Role of motor cortex in the neuropathology of Huntington's disease

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Huntington's disease (HD) is a neurodegenerative disorder caused by a mutation of the huntingtin protein (mhtt) and is phenotypically characterized by motor and cognitive disturbances. Given that the striatum is the most affected area, most of the research has focused on this brain structure. However, it has become clear that cortex, which sends dense projections to the striatum, contributes to the development and worsening of HD phenotypical alterations. During this presentation, I will describe the effect of removing the expression of mhtt only in the cortical pyramidal neurons of a conditional HD model, at electrophysiological and behavioral levels. I will also describe the changes in the activity of cortical microcircuits in the Q175 HD transgenic model as the disease progresses.These results, taken as a whole with new evidence from both HD patients and HD transgenic models suggest that cortical output neuronsplay a critical role in shaping the onset and progression of striataldysfunction in HD.

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NEURAL EFFECTS OF THE PROLACTIN/VASOINHIBIN AXIS

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The prolactin/vasoinhibin axis is a recently defined neuroendocrine axis in which the generation, secretion, and action of the pituitary hormones prolactin and vasoinhibinsare under the control of the hypothalamus, the pituitary, and local factors within the target tissue microenvironment. The functions of this axis includethe regulation of blood vessels,inflammation, survival, growth, and function oforgans such as the retina, cartilage, liver, and brain. Prolactin frequently acquires opposite effects upon these targets after undergoing proteolytic cleavage to vasoinhibins, a family of prolactin fragments that inhibit vasopermeability, vasodilation, and angiogenesisand promoteinflammation, apoptosis, and anxiety-related responses. In view of their opposing effects, the regulation of the proteases responsible for specific prolactin cleavage represents an efficient mechanism for balancing functions. Disturbances of the prolactin/vasoinhibin axis have strong implications in the pathogenesis of severaldiseases including diabetic retinopathy (DR) and depression-related disorders. Vasoinhibins are reduced in the circulation of patients with DR and preclinical studies show that raising systemic prolactin levels leads to vasoinhibin accumulation in the retina. The elevation of intraocular vasoinhibins prevents and reverses diabetes-induced blood retinal barrier breakdown by targeting excessive vasopermeabilityand the outer component of the blood retinal barrier (retinal pigment epithelial cells). Moreover, retinal neurodegeneration influences DR, and prolactin itself is a retinal trophic factorthat reduces retinal cell death and dysfunction in the continuous light-exposure model of retinal degeneration.On the other hand, the reciprocal interplay between prolactin and vasoinhibins may regulate anxiety and depression. Prolactin is anxiolytic and anti-depressive, but acquires anxiogenic and depressive properties after undergoing proteolytic cleavage to vasoinhibins. Exposure to stress increases the circulating and hypothalamic levels of prolactin but downregulates its hypothalamic conversion to vasoinhibins. Anxiety-related responses may involve direct effects on blood vessels but also on neuronal cells. Ongoing studies investigate the regulation of vasoinhibin generation and how prolactin and vasoinhibins are mechanistically related to affect the function of specific targets under health and disease.Supported by Conacyt 247164and 251.

Suckling: its behavioral and neuroendocrine consequences beyond lactation

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Nursing in rabbits occurs inside the maternal nest, built by the mother in late pregnancy. Across lactation doe rabbits nurse their kits only once per day, for around 3 min, with circadian periodicity. These characteristics of nursing remain unchanged throughout lactation (which lasts 30 days) despite a marked increase in milk output across days 1-20 and a gradual decrease thereafter. Moreover, despite the nursing bout's brief duration, lactating rabbits are in a state of anestrus, i.e., their sexual receptivity and proceptivity (scent marking) are markedly reduced. Little is known about the factors that contribute to such behavioral regulation in does but there is evidence indicating that the amount of suckling stimulation received at each nursing bout plays a crucial role in this regard. Thus, reducing litter size below four kits disrupts the circadian periodicity of nursing, increases the duration of suckling bouts, and allows estrus. Moreover, in does kept away from their litters, the likelihood that they will re-enter a kit-containing nest box presented to them at a given time of day is dependent on: a) time elapsed since the last suckling episode and b) size of the litter nursed then. Does that nursed eight kits will not re-enter the nest box 6 hrs later but 60% and 100% of mothers that suckled four or one young, respectively, will. Even at 3 hrs after having nursed a single kit all of these does will re-enter the nest box and nurse again. Taken together, the above evidence indicates that, in rabbits,a threshold of suckling stimulation is essential to allow the normal expression of maternal behavior and the suppression of estrus. The neural pathwaysand neuroendocrine signals that mediate the transduction from a mechano-tactile stimulus (suckling) to the activation or suppression of complex behaviors are largely unknown and warrant future research.

Thyrotropin releasing hormone neurons integrate signals of stress and energy status,and modulatemetabolism

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Paraventricular-hypothalamic (PVN)thyrotropin-releasing hormone (TRH) andcorticotropin-releasing hormone (CRH)hypophysiotropicneuronsdecodemetabolic,neuronal and environmentalsignals, and regulatetwoneuroendocrineaxes: thehypothalamus-pituitary-thyroid (HPT) and theHP-adrenal (HPA)axes. Thyroid hormones and glucocorticoids (Gc) are crucial participants in energy homeostasis. *Trh*expression and HPT axisare activated by energy demandingsituations (cold, exercise) and inhibitedby negative energy balance, such as food restriction or fasting. At the median eminence(ME) level,released TRH may be inactivated, before reaching the thyrotrophs,by the TRH-degrading ectoenzyme (*Trhde)* expressed in tanycytes andmodulated by nutritional status. CRH neurons are activated byacute or chronic stress; theGcreceptor (GR) mediates the effects of Gc duringstress. Gcor acute stress blunt cold-induced activation of the HPT axis (1-3). Cold activates *Trh* expression in the PVN through cAMP response element binding protein (CREB) phosphorylation.

We explored themechanism of Gc interference on cold-induced activationof *Trh*expression. *In vivo*, corticosterone injection prevents cold-inducedstimulation of CREB phosphorylation in TRH-PVN neurons, as well as PVN TRH and pituitary thyrotropin synthesis and release. In hypothalamic cells, dexamethasone (Dex, a GR ligand) inhibits cAMP-induced CREB phosphorylation, pCREB and GR binding to response elements of *Trh*-gene promoter, and*Trh*mRNA levels,suggesting interference occurs before DNA binding. Furthermore, the catalytic subunit of protein kinase A (PKAc) co-immuno-precipitates with GR and, DexdecreasescAMP-induced nuclear translocation of PKAc. Thus, Gc repress neuronal-induced transcriptional activationof the *Trh*gene by protein:protein interaction between GR and PKAc (1,4).

Chronic stress also curtails stimulation of the HPT axis provoked by either acute cold (*poster* A. Gutierrez-Mata) or voluntary exercise (*poster* F. Salmeron). Effects are observed at various levels of the HPT axis and in target organs. Deleterious effects ofstress insults extend topostnatal stress; maternal separation (MS) or isolation (Iso) during puberty-adolescenceaffect HPT axis programmingin a gender-specific manner. PVN *Trh* expression increases inMS females and ME *Trhde*expression in MS males (5). HPT axis responses to fasting (5) or coldare partiallyblunted in adult MS or Isomales (*poster* D.Rodríguez), a status which could affect their adaptation in conditions ofnegative energy balance. The HPT axis response to a palatable diet also varies according to previous stress paradigm and sex, as well as to age at palatable diet introduction (Jaimes-Hoy, in preparation).These results confirm that PVN TRH neurons act as energy sensors,and demonstrate that they are vulnerable to stress. Stress-induced dysfunction of the HPT axis may contribute to development of obesity and metabolic syndrome (CONACYT 180009 (PJB), PN562 (JLC),and DGAPA IN204316(PJB).

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Age Accumulation of circRNAs in the Brain

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Next generation sequencing technologies permit profiling of gene expression changes during aging in diverse organisms. Surprisingly, there appears to be little correlation of the mRNAs up- or down-regulated during aging among various model organisms and humans. This calls in to question the relevance of such studies to the understanding of human aging. In contrast, we have found that circular RNAs (circRNAs) accumulate on a genome-wide scale during aging in *C. elegans*, *Drosophila*, and mice. CircRNAs are a pervasive class of RNAs detected in most forms of life that are most highly expressed in the nervous system. These molecules most commonly arise from backsplicing of protein-coding exons, which involves the joining of the 3´ end of an exon to the 5´ end of the same exon, or a further upstream exon. Due to their lack of free ends, circRNAs are highly stable molecules that resist degradation by exonucleases. Our group has shown that circRNAs accumulate during agingin *Drosophila* heads and sensory neurons, mouse hippocampus and cortex, and also in adult *C. elegans*. In these organisms, many hundreds of circRNAs increase with aging in a manner independent of the general expression of the host gene. Mechanisms to explain the age-accumulation of circRNAs include 1) the high stability of circRNAs in post-mitotic cells, and 2) the deregulation of alternative splicing with advanced age. The age-accumulation trend conserved among*C. elegans*, *Drosophila*, and mice suggests that circRNAs might have relevance to the age-associated reduction in human brain function. The biological consequences of circRNA age-accumulation are currently unknown; however, the discovery that circRNA age-accumulation occurs in three commonly studied model organisms provides many attractive avenues for investigation into their age-related functions.

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Inflammation and neuronal dysfunction in Alzheimer's disease

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The accumulation of β-Amyloid peptides in the cortex and in the hippocampus as well as a severe loss of the cholinergic system are hallmarks of Alzheimer´s disease (AD). Alterations in autophagy, a key homeostatic process involved in the degradation of dysfunctional or unnecessary cellular components (e.g., organelles and proteins), result in β-Amyloid peptides accumulation and neurodegeneration in AD. Accordingly, restoring autophagy in mouse models of AD, reduced β-Amyloid peptides accumulation, plaque formation and attenuated memory loss. In addition to autophagy dysfunction, cumulative experimental evidences have also placed inflammation as central factor in the development of AD. The current idea is that in response to β-amyloid peptides, microglia and neurons through the activation of the NLRP3 and NLRP1 inflammasomes, produces IL-1β, that in turns enhances the production of TNF thus favoring the inflammatory environment that impairs neural function an eventually results in memory loss.
Given that inflammasome activation by β-Amyloid peptides results in an inflammatory process that leads to memory loss and that restoring autophagy ameliorates memory impairment, we evaluated whether β-Amyloid-induced inflammation promotes memory loss by impairing authophagy in the brain of a mouse model of AD. Here we show that deleterious autophagy associated to β-Amyloid peptide accumulation results from inflammasome activation, since inhibition of the caspase-1-mediated inflammatory response restored brain autophagic flux, reduced β-Amyloid plaque formation in the cortex and the hippocampus, and improved learning and memory capacity.

Molecular aspects of the developing hypothalamus: the role of microRNAs

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Gene expression must be precisely regulated for a proper central nervous system (CNS) development. This regulation relies on a very complex interconnected network of genetic and epigenetic events. microRNAs (miRNAs) have been shown to be key regulators of different cell types differentiation within the CNS of several organisms. miRNAs are small non-coding RNAs that negatively regulate gene expression at the post-transcriptional level. miRNAs control a wide range of biologic processes including development, proliferation and cell differentiation. The present study was aimed to characterize the role of miRNAs during hypothalamus development, a brain structure that controls body homeostasis. Using small RNA massive sequencing, we analyzed the expression profile of miRNAs at different stages of mouse hypothalamic development. We found193 differentially expressed miRNAs that were classified in six different clusters according to their expression profiles. Bioinformatic analyses revealed that some of these miRNAs are likely to be co-regulated at specific developmental stages by stage-specific expressed transcription factors (TFs). Interestingly, we identified miR-7 as one of the miRNAs with a very striking change in expression during the hypothalamic development. Moreover, it is known that miR-7 is one of the most enriched miRNAs within the CNS, which is capable of induce neurogenesis and gliogenesis in several cerebral regions. Finally, to identify miR-7 target transcripts within the hypothalamic context, we used a target pull-down technique followed by mRNA massive parallel sequencing. Bioinformatic analyses revealed a total of 1,323 miR-7 putative target transcripts in the hypothalamic context including several TFs and pathway regulators involved in the control of neurogenesis of distinct CNS regions, such as KLF4, TCF4, NGF, SPATA2, ITCH, CRK and REST, among others. Taken together, our data suggest that miRNAs are key regulators of neuronal differentiation in the hypothalamus.

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Keywords: Hypothalamus, Gene regulation, microRNAs, neurogenesis, gliogenesis.

Sex steroid actions in the amygdala

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The posterodorsal medial amygdala (MePD), part of the subcortical “extended amygdala”, has one of the highest expression of gonadal hormone receptors in the brain, is asexually dimorphic area, andelaborates the timely display of social behaviors in rats. Local synaptic transmission is modulated by sex steroid actions on dendritic spines, which receivemostly excitatory inputs.Adut males have more spines than cycling females. The MePD neurons of maleshave a density of 1.1 spines/dendritic µm composedof thin (~ 50%), mushroom-like, stubby/wide, and few ramified or atypical shaped spines. Gonadectomy (GDX) affects the structural integrity of the MePDat the sametime that impairs male mating behavior. Long-term GDX decreasesthe dendritic spine density in the male MePDof both hemisphere.In addition, GDX reduces (i) the number (up to 50%) of thin, mushroom-like, and ramified spines,(ii) the size and the neck length of thin and (iii) the head diameter of ramified spines, but increases the number of stubby/wide spines(up to 140%). In the female MePD, the density and shape of dendritic spineschange during the different phases of the estrous cycle (lowest values in proestrus and estrus), which indicate that a finesynaptic modulation occursfor the neuroendocrine secretion, ovulation, and proceptivesexual behavior.Following GDX, dendritic spine density in the female MePD increases after estrogen injections, a finding potentiated by progesterone, which differs from the actions observed in normally cycling rats.In conjunction, these evidences indicate that gonadal hormones promote a cellular and synaptic reorganization in the adultMePD. By altering the number and shape of connectional elements, sex steroids dynamically elaborate the strength and plasticity of the neural transmission in a spine-specificmanneras well asthe function of brain circuitries in both male and female brain.

Unravelling the Role of Posttranslational Modifications on Alpha-Synuclein Biology and Pathobiology

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The aggregation of alpha-synuclein (ASYN) in Lewy bodies and Lewy neurites is the typical pathological hallmark of Parkinson's disease (PD) and other synucleinopathies. Furthermore, mutations in the gene encoding for ASYN are associated with familial and sporadic forms of PD, suggesting this protein plays a central role in the disease. However, the precise contribution of ASYN to neuronal dysfunction and death is still unclear. There is intense debate on the nature of the toxic species of ASYN, and little is still known about the molecular determinants of oligomerization and aggregation of ASYN in the cell. By taking advantage of studies in model organisms, we are investigating the effect of various posttranslational modifications on the toxicity and aggregation of ASYN. We found that glycation and acetylation are emerging as important modifications affecting ASYN aggregation.In addition, we are also defining the molecular mechanisms triggered by extracellular forms of ASYN, a process associated with the spreading of pathology.
In total, our data shed light into the molecular underpinnings of synucleinopathies, opening novel perspectives for future therapeutic interventions.