SESSIONS OF THE ACADEMIA BRASILEIRA DE CIÊNCIAS

SUMMARY OF COMMUNICATIONS

Themes on Neuroscience

ATOMIC FORCE MICROSCOPY REVEALS DIFFERENT SURFACE MORPHOLOGIES OF FUNCTIONALLY-DIFFERENT GLIAL CELLS*

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Astroglial cells are involved in directional movements of neurons such as migration of the neuronal cell body and growth of neurites. In the mammalian midbrain, medial (M) and lateral (L) radial glia and derived astrocytes differ in their ability to support neuritic growth. In previous work, we have demonstrated that the growth-permissive ability of L astrocytes and non-permissive properties of M astrocytes correlate with the respective composition of the cell surface-associated and secreted glycosaminoglycans (GAGs). Recent work also shows that the GAG-degrading enzyme heparitinase I increases the neurite growth-promoting ability of M midbrain astrocytes (Garcia-Abreu J *et al.* 2000 Glia 29: 260). In agreement with previous AFM studies of living glial cell lines and cells in primary culture, imaging of living L and M cells at similar load forces showed structures identified as F-actin fibers. Moreover, no systematic differences were observed between L and M pictures. By contrast, the surfaces of formaldehyde-fixed lateral (L) and medial (M) astrocytes differ by the presence of conspicuous 250 nm protrusions in the former, and of a fibrillar network in the extracellular matrix of the latter. Furthermore, we show that treatment with heparitinase I leads to disappearance of the fibrils from M cells and, consequently, to the assumption of an L-like appearance. Our results suggest that the formation of fibrils may follow from an ability to form large aggregates by association of HS carbohydrate units as has been unexpectedly detected by AFM for oligomers of polysialic acid or polysialic acid-containing carbohydrate units of N-CAM, with formation of filament bundles (Toikka J *et al.* 1998. J Biol Chem **273:** 28557). Taken together with the functional effects of heparitinase I treatment, our present results demonstrate an important role of the extracellular matrix on the functional properties of astrocytes. They also emphasize the power and potentialities of AFM in the study of the extracellular matrix on the surface of fixed cells. — (*June 27, 2000*) .

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INHIBITION OF ALZHEIMER'S DISEASE β-AMYLOID AGGREGATION, NEUROTOXICITY AND *IN VIVO* DEPOSITION*

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Aggregation of amyloid β peptide (Aβ) into fibrils and deposition as senile plaques are primarily related to neurotoxicity in Alzheimer's Disease (AD). Thus, agents interfering with aggregation may be potentially useful in preventing or decreasing Aβ toxicity. We first studied the effects of guanidine hydrochloride and temperature on the stability of fibrillar Aβ using peptides truncated at different positions. These experiments suggested that hydrophobic interactions mediated by the C-terminal portion of Aβ are important for fibril stability. Based on these results, we found two compounds capable of disaggregating amyloid fibrils at micromolar concentrations, as indicated by light scattering measurements and transmission electron microscopy. When applied to primary cultures of E18 rat hippocampal neurons, both drugs significantly reduced Aβ-induced cell death (as assayed by trypan blue exclusion). One of the drugs was also tested in an *in vivo* model of cerebral amyloid deposition. Aβ was microinjected into the hippocampus of rats in the absence or in the presence of the drug. After 8 days, brain sections were stained with thioflavin-S and the area occupied by amyloid deposits was quantified by image analysis, revealing a marked reduction in amyloid deposition in the presence of the drug. These results raise the possibility that these compounds, or derivatives prepared from them, may be effective in preventing Aβ neurotoxicity and brain deposition in AD. — (*June 27, 2000*) .

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LONG-TERM ACTIVATION OF ADENOSINE RECEPTORS REGULATES THE SURVIVAL AND BLOCKS GLUTAMATE-MEDIATED NEUROTOXICITY IN CULTURES OF RETINAL NEURONS*

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Presented by Fernando G. de Mello

Adenosine (ado), a neuromodulator in the CNS, is taken up and released from developing chick retinal neurons in culture, suggesting a role for this molecule during retinal development. In the present work we show that preincubation of retinal neurons in culture with ado prevents cell death induced when refeeding the cultures with fresh medium or by exposure of cultures to glutamate. Cells dissociated by trypsinization from 8-day-old chick embryo retinas were seeded (8.3×10^2 cells /mm^2) on poly-L-ornithine coated dishes and incubated for 3 days at 37°C in Medium 199 or BME. Under these conditions neurons and photoreceptors differentiate in the absence of glial cells and extensive cell contacts. The number of neurons decreases 50-70% after refeeding the cultures with fresh medium, an effect blocked when cultures are previously treated with ado + EHNA (ado deaminase inhibitor) or with Nitrobenzylthioinosine (NBI, ado uptake blocker) for $24 - 48$ hours. Ado deaminase also promotes cell death even without changing the medium, indicating that endogenous ado is necessary for cell survival. CGS21680, an A2a receptor agonist, but not CHA, an A1 agonist, is able to block cell death, an effect mimicked by 8-bromo cyclic AMP. Refeeding the cultures with a conditioned medium collected during the first 3 days of culture does not promote cell death. The addition of glutamate to cultures incubated in BME, but not in Medium 199, induces the death of about 80% of neurons that was blocked by preincubation with MK-801, an NMDA antagonist, and also with ado EHNA, NBI, the A2a adenosine receptor agonists CGS21680 and DPMA, or the cyclic AMP analogs 8-Bromo cAMP and Sp-cAMP. Maximal death is reached after 8 hours and in concentrations of glutamate as low as 50 μM as determined measuring the remaining LDH intracellular activity. The protective effect by ado is small when added 1 hour before glutamate and is maximal when added 24 hours or longer periods before the amino acid, indicating that the protection is mediated by the synthesis and/or release of trophic factors. The results show that ado promotes the survival and blocks glutamate toxicity in retinal neurons through the long-term activation of A2a receptors and elevation of intracellular cyclic AMP levels. — (*June 27, 2000*) .

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C-AMP-MEDIATED CHANGES IN THE INTRACELLULAR DISTRIBUTION OF THE MYELIN-RELATED PROTEIN CNPase IN OLFACTORY ENSHEATHING GLIA (OEG)*

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The olfactory system exhibits perennial plasticity with uninterrupted renewal of primary afferents and growth-permissive properties of the ensheathing glia. Although OEG may myelinate non-olfactory axons, there is little information on the factors controlling the ability of OEG to express myelin-related markers. We analyzed the expression of the membrane-skeletal protein CNPase in explants of the olfactory bulb (OB) cultured under control or c-AMP stimulated conditions. Explants from OB of young adult rats were cultured onto laminin-coated coverslips in DMEM-F12/ fetal calf serum medium. Explants were treated with $0.1 - 0.5\mu$M dibutyril c-AMP (diBu-c-AMP) or $10 - 100\mu$M forskolin (Fk) or vehicles only for 4 hours. Then they were washed and fixed with 4% paraformaldehyde and reacted with anti-CNPase or anti-MBP and anti-S100 or anti-GFAP or anti-vimentin antibodies and with either Cy3- or FITC-labeled secondary antibodies. Within the core of explants fixed after 3 days *in vitro*, there were GFAP+ astrocytes and cells with morphology typical of oligodendrocytes showing strong CNPase staining and a fragmented distribution of MBP immunoreactivity. GFAP+ cells of both fibroblast-like and multipolar morphology appeared halfway from the explant rim to the periphery. Outside of the control explants, there were short, radiating neurites and S100+ bipolar or tripolar cells which showed no anti-MBP binding. However, some of these cells displayed weak and diffuse CNPase immunoreactivity. After diBu-c-AMP or Fk, the proportion of S100+/ CNPase++ bipolar cells decreased in a dose-dependent manner, replaced by velate cells, also S100+/CNPase++, but with distributions of these markers different from that of bipolar cells. S100 immunoreactivity could usually be found far more distally than CNPase, extending to flat membrane expansions that were not CNPase+. In addition, CNPase became redistributed, showing an “interrupted-lines” pattern both near the cell nucleus and in veins within proximal regions. Very similar patterns were obtained for highly-biotinylated proteins that are reliable markers for mitochondria which, by their turn, may reflect the location of stable microtubules. Our results show that OEG express CNPase and that cAMP plays a role in the control of the expression of a myelinating phenotype. — (*June 27, 2000*) .

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THYROID HORMONE DEFFICIENCY IMPAIRS MYELIN COMPACTION*

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Presented by Leny A. Cavalcante

We have shown that myelinated nerve fibers from hypothyroid rats display a continuous pattern of immunostaining as revealed by a monoclonal antibody against 2’3’cyclic nucleotide 3’phosphodiesterase (anti-CNPase). This finding contrasts with the pattern shown by the normal animal, suggesting a possible role for thyroid hormones on myelin compaction. To study the effects of thyroid hormone deficiency during CNS myelinogenesis, we used two approaches: 1. The sequence of expression of myelin basic protein (MBP) and myelin-associated/oligodendrocytic basic protein (MOBP) as detected by immunoblotting in the cerebellum (Cb) and corpus callosum (cc) of postnatal normal (C) and hypothyroid (H) animals from 10 to 60 days (P10 to P60); 2. The morphology of myelinated fibers as observed by electron microscopy in cc from C and H groups at P60 and P90. We evaluated the frequency of morphological abnormalities (multiple inner and outer loops and redundant myelin) and performed a morphometric analysis of myelin sheath thickness (ShT) and cytoplasmic loop thickness (CL). The onset of expression of both MOBP isoforms occurred at P25 and P30 in cc and Cb, respectively, in the C group. However, all the MOPB isoforms were weakly detectable in both regions from the H group at P30 and the higher molecular weight isoform remained reduced in cc as late as P60. The expression of MBP proteins was also delayed in the H group, but showed a recovery in both structures at P45. The morphometric analysis of the axons did not show significant differences in ShT and CL in either age. Furthermore, the frequency of multiple inner loops was higher in the H group at P60, with no significant differences at P90. Our findings suggest that 1. Hypothyroidism affects the developmental pattern of late oligodendrocytic/myelin markers and selectively impairs MOBP protein expression; 2. The thyroid hormone may modulate axo-oligodendroglial relationships as indicated by the

higher frequency of multiple inner loops and the apparent decrease of compact lamellae in H group. Taken together, these data reinforce the hypothesis of a role for thyroid hormone on myelin compaction. — (*June 27, 2000*) .

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CHARACTERIZATION OF CRUSTACEAN CENTRAL GLIA*

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The functions of the nervous system result from the interaction not only among neurons, but also between neurons and glial cells. In some invertebrates, peripheral glial cells show a great variety of types that have been relatively well characterized by ultrastructural and physiological criteria. Less is known about central glia, particularly in superior invertebrates such as crustaceans. In view of differences between the axonal ensheathment in crustaceans and vertebrates, we have tried to use the immunohistochemical detection of 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase), an actin-binding protein detected in non-compacted oligodendroglial and Schwann cells ensheathments, to characterize central glial cells in 2 crustaceans: the crab *Ucides cordatus* and post-larval stages of the giant prawn *Macrobrachium rosenbergii.* In the protocerebrum of *U. cordatus*, CNPase immunoreactivity was observed in cell bodies and processes in the basal membrane, lamina ganglionaris, external, internal and terminal medullae and in the protocerebral tract. The same structures were also immunoreactive in the post-larval stages of *M. rosenbergii*. CNPase immunohistochemistry was also found in the ganglionic X-organ, including neurosecretory neurons with diameters larger than 30 μm. In the deutocerebrum, CNPase labeling was observed in the olfactory lobe. Glutamine synthetase (GS), also used as a glial cell label in vertebrates, was tested in the same crustaceans. In post-larval prawns, immunohistochemical localization of GS could be observed in the lamina ganglionaris and other subdivisions of the optic lobes. The sites where this enzyme was detected are comparable to the sites where CNPase is expressed although the density of label varies. Our results indicate that both CNPase and glutamine synthetase are phylogenetically conserved and that they could be considered useful labels to identify crustacean central glial cells as well as large diameter neurons of the ganglionic X-organ. — (*June 27, 2000*) .

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SELECTIVE DEGENERATION OF PHOTORECEPTORS IN RETINAL TISSUE IN VITRO: A NEW EXPERIMENTAL MODEL FOR RETINITIS PIGMENTOSA*

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Retinitis pigmentosa (RP) is a degenerative retinal disease, that starts with the death of rod photoreceptors. Various forms of RP are mapped to at least 23 chromosomal loci, including more than 100 mutations. Many of these affect components of the visual transduction cascade, but the mechanisms of induction of cell death are unknown. Apart from attempts at selective gene therapy for specific mutations, photoreceptor protective measures may help the design of novel treatments for RP. We established a model of selective photoreceptor apoptosis within retinal tissue *in vitro*. Retinal explants from 5-6 day-old rats were maintained *in vitro* for 24 hours in the presence of thapsigargin, an inhibitor of Calcium-ATPase of the endoplasmic reticulum; okadaic acid, a phosphatase inhibitor; anisomycin, an inhibitor of protein synthesis; or forskolin, an activator of adenylyl cyclase. Sections of the explants were examined for apoptosis by either Neutral-Red staining or TUNEL. Photoreceptors were identified by rhodopsin immunohistochemistry. Protein synthesis-dependent apoptosis of photoreceptors was selectively induced by either thapsigargin or okadaic acid, and was blocked by an increase of intracellular cAMP. Thus, apoptosis may be selectively induced in photoreceptors within the histotypical environment of retinal tissue in controlled *in vitro* conditions. It is not clear

why photoreceptors are selectively vulnerable to these two metabolic inhibitors, which affect many intracellular processes in all retinal cells. The redox factor/AP endonuclease Ref-1 (APE, APEX, HAP1) affects both DNA repair and the activity of various transcription factors, and controls sensitivity to genotoxic insults. Ref-1 protein was detected immunohistochemically both in retinae of various ages and in explants *in vitro*. Ref-1 content increased progressively within the nucleus of differentiating retinal cells, but remained less in rod photoreceptors than in other cells of the mature retina. During cell death, Ref-1 invariably disappeared from the nucleus of apoptotic cells. Inhibition of protein synthesis both prevented the loss of Ref-1 and rescued the neurons. The data suggest that Ref-1 is an anti-apoptotic protein associated with cell differentiation in the retina. This study indicates that a low content of Ref-1 may be associated with the highest sensitivity of photoreceptors to degeneration, and warrants attempts at controlling photoreceptor cell death by targeted overexpression of Ref-1. — (*June 27, 2000*) .

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NEUROPROTECTIVE FUNCTION OF THE ENDOGENOUS PRION: A NEW PERSPECTIVE FOR SPONGIFORM ENCEPHALOPATHIES*

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Spongiform encephalopathies are attributed to conformational conversion of the GPI-anchored endogenous prion protein (PrPc) into a pathogenic isoform. The relative contribution of either the amyloid deposition of converted protein, or the loss of function of the prion protein, to pathogeny of prion diseases remains to be elucidated. Despite the abundance of PrPc in the central nervous system (CNS), its normal functions are largely unknown. A 16-aminoacid synthetic peptide designed on the basis of complementary hydropathy, has been used to produce an antiserum that recognizes a PrPc-binding 66-kDa protein (Martins VR *et al.* 1997, Nature Med 3: 1376). Here we show that activation of PrPc by this peptide has an anti-apoptotic effect mediated by cAMP-dependent protein kinase in developing nervous tissue. Histotypical retinal explants are used as a model to study the mechanisms of apoptosis in the developing CNS (Linden R *et al.* 1999, Prog. Ret Eye Res 18: 133). Explants of the retina of neonatal rats or mice were kept *in vitro* for 24 h. Inhibition of protein synthesis with anisomycin (ANI, $1 - 3.2\mu$g/ml) induced apoptosis of differentiating cells within the immature neuroblastic layer. The 16 aa. peptide partially prevented apoptosis induced by ANI in explants of the retina from wild-type rats and mice, but not from transgenic PrPc $-/-$ mice. The anti-apoptotic effect of the PrPc-ligand peptide was abolished by pre-incubation of explants with PI-PLC (3μg/ml, 1 h at 37°C), a procedure that releases GPI-anchored proteins from membranes. The PrPc-binding peptide induces in retinal tissue an increase in both cAMP and in the activity of PKA, and increased activation of Erk. Inhibition of cAMP-dependent protein kinase, but not inhibition of the Erk activation pathway abolished the neuroprotective effect of the prion-binding peptide. The results suggest that binding of the 66-kDa ligand protein activates PrPc, which triggers downstream anti-apoptotic signals through the activation of PKA. Thus the endogenous PrPc protein transduces neuroprotective signals in the developing nervous system. These findings are consistent with the hypothesis that the neurological deficits associated with spongiform encephalopathies may depend on loss of function of the endogenous prion protein, leading to increased neuronal vulnerability. — (*June 27, 2000*) .

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IMMUNOHISTOCHEMICAL CHARACTERIZATION OF NMDA, KAINIC ACID AND ASPARTATE-INDUCED RELEASED OF GABA IN CHICK RETINA*

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It has been shown that glutamate and its agonists, NMDA, kainic acid (KA) and aspartate (ASP) can promote the release of GABA from isolated retina and retina cell cultures. In addition, dopamine (DA) modulates the

release induced by NMDA. The aim of this work is to determine, qualitatively and quantitatively the GABAergic cell types that are affected by glutamatergic agonists and DA in isolated mature and embryonic chick retina. Embryonic day fourteen (E14) and two- to seven-day post-hatched (P2-7) retinas were incubated with different glutamatergic agonists and DA at 37°C. GABA containing neurons (GABA+) were identified immunohistochemically. In P7 animals, the stimulation of GABA release with NMDA or ASP resulted in 50% decrease in the number of GABA+ amacrine cells. No change in GABA+ horizontal cell number was detected. DA partially inhibited (50%) the decrease in GABA+ amacrine cells by the treatment with either NMDA or ASP. KA induced a decrease of both GABA+ amacrine (60%) and horizontal cells (50%). However, DA did not interfere with the release stimulated by KA. NMDA, KA and ASP stimulated retinas show a punctate labeling of the inner plexiform layer, differing from the uninterrupted labeling in the control retina. The NMDA effect on GABAergic cell number was the same for E14 or P2-7 retinas, i.e., a 50% decrease in the number of GABA+ amacrine cell number. In addition, DA partially (50%) reduced the NMDA effect. The KA effect on the embryonic retina repeated the pattern seen in P2-7 retinas, a reduction of both GABA+ amacrine (60%) and horizontal cells (50%). However, as opposed to what was observed in P2-7 retinas, DA significantly reduced the decrease of GABA+ cells induced by KA in E14 retinas. From this data, it can be concluded that NMDA induced GABA release from amacrine cells is modulated by dopamine. This effect is independent of the developmental stage of the retina, since it is observed in both, E14 and P2-P7. On the other hand, KA stimulates GABA release from both types in E14 and P2-P7 chicken. However DA modulates this process in E14 retina, but not in P2-7 retinas. — (*June 27, 2000*) .

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REGULATION OF GLUTAMIC ACID DECARBOXYLASE OF CHICK AND RAT RETINA CELLS BY GABA AND EXCITATORY AMINO ACIDS*

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GABA added to cultured retina cells inhibits the expression of glutamic acid decarboxylase (GAD) molecules and activity. In the present work using chick and rat retina cultures, we studied the mechanism of GAD regulation by GABA and excitatory amino acids (EAAs) using immunohistochemical and Page-immunoblot detection of the enzyme, as well as by measuring the enzyme activity. Retina cells were obtained from chick embryos ($E_8 - E_9$) and aggregate cultures were prepared. For organotypical cultures chick embryos (E_{14}), post-hatched chick and rat (P_{21}) retinas were used. The treatment with GABA (1 to 20mM) fully prevented the expression of the enzyme in aggregate and organotypical cultures from retinas of chick embryos, as compared to the control tissue. A substantial reduction of GAD was also observed in organotypical cultures of post-hatched chicken and rat retinas. Even though a clear reduction of GAD was observed, part of the enzyme was relatively resistant to the regulation by GABA. The GABA effect was not mimiced by THIP, baclofen or CACA, agonists of GABAa, b, and c receptors, respectively. These drugs did not significantly affect GAD immunoreactivity or activity as compared to control groups. The pre-treatment with NNC-711 a potent GABA carrier inhibitor, prevented GAD reduction induced by GABA and caused a 50% reduction in the inhibition of GAD activity promoted by GABA. These results together indicate that GAD regulation by GABA does not involve known GABAergic receptors activation and requires the transmitter uptake by GABAergic cells. The treatment of aggregates, pre-exposed to GABA, with glutamate or kainate induced an intense GAD-like immunoreactivity in several cell bodies but not in plexus areas. Immunoblotting analysis revealed an immunoreactive fraction corresponding to a protein in the region of 67kD. However GAD activity was not detected in these aggregates. The lack of activity could be a consequence of the production of NO induced by EAAs. In fact treatment of aggregates or retina homogenates with SNAP (but not with its inactive form) induced a reduction of more than 60% in GAD activity. — (*June 27, 2000*) .

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SYNPHILIN-1: A POSSIBLE MOLECULAR DETERMINANT FOR PARKINSON'S DISEASE*

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Presented by ROBERTO LENT

Parkinson's disease (PD) is one of the most common neurodegenerative diseases. The disease is characterized by a set of motor signs including, tremor, bradykinesia and rigidity. Examination of post-mortem PD brains show loss of neurons in the substantia nigra and the presence of cytoplasmic inclusions in the surviving neurons, termed Lewy bodies. PD is mostly sporadic, but some families inherit PD in an autosomal dominant manner. Mutations in the alpha-synuclein gene lead to some forms of familial PD. In addition, alpha-synuclein was found to be a major component of Lewy bodies in patients with sporadic PD, suggesting that alpha-synuclein may have an important role in the pathogenesis of PD. We recently found that alpha-synuclein interacts *in vivo* with a novel protein we have called synphilin-1. Synphilin-1 has no homology to any other protein in the database. It contains an ATP,GTP-binding domain and two protein-protein interaction domains, ankyrin-like repeats and coil-coiled domain. When synphilin-1 is co-transfected into mammalian cells with alpha-synuclein we observe the formation of eosinophilic inclusions resembling Lewy bodies, suggesting that synphilin-1 could modulate alpha-synuclein aggregation. We also found that, like alpha-synuclein, synphilin-1 is present in the majority of Lewy bodies of patients with PD. Synphilin-1 is present in almost 90% of Lewy bodies from substantia nigra and other regions of the brain, such as cerebral cortex, but it is absent in amyloid plaques from patients with Alzheimer's disease, suggesting that synphilin-1 could be important to the pathogenesis of PD. We have now cloned the human synphilin-1 gene, determined the organization of its 10 exons and localized it to chromosome 5q23.1-23.3. Mutation analysis of synphilin-1 may further clarify its role in the pathogenesis of genetic PD. To determine the function of synphilin-1, we are currently searching for its protein partners. Using the yeast two-hybrid system, we found that the N-terminus of synphilin-1 interacts with a protein that is still under characterization. We also found that the N-terminus of synphilin-1 is responsible for the interaction with alpha-synuclein. Proteins that specifically interact with the N-terminal portion of synphilin-1 may modulate the interaction between synphilin-1 and alpha-synuclein, and perhaps influence the formation of Lewy bodies and subsequent manifestation of the disease. Identification of additional protein partners of synphilin-1 will help understand its normal function and perhaps its role in the pathogenesis of PD. — (*June 27, 2000*) .

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MODULATION OF GFAP GENE PROMOTER BY NEURONS DURING DEVELOPMENT*

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Neuron-glial interactions play pivotal role in several steps of CNS morphogenesis, since the early stages of neurogenesis until the later events of neural connections establishment. Most of our knowledge concerning such interactions lies on data obtained from glial cells effects on neuronal morphogenesis. However, several evidences have been accumulated in the past years pointing to a mutual influence between these two cells. While there is compelling evidence of neuronal factors on oligodendrocytes and Schwann cells, there is still lack of data of their effects on astrocytes. In order to access this question we have established an astrocyte-neuron coculture system by using a transgenic mice bearing part of the astrocyte maturation marker glial fibrillary acidic protein (GFAP) gene promoter linked to the β-galactosidase (β-gal) reporter gene. New insights into the biological function of GFAP have been provided by the generation of GFAP transgenic and null mice. Increasing evidences have accumulated pointing to a role of GFAP in neuron-glia interactions such as modulation of astrocyte stellation, axon sprouting and regeneration. We have recently demonstrated that cortical neurons can induce GFAP gene promoter followed by transgenic astrocyte differentiation, by secreting brain region-specific soluble factors (Gomes F *et al.* 1999 Glia 26: 97). Further, neuronal mediated astrocyte differentiation is dependent on neurons and astrocyte developmental stage. Younger neurons derived from 14-16 embryonic days (E14-16) wild type mice are more efficient in promoting astrocyte differentiation than those derived from E18 mice. Similarly, astrocytes also exhibit a timed sched-

ule developed responsiveness to neuronal influences with embryonic astrocytes showing to be more responsive to neuronal influence than newborn and late postnatal astrocytes.

Together these data support the concept that within the context of brain development, neuron-glia interactions are not unique, rather they present a great complexity and heterogeneity throughout CNS. Although neuronal effects mechanisms on astrocytes are still far from being well understood, we have demonstrated that neurons are able to activate GFAP gene promoter and astrocytic differentiation program guided by a development clock. Those data might provide new insights on astrocytes precursors differentiation and implicate neuron-glial interactions in gliogenesis as well as in the developmental plasticity of the brain. — (*June 27, 2000*) .

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THE CEREBELLUM AS A MODEL FOR IN VITRO AND IN SITU GAP JUNCTIONAL COUPLING STUDIES*

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Here we consider the phenomenon of gap junction-mediated intercellular communication (GJC) in the young cerebellum from three different experimental perspectives. By intracellular iontophoretic application of fluorochromes, we were able to characterize the temporal profile of homo- and heterocellular coupling in primary cocultures of cerebellar neurons onto monolayered astrocytes, dissociated from P0 rats. Dye injections of Lucifer yellow (LY) were performed everyday, between the first and fourth days *in vitro*, and then at the seventh day. Coupling between neurons and between these and astrocytes displayed inverted profiles, with older cocultures enriched in heterocellular coupling. In contrast, coupling between astrocytes was roughly constant. Such increase in neuron/astrocyte communication was accompanied by a decrease in cell proliferation, which paralleled the neuronal uncoupling and gradual neuronal maturation evidenced by morphological and immunolabeling criteria. These results were crossed with a topographic view of dye coupling in cerebellum slices, revealed by the "transection loading technique" (Menezes J *et al.* 2000 Dev Neurosci 22:34). Thick (800μm) sagittal sections of P4 cerebella were immersed in a combination of LY and rhodamine-conjugated dextran (RD, 3kDa), washed and fixed in paraformaldehyde, prior to blocking and cryostat resectioning. Directly loaded cells, LY+ and RD+, were visualized along the cut edges of cerebellar slices. LY+ coupled cells, some of them presenting typical migratory aspects could be identified in the inner granule and the molecular layers and were absent in the proliferative external granule layer, in agreement with previous findings. Using a third experimental model, the explant culture, cell migration could also be approached. Explants from the external granule layer (P4) were kept for up 5 days in culture onto polylisine-treated coverslips or, alternatively, onto brain astrocytic monolayers. Centrifugal migration from explants was examined in presence of the uncoupler agent, carbenoxolone (CARBEN). Blockage of GJC had opposite consequences in polylisine and astrocytic monolayers. Briefly, migration of neural precursors was impaired by CARBEN in explant cultures on coverslips and enhanced in monolayers, reverting the patterns evident in control conditions. Taken together, our results point to a range of functional cell pairs, homo- and heterocellular, at early stages of the cerebellum development involved in different aspects of cell differentiation. — (*June 27, 2000*) .

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GAP JUNCTIONS ARE INVOLVED ON THE MIGRATION OF POSTNATAL SUBVENTRICULAR ZONE CELLS*

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Progenitor cells within the postnatal subventricular zone are remarkable as they migrate and proliferate simultaneously. These cells and their progeny migrate rostrally to the olfactory bulb where they will differentiate into

interneurons. This process, called the rostral migratory stream (RMS), is massive in the first two postnatal weeks, and lingers, somewhat smaller, well into adulthood. Recently, we have demonstrated gap junction mediated cell coupling (GJC) within this layer (Menezes J *et al.* 2000 Dev Neurosci 22:34). Futhermore, GJC matches spatially the distribution of S-phase cells, and is absent where most migratory cells are concentrated. In another germinal layer, the embryonic ventricular zone, cell coupling has been implicated in maintaining cells in the proliferative cycle (Bittman J *et al.* 1997 J Neurosci 17:7037). To investigate whether GJC plays a role on the proliferative and migratory behavior of SVZ/RMS, we have used an *in vitro* approach. Briefly, SVZ explants were obtained from 3-4 days postnatal rat pups and cultured directly over poly-ornithine/polylisine treated coverslips; 12 hours after plating, carbenoxolone (10μM), a pharmacological inhibitor of GJC, was added to the culture medium; 3-5 days later, centrifugal migration was scored in treated and untreated explants. Outward migration was robust in untreated explants, displaying chains of small migrating cells. In treated explants, migration was greatly reduced or absent. This effect was partially reversed after interrupting carbenoxolone treatment and keeping the explants *in vitro* for two more days. Interestingly, recovered explants, in addition to the small migratory cells, also exhibited elongated cells radiating from the explant, which resembled radial glial cells. Migratory cells were preferentially distributed over these elongated glial cells, and did not seem to form chains as seen in control explants. Our results indicate that gap junction mediated cell coupling may be involved in regulating cell migration of SVZ precursors cells. This effect may be directly over the migratory cells, possibly triggering cell migration. Alternatively, it may be mediated by homo- or heterologous cell coupling of glial supporting cells present within the SVZ. — (*June 27, 2000*) .

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FORMATION OF CORTICAL TISSUE FROM SLICES MAINTAINED IN VITRO: A MODEL FOR RADIAL AND TANGENTIAL MIGRATION STUDIES*

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During cerebral cortex development, neurons cease to proliferate in the ventricular zone and migrate predominantly on radial glia (RG) to the surface of the cortical plate. There they uncouple from the RG and differentiate. However, recently, neurons that originate in extracortical proliferative regions were shown to migrate tangentially to the cortex giving rise to inhibitory neurons. We propose a new model to study cellular and molecular interactions in these different migratory streams based on an *in vitro* slice culture assay. Coronal slices (350μm) of E15 hamster brains were obtained with a tissue chopper and plated in Petriperm membranes where culture medium was added. After 2-7 days in the incubator (5%CO_2) a thin layer of tissue was apparent outside the slice. Vimentin and GFAP immunoreactivity demonstrated that radial glial processes emerge from the outside of the slice border in two ways: unfasciculated, in which case the newly formed tissue emerged just outside of the slice border, or in bundles which defasciculated further out. DIC imaging showed round cells closely adhered to the glial processes. Double-labeling of GFAP and MAP-2 characterized these cells as neuronal precursors attached to glial fibers. Class III β tubulin immunoreactivity revealed differentiated neurons in a denser neuronal plexus where RG processes defasciculated. Specific markers were used to further characterize their neuronal identity and neurons were immunolabeled for MAP-2, 9-O-acetylated gangliosides and LAMP. Differentiated astrocytes were also found in the tissue. Neurons within the marginal zone (MZ) of the slice were immunolabeled for calretinin and reelin. A subpopulation of these calretinin positive neurons could be found attached to radial glia out of the slice. Many migratory profiles were found both within the MZ, seemingly migrating horizontally, and attached to the radial glial fascicles outside of the slice migrating radially. Our results show that a cortical tissue is organized from brain slice cultures based on the outward migration of neuronal precursors on radial glia. Migrating cells derived from at least two origins were identified - MZ and VZ neuronal precursors. These cells are able to migrate and differentiate several hundred microns from the slice border. MZ cells are capable of switching from a tangential migratory route into radial migration supported by glia.

We propose that this model will be extremely useful to study cellular and molecular mechanisms underlying migration in the cerebral cortex. — (*June 27, 2000*) .

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FUNCTION OF GANGLIOSIDE 9-O-ACETYL GD3 IN NEURONAL MIGRATION*

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Neuronal migration occurs in many regions of the developing mammalian central nervous system and normal histogenesis is dependent on the precise migration of neurons during development. In the cerebellum, granule cell precursors migrate along tangential paths from the most caudal portion of the cerebellar ventricular zone onto the surface of the cerebellum where they form the external granular layer (EGL). During the early postnatal period in rodents, granule cells in the proliferative EGL migrate down into the cerebellar cortex to form the internal granular layer (IGL). It has been proposed that granule cells use the processes of radial glia to migrate from the EGL to the IGL. Although several molecules have been proposed to be involved in this process the molecular mechanisms influencing granule cell migration are not yet fully understood. In the present study, we provide evidence that the ganglioside 9-O-acetyl GD3 recognized by the monoclonal antibody Jones (Jones mAb) is involved in the migration of granule cells in the developing rat cerebellum. Gangliosides constitute a major group of cell-surface molecules that have been implicated in numerous functions in the developing and adult mammalian nervous system. The expression of 9-O-acetyl GD3 correlates specifically with times of granule cell migration in the cerebellum suggesting a possible role for this molecule in the glial-guided migration of these cells. Electron microscopic immunocytochemistry revealed that this ganglioside was localized at the contact sites between migrating granule neurons and radial glia in the external granule layer and prospective molecular layer. To investigate the function of 9-O-acetyl GD3 in this system we added Jones mAb to cerebellar cultures. It was possible to demonstrate that granule cell migration was blocked in the presence of the antibody. Our results suggest that 9-O-acetyl GD3 is involved in neuronal migration. — (*June 27, 2000*) .

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THYROID HORMONE ACTIONS ON THE MICROGLIAL DEVELOPMENT*

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In addition to infiltration of the CNS by mesodermal precursors, the development of microglia requires that these cells survive, proliferate and develop ramified cell processes. These cellular events are most probably controlled by physiological extracellular or diffusible signals which have not been thoroughly characterized. We have looked for a possible role of thyroid hormone (TH). The distribution of microglial cells was analyzed in the forebrain of developing rats rendered hypothyroid by pre- and postnatal treatment with methyl-thiouracil. TH deprivation markedly altered the growth of microglial cells labeled with isolectin B4 or OX-42 monoclonal antibodies. Microglial processes in forebrain regions from hypothyroid pups were less developed than in age-matched normal animals from post-natal day 4 (P4) up to at least P21. Both a delay in processes extension and a decrease in the number of microglial cell bodies, as shown by cell counts in the developing cingulate cortex of normal and hypothyroid animals, were responsible for these differences. Conversely, neonatal hyperthyroidism obtained by daily injection of rat pups with triiodothyronine (T3) accelerated the extension of microglial processes and increased the number of cortical microglial cell bodies above physiological levels, during the first postnatal week of life. In cultures of rat ameboid microglial cells, the effects of T3 on survival and morphology were consistent with the trophic and morphogenetic effects of TH observed *in situ*. Cultured microglia degenerated when the cells were kept at low cell density in a medium with low or no TH-free serum content. Addition of T3 to the medium significantly reduced microglial degeneration. In addition to its effects on survival, quantitative morphological assessment of cul-

tured cells indicated that T3 stimulated the *in vitro* growth of microglial processes. RT-PCR and immunological analyses showed that the cultured microglia expressed nuclear TH receptors. Our results demonstrate that TH contributes to the regulation of microglial growth and differentiation during development. — (*June 27, 2000*) .

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HYPOTHALAMIC NEUROHORMONES REGULATE ANTERIOR PITUITARY NEUROMEDIN B EXPRESSION*

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Presented by Leny A. Cavalcante

Hypothalamic neurohormones, TRH (thyrotropin-releasing hormone) and somatostatin regulate pituitary thyroid-stimulating hormone (TSH). TRH is the most important stimulator of TSH release, and somatostatin inhibits TSH release, as well as, thyroid hormones. We had shown before that neuromedin B (NB), a bombesin-like peptide, highly concentrated in the pituitary gland, due to its local synthesis, has an inhibitory action on TSH release, acting as an autocrine regulator. Anterior pituitary (AP) NB expression is positively regulated by thyroid hormones and probably also somatostatin, since we had demonstrated that octreotide, long-acting somatostatin analogue, increased NB content in the AP. Here we investigated, in rats, regulation of AP NB expression by acute administration of TRH, acute cold exposure as well as by leptin administration. NB mRNA was determined by RPA. AP NB was measured by specific RIA, as well as serum TSH, T4 and T3. A single injection of TRH (1.5μg/rat) decreased the content of NB mRNA and peptide within 15 minutes (NB mRNA-C: 1.0, 15min: 0.28 NB/βactin DO; NB:C: 103 $\pm$ 15, 15 min: 70 $\pm$ 6.5* fmol/mg ptn, $^*P < 0.05$), in concomitance with an increase in serum TSH. Acute cold exposure, which increased TSH release within 30 minutes (C: 1.7 $\pm$ 0.2 and 30 min: 9.9 $\pm$ 1.5 ng/ml), was associated with a progressive decrease in NB pituitary content, which was statistically significant after 2h (C: 97 $\pm$ 22; 15 min: 79 $\pm$ 7.5; 30 min: 69 $\pm$ 9.2; 1 h: 61 $\pm$ 7.4 and 2 h: 46 $\pm$ 4.8* fmol/mg ptn, $^*P < 0.05$). We suggest that the decrease of NB expression can be one of the mechanisms by which TRH increases TSH release. Leptin, a protein that was first found in adipose tissue but that now has been found in central nervous system, may be involved. After 2 hours of leptin administration into normal rats (8μg/100 g B.W.), pituitary NB content decreased (C:109 $\pm$ 10 and 2h: 72 $\pm$ 3* fmol/mg ptn, $^*P < 0.05$) and serum TSH increased. Therefore, data support the concept that regulation of pituitary NB expression and of TSH release are closely related in time in a manner that favours the hypothesis that NB exerts an important role in the local regulation of TSH release and that NB can be one intermediary of the effects of neurohormones that regulate TSH release. — (*June 27, 2000*) .

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SUBCORTICAL CONNECTIONS OF AREA V4 IN THE MACAQUE*

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To determine the subcortical efferent and afferent connections o visual area V4, we injected tritiated amino acids, wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP), and the retrograde fluorescent tracers, fast blue, diamidine yellow, and bisbenzimide under electrophysiological guidance into 20 sites in V4 in 10 hemispheres of 9 macaque monkeys. The injection sites included the representations raging from the fovea to far peripheral eccentricities in both the upper (4) and lower visual field (17). The results indicated that V4 receives afferent inputs from dorsal raphe, medial raphe, locus coeruleus, and the ventral tegmentum. V4 has bi-directional connections with the lateral basal nuclei of the amigdala, the pulvinar and the claustrum. It has bi-directional topographic projections with four different portions of the inferior and lateral pulvinar and two

different portions of the claustrum. V4 projects to the superficial and intermediate layers of the superior colliculus, to the thalamic reticular nucleus, to the interlaminar portions of the lateral geniculate nuclei, the posterior portion of the putamen and virtually the entire caudate nuclei. The projections to the caudate nuclei occupy the dorsomedial portion of the head, the entire body, and posterior part of the tail of the nuclei. — (*June 27, 2000*) .

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CORTICAL CONNECTIONS OF AREA V4 IN THE MACAQUE*

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To determine the locus, extent, and topographic organization of cortical projections of area V4, we injected tritiated amino acids, WGA-HRP, and retrograde fluorescent tracers under electrophysiological guidance into 21 sites in V4 in 9 macaques. The injection sites included the representation of the fovea and representations ranging from central to far peripheral eccentricities in both the upper (4) and lower visual field (18). The results indicated that all V4 sites receive and project topographically back to V2 and V3 and forward to V3A, V4t, MT, TEO, LIPv, LIPd, TEp and TEm. In addition to these projections to occipital visual areas, V4 sites representing eccentricities of about 30° and greater project to visual areas in parietal cortex, namely, areas DP, 7, PO, and ventral intraparietal (VIP) areas. This peripheral field representation of V4 also projects to area TF on the posterior parahippocampal gyrus. Projections from the peripheral field representation of V4 to parietal areas could provide a direct route for rapid activation of circuits serving spatial vision and spatial attention. The convergence of projections from central and peripheral field representation of V4 to temporal areas could provide the necessary means for the translation of oculocentric coordinates to object centered coordinates. — (*June 27, 2000*) .

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THEMES ON NEUROSCIENCE (a session in honor of CARLOS CHAGAS FILHO)

Organizers:

Leny A. Cavalcante and Roberto Lent