17(11):1428-33.**
AUTORES **Torres JM, Ortega E.**

Abstract:

The enzyme 5alpha-reductase (5alpha-R) is present in many mammalian tissues, including the brain. The physiological importance of 5alpha-R in the brain derives from its capability to convert testosterone (T) to a more potent androgen, dihydrotestosterone (DHT), and to convert progesterone and deoxycorticosterone (DOC) to their respective 5alpha-reduced derivatives, precursors of allopregnanolone and tetrahydroDOC, potent allosteric modulators of the gamma-aminobutyric acid receptor (GABA(A)-R). 5alpha-R occurs as two isoforms, 5alpha-R type 1 (5alpha-R1) and 5alpha-R type 2 (5alpha-R2). We studied the effects of T and DHT on the mRNA levels of both 5alpha-R isozymes in the prefrontal cortex of the adult rat, using an accurate and precise method that combines the high specificity of one-step quantitative RT-PCR with the sensitivity of capillary electrophoresis. Our results demonstrate that both isozymes of 5alpha-R are expressed in the cerebral cortex of adult rats. The gene expression of 5alpha-R type 2 is under the positive control of T and DHT. The gene that codes for 5alpha-R type 1 is not constitutive, because its expression is negatively regulated by T and DHT. These results open up a new research line that may lead to a better understanding of the role of 5alpha-R isozymes in the physiology of the central nervous system.

AÑO 2004

PREMIADA: **Elisa García García**

TÍTULO: **The generation of dopaminergic neurons by human neural stem cells is enhanced by Bcl-XL, both in vitro and in vivo.**

REFERENCIA: **J Neurosci. 2004 Dec 1;24(48):10786-95.**

AUTORES **Liste I, García-García E, Martínez-Serrano A.**

Abstract:

Progress in stem cell biology research is enhancing our ability to generate specific neuron types for basic and applied studies and to design new treatments for neurodegenerative diseases. In the case of Parkinson's disease (PD), alternative human dopaminergic (DAergic) neurons other than primary fetal tissue do not yet exist. One possible source could be human neural stem cells (hNSCs), although the yield in DAergic neurons and their survival are very limited. [see figure]. In this study, we found that Bcl-X(L) enhances (one-to-two orders of magnitude) the capacity for spontaneous dopaminergic differentiation of hNSCs, which then exceeds that of cultured human ventral mesencephalic tissue. Bcl-X(L) also enhanced total neuron generation by hNSCs, but to a lower extent. Neuronal phenotypes other than DA were not affected by Bcl-X(L), indicating an exquisitely specific effect on DAergic neurons. In vivo, grafts of Bcl-X(L)-overexpressing hNSCs do generate surviving human TH+ neurons in the adult rat 6-OH-dopamine lesioned striatum, something never seen when naive hNSCs were transplanted. Most of the data obtained here in terms of the effects of Bcl-X(L) are consistent with an enhanced survival type of mechanism and not supportive of induction, specification, or proliferation of DAergic precursors. From this in vitro and in vivo evidence, we conclude that enhancing Bcl-X(L) expression is important to obtain human DAergic neurons from hNSCs. These findings may facilitate the development of drug-screening and cell-replacement activities to discover new therapeutic strategies for PD.

AÑO 2005

PREMIADA: **Beatriz Cubelos**

TÍTULO: **Localization of the GLYT1 glycine transporter at glutamatergic synapses in the rat brain.**

REFERENCIA: **Cereb Cortex.15:448-459 (2005).**

AUTORES **Cubelos B, Giménez C, Zafra F.**

Abstract:

In this study, we present evidence that a glycine transporter, GLYT1, is expressed in neurons and that it is associated with glutamatergic synapses. Despite the presence of GLYT1 mRNA in both glial cells and in glutamatergic neurons, previous studies have mainly localized GLYT1 immunoreactivity to glial cells in the caudal regions of the nervous system. However, using novel sequence specific antibodies, we have identified GLYT1 not only in glia, but also in neurons. The immunostaining of neuronal elements could best be appreciated in forebrain areas such as the neocortex or the hippocampus, and it was found in fibers, terminal boutons and in some dendrites. Double labeling confocal microscopy with the glutamatergic marker vGLUT1 revealed an enrichment of GLYT1 in a subpopulation of glutamatergic terminals. Moreover, through electron microscopy, we observed an enrichment of GLYT1 in both the presynaptic and the postsynaptic aspects of putative glutamatergic terminals that established asymmetric synapses. In addition, we demonstrated that GLYT1 was physically associated with the NMDA receptor in a biochemical assay. In conclusion, the close spatial association of GLYT1 and glutamatergic synapses strongly supports a role for this protein in neurotransmission mediated by NMDA receptors in the forebrain, and perhaps in other regions of the CNS.

AÑO 2006

PREMIADO: **Juan de Dios Navarro López**

TÍTULO: **Cooperative glutamatergic and cholinergic mechanism generate short-term modifications of synaptic effectiveness in prepositus hypoglossi neurons.**

REFERENCIA: **J Neurosci. 2005 Oct 26;25(43):9902-6.**

AUTORES **Navarro-López J de D, Delgado-García JM, Yajeya J.**

Abstract:

To maintain horizontal eye position on a visual target after a saccade, extraocular motoneurons need a persistent (tonic) neural activity, called "eye-position signal," generated by prepositus hypoglossi (PH) neurons. We have shown previously in vitro and in vivo that this neural activity depends, among others mechanisms, on the interplay of glutamatergic transmission and cholinergic synaptically triggered depolarization. Here, we used rat sagittal brainstem slices, including PH nucleus and paramedian pontine reticular formation (PPRF). We made intracellular recordings of PH neurons and studied their synaptic activation from PPRF neurons. Train stimulation of the PPRF area evoked a cholinergic-sustained depolarization of PH neurons that outlasted the stimulus. EPSPs evoked in PH neurons by single pulses applied to the PPRF presented a short-term potentiation (STP) after train stimulation. APV (an NMDA-receptor blocker) or chelerythrine (a protein kinase-C inhibitor) had no effect on the sustained depolarization, but they did block the evoked STP, whereas pirenzepine (an M1 muscarinic antagonist) blocked both the sustained depolarization and the STP of PH neurons. Thus, electrical stimulation of the PPRF area activates both glutamatergic and cholinergic axons terminating in the PH nucleus, the latter producing a sustained depolarization probably involved in the genesis of the persistent neural activity required for eye fixation. M1-receptor activation seems to evoke a STP of PH neurons via NMDA receptors. Such STP could be needed for the stabilization of the neural network involved in the generation of position signals necessary for eye fixation after a saccade.

AÑO 2007

PREMIADO: **Enrique José Cobos del Moral**

TÍTULO: **Irreversible blockade of sigma-1 receptors by haloperidol and its metabolites in guinea pig brain and SH-SY5Y human neuroblastoma cells.**

REFERENCIA: **J. Neurochem. 102:812-825 (2007).**

AUTORES **Cobos EJ, Del Pozo E, Baeyens JM.**

Abstract:

We evaluated the effect of haloperidol (HP) and its metabolites on [(3)H](+)-pentazocine binding to sigma(1) receptors in SH-SY5Y human neuroblastoma cells and guinea pig brain P(1), P(2) and P(3) subcellular fractions. Three days after a single i.p. injection in guinea pigs of HP (but not of other sigma(1) antagonists or (-)-sulpiride), [(3)H](+)-pentazocine binding to brain membranes was markedly decreased. Recovery of sigma(1) receptor density to steady state after HP-induced inactivation required more than 30 days. HP-metabolite II (reduced HP, 4-(4-chlorophenyl)-alpha-(4-fluorophenyl)-4-hydroxy-1-piperidinebutanol), but not HP-metabolite I (4-(4-chlorophenyl)-4-hydroxypiperidine), irreversibly blocked sigma (1) receptors in guinea pig brain homogenate and P(2) fraction in vitro. We found similar results in SH-SY5Y cells, which suggests that this process may also take place in humans. HP irreversibly inactivated sigma(1) receptors when it was incubated with brain homogenate and SH-SY5Y cells, but not when incubated with P (2) fraction membranes, which suggests that HP is metabolized to inactivate sigma (1) receptors. Menadione, an inhibitor of the ketone reductase activity that leads to the production of HP-metabolite II, completely prevented HP-induced inactivation of sigma(1) receptors in brain homogenates. These results suggest that HP may irreversibly inactivate sigma(1) receptors in guinea pig and human cells, probably after metabolism to reduced HP.

AÑO 2008

PREMIADO: David Soto del Cerro

TÍTULO: Stargazin attenuates intracellular polyamine block of calcium-permeable AMPA receptors.

REFERENCIA: Nat Neurosci. 2007 Oct;10(10):1260-7. Epub 2007 Sep 16.

AUTORES

Abstract:

Erratum in: Nat Neurosci. 2007 Dec;10(12):1634.

Endogenous polyamines profoundly affect the activity of various ion channels, including that of calcium-permeable AMPA-type glutamate receptors (CP-AMPARs). Here we show that stargazin, a transmembrane AMPAR regulatory protein (TARP) known to influence transport, gating and desensitization of AMPARs, greatly reduces block of CP-AMPARs by intracellular polyamines. By decreasing CP -AMPAR affinity for cytoplasmic polyamines, stargazin enhances the charge transfer following single glutamate applications and eliminates the frequency-dependent facilitation seen with repeated applications. In cerebellar stellate cells, which express both synaptic CP-AMPARs and stargazin, we found that the rectification and unitary conductance of channels underlying excitatory postsynaptic currents were matched by those of recombinant AMPARs only when the latter were associated with stargazin. Taken together, our observations establish modulatory actions of stargazin that are specific to CP-AMPARs, and suggest that during synaptic transmission the activity of such receptors, and thus calcium influx, is fundamentally changed by TARPs.

AÑO 2009

PREMIADA: María del Carmen Inda

TÍTULO: The distribution of chandelier cell axon terminals that express the GABA plasma membrane transporter GAT-1 in the human neocortex.

REFERENCIA: Cerebral Cortex 2007, 17:2060-2071.

AUTORES Inda MC, Defelipe J, Muñoz A.

Abstract:

Chandelier cells represent a unique type of cortical GABAergic interneuron whose axon terminals (Ch-terminals) form synapses exclusively with the axon initial segments of pyramidal cells. In this study, we have used immunocytochemistry for the high-affinity plasma membrane transporter-1 (GAT-1) to analyze the distribution and density of Ch-terminals in various cytoarchitectonic and functional areas of the human neocortex. The lowest density of GAT-1-immuoreactive (-ir) Ch-terminals was detected in the primary and secondary visual (areas 17 and 18) and in the somatosensory areas (areas 3b and 1). In contrast, an intermediate density was observed in the motor area 4 and the associative frontolateral areas 45 and 46, whereas the associative frontolateral areas 9 and 10, frontal orbitary areas 11, 12, 13, 14, and 47, associative temporal areas 20, 21, 22, and 38, and cingulate areas 24 and 32 displayed the highest density of GAT-1-ir Ch-terminals. Despite these differences, the laminar distribution of GAT-1-ir Ch-terminals was similar in most cortical areas. Hence, the highest density of this transporter was observed in layer II, followed by layers III, V, VI, and IV. In most cortical areas, the density of GAT-1-ir Ch-terminals was positively correlated with the neuronal density, although a negative correlation was detected in layer III across all cortical areas. These results indicate that there are substantial differences in the distribution and density of GAT-1-ir Ch-terminals between areas and layers of the human neocortex. These differences might be related to the different functional attributes of the cortical regions examined

AÑO 2010

PREMIADA: **Angela del Carmen Fontán Lozano**

TÍTULO: **Histone h1 poly[adp]-ribosylation regulates the chromatin alterations required for learning consolidation.**

REFERENCIA: **J Neurosci. 2010 Oct 6;30(40):13305-13.**

AUTORES **Fontán-Lozano A, Suárez-Pereira I, Horrillo A, Del-Pozo-Martín Y, Hmadcha A, Carrión AM.**

Abstract:

Memory formation requires changes in gene expression, which are regulated by the activation of transcription factors and by changes in epigenetic factors. Poly [ADP]-ribosylation of nuclear proteins has been postulated as a chromatin modification involved in memory consolidation, although the mechanisms involved are not well characterized. Here we demonstrate that poly[ADP]-ribose polymerase 1 (PARP-1) activity and the poly[ADP]-ribosylation of proteins over a specific time course is required for the changes in synaptic plasticity related to memory stabilization in mice. At the molecular level, histone H1 poly[ADP]-ribosylation was evident in the hippocampus after the acquisition period, and it was selectively released in a PARP-1-dependent manner at the promoters of cAMP response element-binding protein and nuclear factor-κB dependent genes associated with learning and memory. These findings suggest that histone H1 poly[ADP]-ribosylation, and its loss at specific loci, is an epigenetic mechanism involved in the reprogramming of neuronal gene expression required for memory consolidation.

AÑO 2011

PREMIADA: **Isabel María Úbeda Bañón**

TÍTULO: **Alpha-Synucleinopathy in the human olfactory system in Parkinson's disease: involvement of calcium-binding protein - and substance P-positive cells.**

REFERENCIA: **Acta Neuropathol. 2010 Jun;119(6):723-35.**

AUTORES **Ubeda-Bañon I, Saiz-Sanchez D, De La Rosa-Prieto C, Argandoña-Palacios L, Garcia-Muñozguren S, Martinez-Marcos A.**

Abstract:

Hyposmia is an early symptom of idiopathic Parkinson's disease but the pathological bases of such dysfunction are largely unknown. The distribution of alpha-synuclein, which forms Lewy bodies and Lewy neurites, and the types of neurons (based on their neurotransmitters) affected by alpha-synucleinopathy were investigated in the olfactory system in Parkinson's disease. Immunohistochemical distribution of alpha-synuclein and its co-localization with tyrosine hydroxylase, somatostatin, calbindin, calretinin, parvalbumin and substance P in the olfactory bulb, anterior olfactory nucleus, olfactory tubercle and piriform, periamygdaloid and rostral entorhinal cortices of idiopathic Parkinson's disease cases (n = 11) and age-matched controls (n = 11) were investigated. Lewy bodies and Lewy neurites were present in the olfactory bulb, particularly in mitral cells and in the inner plexiform layer. alpha-synuclein was particularly abundant in the different divisions of the anterior olfactory nucleus (bulbar, intrapeduncular, retrobulbar and cortical). In contrast, Lewy bodies and Lewy neurites were less abundant in the olfactory tubercle and olfactory cortices. In the olfactory bulb, anterior olfactory nucleus and olfactory cortices, cells affected by alpha-synucleinopathy rarely co-localized tyrosine hydroxylase or somatostatin, but they frequently co-localized calbindin, calretinin, parvalbumin and substance P. The present data provide evidence that alpha-synucleinopathy affects neurons along the olfactory pathway. Dopamine- and somatostatin-positive cells are rarely affected; whereas the cell types most vulnerable to neurodegeneration include glutamate- (mitral cells), calcium-binding protein- and substance P-positive cells. These results provide data on the distribution and cell types involved by alpha-synucleinopathy in the human olfactory system during Parkinson disease that may be useful for future clinical investigation.

AÑO 2012

PREMIADO: Daniel Duque Doncos

TÍTULO: Topographic distribution, frequency, and intensity dependence of stimulus-specific adaptation in the inferior colliculus of the rat.

REFERENCIA: J Neurosci. 2012 Dec 5;32(49):17762-74.

AUTORES Duque D, Pérez-González D, Ayala YA, Palmer AR, Malmierca MS.

Abstract:

The ability to detect unexpected sounds within the environment is an important function of the auditory system, as a rapid response may be required for the organism to survive. Previous studies found a decreased response to repetitive stimuli (standard), but an increased response to rare or less frequent sounds (deviant) in individual neurons in the inferior colliculus (IC) and at higher levels. This phenomenon, known as stimulus-specific adaptation (SSA) has been suggested to underpin change detection. Currently, it is not known how SSA varies within a single neuron receptive field, i.e., it is unclear whether SSA is a unique property of the neuron or a feature that is frequency and/or intensity dependent. In the present experiments, we used the common SSA index (CSI) to quantify and compare the degree of SSA under different stimulation conditions in the IC of the rat. We calculated the CSI at different intensities and frequencies for each individual IC neuron to map the neuronal CSI within the receptive field. Our data show that high SSA is biased toward the high-frequency and low-intensity regions of the receptive field. We also find that SSA is better represented in the earliest portions of the response, and there is a positive correlation between the width of the frequency response area of the neuron and the maximum level of SSA. The present data suggest that SSA in the IC is not mediated by the intrinsic membrane properties of the neurons and instead might be related to an excitatory and/or inhibitory input segregation.

AÑO 2013

PREMIADA: María de los Ángeles Marqués Torrejón

TÍTULO: Cyclin-dependent kinase inhibitor p21 controls adult neural stem cell expansion by regulating Sox2 gene expression.

REFERENCIA: Cell Stem Cell. 2013 Jan 3;12(1):88-100.

AUTORES Marqués-Torrejón MA, Porlan E, Banito A, Gómez-Ibarlucea E, Lopez-Contreras AJ, Fernández-Capetillo O, Vidal A, Gil J, Torres J, Fariñas I.

Abstract:

In the adult brain, continual neurogenesis of olfactory neurons is sustained by the existence of neural stem cells (NSCs) in the subependymal niche. Elimination of the cyclin-dependent kinase inhibitor 1A (p21) leads to premature exhaustion of the subependymal NSC pool, suggesting a relationship between cell cycle control and long-term self-renewal, but the molecular mechanisms underlying NSC maintenance by p21 remain unexplored. Here we identify a function of p21 in the direct regulation of the expression of pluripotency factor Sox2, a key regulator of the specification and maintenance of neural progenitors. We observe that p21 directly binds a Sox2 enhancer and negatively regulates Sox2 expression in NSCs. Augmented levels of Sox2 in p21 null cells induce replicative stress and a DNA damage response that leads to cell growth arrest mediated by increased levels of p19(Arf) and p53. Our results show a regulation of NSC expansion driven by a p21/Sox2/p53 axis.

AÑO 2014 (Modalidad Básica)

PREMIADO: **Augusto Escalante Rodríguez**

REFERENCIA: **Neuron 2013, 80:1392–1406.**

TÍTULO: **Zic2-Dependent Axon Midline Avoidance Controls the Formation of Major Ipsilateral Tracts in the CNS.**

AUTORES **Escalante A, Murillo B, Morenilla-Palao C, Klar A, Herrera E.**

Abstract:

In bilaterally symmetric organisms, interhemispheric communication is essential for sensory processing and motor coordination. The mechanisms that govern axon midline crossing during development have been well studied, particularly at the spinal cord. However, the molecular program that determines axonal ipsilaterality remains poorly understood. Here, we demonstrate that ipsilateral neurons whose axons grow in close proximity to the midline, such as the ascending dorsospinal tracts and the rostromedial thalamocortical projection, avoid midline crossing because they transiently activate the transcription factor Zic2. In contrast, uncrossed neurons whose axons never approach the midline control axonal laterality by Zic2-independent mechanisms. Zic2 induces EphA4 expression in dorsospinal neurons to prevent midline crossing while Robo3 is downregulated to ensure that axons enter the dorsal tracts instead of growing ventrally. Together with previous reports, our data reveal a critical role for Zic2 as a determinant of axon midline avoidance in the CNS across species and pathways.

AÑO 2014 (Modalidad Clínica)

PREMIADA: **Oren Contreras Rodríguez**

TÍTULO: **Functional Conectivity Bias in the Prefrontal Cortex of Psychopaths.**

REFERENCIA: **Biol Psychiatry. 2015 Nov 1;78(9):647-55.**

AUTORES **Contreras-Rodríguez O, Pujol J, Batalla I, Harrison BJ, Soriano-Mas C, Deus J, López-Solà M, Macià D, Pera V, Hernández-Ribas R, Pifarré J, Menchón JM, Cardoner N.**

Abstract:

BACKGROUND: Psychopathy is characterized by a distinctive interpersonal style that combines callous-unemotional traits with inflexible and antisocial behavior. Traditional emotion-based perspectives link emotional impairment mostly to alterations in amygdala-ventromedial frontal circuits. However, these models alone cannot explain why individuals with psychopathy can regularly benefit from emotional information when placed on their focus of attention and why they are more resistant to interference from nonaffective contextual cues. The present study aimed to identify abnormal or distinctive functional links between and within emotional and cognitive brain systems in the psychopathic brain to characterize further the neural bases of psychopathy. **METHODS:** High-resolution anatomic magnetic resonance imaging with a functional sequence acquired in the resting state was used to assess 22 subjects with psychopathy and 22 control subjects. Anatomic and functional connectivity alterations were investigated first using a whole-brain analysis. Brain regions showing overlapping anatomic and functional changes were examined further using seed-based functional connectivity mapping. **RESULTS:** Subjects with psychopathy showed gray matter reduction involving prefrontal cortex, paralimbic, and limbic structures. Anatomic changes overlapped with areas showing increased degree of functional connectivity at the medial-dorsal frontal cortex. Subsequent functional seed-based connectivity mapping revealed a pattern of reduced functional connectivity of prefrontal areas with limbic-paralimbic structures and enhanced connectivity within the dorsal frontal lobe in subjects with psychopathy. **CONCLUSIONS:** Our results suggest that a weakened link between emotional and cognitive domains in the psychopathic brain may combine with enhanced functional connections within frontal executive areas. The identified functional alterations are discussed in the context of potential contributors to the inflexible behavior displayed by individuals with psychopathy.

AÑO 2015

PREMIADO: **Marc Schneeberger Pané**

TÍTULO: **Mitofusin 2 in POMC Neurons Connects ER Stress with Leptin Resistance and Energy Imbalance.**

REFERENCIA: **Cell. 2013 Sep 26;155(1):172-87.**

AUTORES **Schneeberger M, Dietrich MO, Sebastián D, Imbernón M, Castaño C, Garcia A, Esteban Y, Gonzalez-Franquesa A, Rodríguez IC, Bortolozzi A, Garcia-Roves PM, Gomis R, Nogueiras R, Horvath TL, Zorzano A, Claret M.**

Abstract:

Mitofusin 2 (MFN2) plays critical roles in both mitochondrial fusion and the establishment of mitochondria-endoplasmic reticulum (ER) interactions. Hypothalamic ER stress has emerged as a causative factor for the development of leptin resistance, but the underlying mechanisms are largely unknown. Here, we show that mitochondria-ER contacts in anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamus are decreased in diet-induced obesity. POMC-specific ablation of Mfn2 resulted in loss of mitochondria-ER contacts, defective POMC processing, ER stress-induced leptin resistance, hyperphagia, reduced energy expenditure, and obesity. Pharmacological relieve of hypothalamic ER stress reversed these metabolic alterations. Our data establish MFN2 in POMC neurons as an essential regulator of systemic energy balance by fine-tuning the mitochondrial -ER axis homeostasis and function. This previously unrecognized role for MFN2 argues for a crucial involvement in mediating ER stress-induced leptin resistance.

AÑO 2016

PREMIADO: **Constantino Méndez Bértolo**

TÍTULO: **A fast pathway for fear in human amygdala**

REFERENCIA: **Nature Neuroscience Aug; 19 (8): 1041-1049.**

AUTORES **Méndez-Bértolo C, Moratti S, Toledano R, Lopez-Sosa F, Martínez-Alvarez R, Mah YH, Vuilleumier P, Gil-Nagel A, Strange BA.**

Abstract:

A fast, subcortical pathway to the amygdala is thought to have evolved to enable rapid detection of threat. This pathway's existence is fundamental for understanding nonconscious emotional responses, but has been challenged as a result of a lack of evidence for short-latency fear-related responses in primate amygdala, including humans. We recorded human intracranial electrophysiological data and found fast amygdala responses, beginning 74-ms post-stimulus onset, to fearful, but not neutral or happy, facial expressions. These responses had considerably shorter latency than fear responses that we observed in visual cortex. Notably, fast amygdala responses were limited to low spatial frequency components of fearful faces, as predicted by magnocellular inputs to amygdala. Furthermore, fast amygdala responses were not evoked by photographs of arousing scenes, which is indicative of selective early reactivity to socially relevant visual information conveyed by fearful faces. These data therefore support the existence of a phylogenetically old subcortical pathway providing fast, but coarse, threat-related signals to human amygdala.

FE DE ERRATAS

AÑO 2011

PREMIADA: María América Davis López de Carrizosa

TÍTULO: Nerve growth factor regulates the firing patterns and synaptic composition of motoneurons.

REFERENCIA: J Neurosci. 2010 Jun 16;30(24):8308-19.

AUTORES Davis-López de Carrizosa MA,Morado-Díaz CJ, Morcuende S, de la Cruz RR, Pastor AM.

Abstract:

Target-derived neurotrophins exert powerful synaptotrophic actions in the adult brain and are involved in the regulation of different forms of synaptic plasticity. Target disconnection produces a profound synaptic stripping due to the lack of trophic support. Consequently, target reinnervation leads to synaptic remodeling and restoration of cellular functions. Extraocular motoneurons are unique in that they normally express the TrkA neurotrophin receptor in the adult, a feature not seen in other cranial or spinal motoneurons, except after lesions such as axotomy or in neurodegenerative diseases like amyotrophic lateral sclerosis. We investigated the effects of nerve growth factor (NGF) by retrogradely delivering this neurotrophin to abducens motoneurons of adult cats. Axotomy reduced the density of somatic boutons and the overall tonic and phasic firing modulation. Treatment with NGF restored synaptic inputs and firing modulation in axotomized motoneurons. When K252a, a selective inhibitor of tyrosine kinase activity, was applied to specifically test TrkA effects, the NGF-mediated restoration of synapses and firing-related parameters was abolished. Discharge variability and recruitment threshold were, however, increased by NGF compared with control or axotomized motoneurons. Interestingly, these parameters returned to normal following application of REX, an antibody raised against neurotrophin receptor p75 (p75(NTR)). In conclusion, NGF, acting retrogradely through TrkA receptors, supports afferent boutons and regulates the burst and tonic signals correlated with eye movements. On the other hand, p75(NTR) activation regulates recruitment threshold, which impacts on firing regularity. To our knowledge, this is the first report showing powerful synaptotrophic effects of NGF on motoneurons in vivo.