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INTERNATIONAL BEHAVIOURAL
AND NEURAL GENETICS SOCIETY

INTERNATIONAL BEHAVIOURAL AND NEURAL GENETICSOCIETY

Fifth Annual Meeting
July 11-12, 2002
Université F Rabelais, Faculté de Pharmacie
Tours, France

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The meeting was generously sponsored by :

Université F Rabelais, Tours
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Program and Abstracts

Program

July 11th 2002

9.00-11.00 Symposium: *Down syndrome: from genes to humans*, organized by Mara Dierssen (Barcelona, Spain); Chair Mara Dierssen (Barcelona, Spain)

9.00-9.30: Jean Delabar (Paris, France), "Brain phenotypes of DCR1 YAC transgenic mice"

9.30-10.00: I. Ballesteros-Yáñez (Spain) "Implication of Dyrk1a (minibrain) in morphological alterations of cortical pyramidal neurons associated with Down syndrome."

10.00-10.30 Ceri Davies (UK), "What do murine genetic models of Down syndrome and Alzheimer's disease actually model?"

10.30-11.00 Mara Dierssen (Barcelona, Spain), "Single gene transgenics and their contribution to the understanding of Down syndrome phenotype".

11.00-11.30 coffee

11.30-12.30 Poster session
List of posters at the end of the program

12.30-14.00 lunch

14.00-16.00 Symposium: *Does genetic invalidation of proteins parallel pharmacologic invalidation of the protein*? organized by Catherine Belzung (Tours, France), Chairs John Crabbe (Portland, USA) and Catherine Belzung (Tours, France)

14.00-14.30 Florence Crestani (Zurich, CH), "GABAA receptor subtypes: dissecting their pharmacological functions"

14.30-15.00 John Crabbe (Portland, OR, USA), "Phenotypic complexities of behavioral studies targeting single proteins"

15.00-15.30 François Tronche (Paris, France), "Stress and transcription, conditional mutagenesis of the glucocorticoid receptor"

15.30-16.00 Catherine Belzung (Tours, France), "Involvement of 5-HTa receptors in the anti-depressant effects of fluoxetine: evidence that gene invalidation does not mimick the effects of a pharmacological antagonism"

16h00-16h30 coffee

16h30-17h30 Free communications, Chair Wim Crusio (Worcester, USA)

16.30-16.50 L. Lewejohann, H. Prior, J. Brosius, N. Sachser, B. Skryabin "Behavioural phenotyping of mice lacking BC1, a non-protein coding gene"

16.50-17.10 Dae Jong Jeon, Yu-Mi Yang, Myung-Jin Jeong, Kenneth D. Philipson, Hyewhon Rhim, and Hee-Sup Shin “Enhanced Long-Term Potentiation, Learning, and Memory in Mice Lacking Na+/Ca2+exchanger 2”

17.10-17.30 Marco Angelo and Karl Peter Giese “Forebrain-restricted overexpression of p25 improves learning and increases aggression”

17.30-18.30 IBANGS business meeting

19.00 banquet

July 12th 2002

8.30-11.30 Symposium *Mouse models of neurodegeneration: what is the problem?* organized by Fred van Leuven (Leuven, Belgium); Chair Fred van Leuven (Leuven, Belgium)

8.30-9.00 Philip Kahle (Munich, Germany) "Transgenic mouse models of neuronal and glial - synucleinopathy"

9.00- 9.30 Hans-Peter Lipp (Zurich, Switzerland) “Functional correlates of neurodegeneration in mice by continuous in-cage monitoring: analysis of circadian activity differentiates between prion strains”

9.30-10.00 Thomas Bayer (Bonn, Germany) "Molecular events in the aging brain of Alzheimer mouse models”

10.00-10.30 Paul Chapman (Cardiff, UK) "Episodic-like memory and synaptic function in an AD mouse model"

10.30-11.00 Chris Janus (Toronto, Canada) "Analysis of behavior and effect of vaccination in APP-transgenic mice"

11.00-11.30 Fred van Leuven (Leuven, Belgium) "Mice with a mutant or a deficient APP and/or PS1 gene"

11.30-12.00 coffee

12.00-13.00 Free communications; Chair C. Andres (Tours)

12.00-12.20 Josh Dubnau, Scott Gossweiler, Lori Grady, Jodi Barditch, Pat Smith, Jim Dezazzo, Ulli Certa, Clemens Broger, Rod Scott, Ann-shyn Chiang and Tim Tully. “DNA chips reveal the involvement in memory of multiple components mRNA localization machinery”

12.20-12.40 Roussot, Pitel, Vignal, Faure, Mills, Guémené, Leterrier, Mignon-Grasteau, Le Roy, Perez-Enciso and C. Beaumont “QTL Research on duration of tonic immobility in quail”

12.40-13.00 S. Richard, J.M. Faure, A.D. Mills, D.C. Davies “Mechanisms of fear behaviour in Japanese quail”

13.00-14.30 lunch

14.30-17.00 Symposium *Drosophila behavioral neurogenetics,* organized by Gert Pflugfelder (Wurzburg, Germany), Chair G. Pflugfelder

14.30-15.00 Alberto Ferrus (Madrid, Spain), "The role of synapse number for sensory perception in *Drosophila*"

15.00-15.30 Jean-Rene Martin (Paris, France), "Neuroendocrine control of the sexually dimorphic locomotor behavior in *Drosophila melanogaster*"

15.30-16.00 Henrike Scholz (San Francisco, CA, USA), "Genetic dissection of ethanol-induced behavior in *Drosophila*"

16.00-16.30 Kevin O´Dell (Glasgow, Scotland, UK), "*Drosophila* as a model of mitochondrial deafness"

16.30-17.00 Gert O. Pflugfelder (Wuerzburg, Germany), "Behavioural deficits in polyglutamine-expressing flies".

17.00 Coffee

POSTER SESSION The numbers are board numbers.

P1. Arabo, A.*, Costa, O.**, Tron, F.**, Caston, J.*
Impairment of spatial cognition in the lupus-prone NZW/BXSB mice

P2. Arguel, E.*, Costa, O.**, Tron, F.**, Caston, J.*
Anxious-like behaviors in the NZW/BXSB lupus-prone mice.

P3. V.Besson1, V.Blanquet1, A.Puech2, Y.Hérault1.
An ENU-induced mutagenesis screen for recessive mutation affecting basic behaviour.

P4. Bichler Z.1, Migliore-Samour D.1, Gonzalez M-C.1, and Branchi I.2.
Neurobehavioural alterations in YAC transgenic mouse model of Down syndrome: a possible implication of DYRK1A gene, the human homologue of Drosophila minibrain

P5. J.A. Bouwknecht and R. Paylor
Mice lacking the BETA-4 subunit in nicotinic acetylcholine receptors show reduced anxiety on the elevated plus maze

P6. Richard E. Brown, Lianne Stanford, Martin Williamson, Krista Luedemann and Christianne Hawken
Strain and sex differences in rotarod performance in mice are confounded by body weight

P7. P. Chapillon1; C. Belzung2 and C. André3
Behavioural effects of b2-adrenergic receptor over-expression in mice.

P8. J.S. Chen, G. Preston, J.M. Pickel, B.S. Kolachana, J.W. Nagle, M.F. Egan and D.R. Weinberger
DEVELOPMENT OF INDUCIBLE TRANSGENIC MICE CARRYING HUMAN CATECHOL-O-METHYLTRANSFERASE VAL AND MET ALLELES.

P9. Cécile Ducottet and Catherine Belzung

DIVERSITY IN THE RELATIONSHIP BETWEEN ANXIETY LEVEL AND SENSIBILITY TO SUB-CHRONIC UNPREDICTABLE STRESS AMONG EIGHT STRAINS OF MICE

P10. Galaeva I.P., Garibova T.L., Voronina T.A., Krajneva V.A., Borlikova G.G., Makarenko A.M.
NOOGLUTYL CORRECTS HEMORRHAGIC STROKE-INDUCED NEUROLOGICAL DISTURBANCES IN THE RAT

P11. M. Labbe, L. Magnol, A. Duchon and Y. Herault.
Creation and phenotypic analysis of a new mouse model for Down Syndrome

P12. L. Liu1, C. Fernandes1, M. J. Galsworthy1, J. L. Paya-Cano1, S. Monleon2, R Plomin1 and L. C. Schalkwyk1.
Constructs of Exploratory Activity and Anxiety in Heterogeneous Stock (HS) Mice

P13. R. Madani, S. Kozlov, A. Vyssotski, G. Dell'Omo, A. Akhmedov, J. Kinter, H-P Lipp, P. Sonderegger, D.P. Wolfer.
Altered expression of the extracellular protease inhibitor neuroserpin interferes with exploratory behavior and reaction to novelty.

P14. B. Martin 1,2, D. Rinaldi 1,2,3 and A. Depaulis 2
A common genetic mechanism involved in GABA- and glutamate-induced seizure susceptibility revealed by a mouse model for absence-epilepsy.

P15. Yann S. Mineur1, Daniel J. Prasol1, Wim E. Crusio1 and Paul R. Dobner2.
What role does Neurotensin play in D-Amphetamine sensitization?

P16. J. L. Paya-Cano1, M. J. Galsworthy1, C. Fernandes1, L. Liu1, S. Monleon2, L. C. Schalkwyk1 and R. Plomin1
General cognitive ability does not vary with brain, cerebellum or hippocampus weights in heterogeneous (HS) mice

P17. W.PINOTEAU, L.NICOLAS, S.ROUTIER, D.MIGLIORE-SAMOUR, P.ROUBERTOUX and S.MORTAUD
Postnatal administration of COUMATE, a STEROID SULFATASE inhibitor, affect behavioral development in CBA/H mice

P18. Claudia F. Plappert, Peter K. D. Pilz, H.-U. Schnitzler
Prepulse inhibition and prepulse facilitation of the acoustic startle response is variably influenced by stimulus parameters and stimulus habituation in different mouse strains

P19. S. Pothion, C. Belzung, JC. Bizot.
Effect of chronic unpredictable mild stress on anhedonia and memory in two strains of mice.

P20. Laetitia Prut; F. Crestani; R. Keist; J.-M. Fritschy; D. Benke;; H. Blüthmann; H. Möhler; U. Rudolph
TRACE FEAR CONDITIONING INVOLVES HIPPOCAMPAL α_5 $GABA_A$ RECEPTORS

P21. Daisy Rinaldi 1,2,3; Antoine Depaulis 2 and Benoit Martin 2,3
BS/Orl and BR/Orl, two genetic mouse models for absence epilepsy

P22. Thomas S., Thiery E., Aflalo R., Vayssettes C., Verney C., Berthuy I., Créau N.

The expression of PCP4 (PEP19), the chromosome 21 camstatin, is regulated during early development and aging

P23. V.V.Voznessenskaya1, C.J.Wysocki2
Mammalian Model of Aggression and Smell

P24. Wolfer DP (1), Plath N (2), Kuhl D (2), Mohajeri MH (3), Minichiello L (4), Drescher I (1), Madani R (1), Lipp HP (1)
Spatial and non-spatial deficits in the watermaze distinguished by automatic identification and classification of swimming strategies

Abstracts and Symposia

Branchi I[1-2], Bichler Z[1], Migliore-Samour D[1], Rachidi M [3], Lopes C[3], Chabert C[1], Roubertoux P[1], Rubin EM[4], Delabar JM[3]

Brain phenotypes of DCR1 YAC transgenic mice

Down syndrome (DS), the most frequent genetic cause of mental retardation (1/700 newborn), is a good model for complex trait analysis. Smith et al. tried to identify loci from a region critical for Down syndrome (DCR-1), that, when present at a higher copy number than usual, contributed to learning difficulties. They generated low-copy-number transgenic mice containing four different yeast artificial chromosomes (YACs) that together covered approximately 2 Mb of a region critical for Down syndrome (DCR-1); this panel constitutes an *in vivo* library for phenotypic screening. We carried out a neuropathological study of these transgenic lines and found that the integration of two of these YACs, 230-E8 (650kb) and 152-F7 (550kb), caused major morphogenetic changes: YAC 230-E8 mice showed an abnormal cerebellar folial pattern, a decrease in the size of the cerebellum and an increase in cortical cell density; YAC 152-F7 mice showed an increased brain weight with an increased neuronal number, as observed in the cholinergic system, and a clear learning impairment. These results evidenced that DCR-1 contains important genes involved in neurogenesis. C21orf5, a patterning gene, is probably responsible for the phenotypic changes observed in 230-E8 transgenics. DYRK1A, a serine threonine kinase, ortholog of which is a cell cycle regulator in yeast, is involved in the developmental defects observed in 152-F7 transgenics and might be a key factor controlling the brain growth.

[1] *FRE 2134 2358 CNRS, Génétique Neurogénétique Comportement,3b Rue de la Ferollerie, 45071 Orléans, France*

[2] *Section of Behavioral Pathophysiology,Laboratorio di Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanità, Viale Regina Elena 299,00161 Roma, Italy*

[3] *EA 3508, Univ. Denis Diderot Paris7, Paris, 75251*

[4] *Genome Sciences Department, Lawrence Berkeley National Laboratory, Berkeley, CA 94720*

I. Ballesteros-Yáñez*, M. Dierssen, R. Benavides-Piccione*, C. Fillat, X. Altafaj, X. Estivill, J. de Felipe*.

Implication of *Dyrk1a (minibrain)* in morphological alterations of cortical pyramidal neurons associated with Down syndrome.

DYRK1A, the human homologue of the *Drosophila minibrain* (*mnb*) maps to the Down syndrome (DS) critical region of the chromosome 21. It is a candidate gene to cause some of the neurological defects associated with DS. Dyrk1A belongs to a family of serine/threonine kinases presumably involved in brain development, especially in *Drosophila* neuroblast proliferation during postembrionic neurogenesis. The characterization of the possible change in the distribution of Dyrk1A protein during development and an accurate information on its expression pattern in the adult are essential information to define the physiological role of this kinase. The present study is aimed at analysing the implication of *Dyrk1A* in the morphological alterations of cortical neurons features of Down syndrome. We injected 96 cortical neurones from mice transgenic for *Dyrk1A* (TgDyrk1A) and their control littermates, to examine the dendritic arborisation pattern and spine dendrites of pyramidal cells. TgDyrk1A mice present neurodevelopmental retardation and motor and cognitive alterations in the adult that suggest a possible alteration of the information processing in the cerebral cortex. In adult mice, pyramidal cells sampled from TgDyrk1A animals were considerably less branched and less spinous than those sampled from control with no differences in the basal dendritic field area. As each spine receives an excitatory synapse, the present results suggest that the capacity of pyramidal neurones to integrate excitatory inputs is greater in adult control animals than in adult TgDyrk1A animals.

The number of spines is determined by both genetic and epigenetic features. Thus, it will be interesting to perform studies early in development to determine the capability of TgDyrk1A animals to respond to treatment These studies will contribute to the understanding of the physiological role of Dyrk1A under normal and pathological conditions. Down Syndrome Research Group, Genes and Disease Program, Genomic Regulation Center, Barcelona, Spain. *****Cajal Institute, Madrid, Spain.Supported by AP2001-0671, Jerôme Lejeune Foundation and FIS

D. C. Davies.
What do murine genetic models of Down syndrome and Alzheimer's disease actually model?

A number of genes and markers on HSA21 have been mapped to mouse chromosome 16 and therefore, mice trisomic (Ts) for MMU16 have been developed as an animal model of Down syndrome (DS). The foetal Ts16 somatic phenotype shares a number of characteristics with that of DS and development of the cerebral wall is impaired in Ts16 mice. However, it is not known whether this impaired cerebral development persists into adulthood or whether it is associated with mental retardation, because Ts16 mice rarely survive to term and if they do, they die shortly after birth. In order to overcome this problem of neonatal death, a segmental Ts mouse has been developed using a reciprocal translocation. These Ts65Dn mice possess the distal region of MMU16 that is homologous to the q22 region of human chromosome 21. Adult Ts65Dn mice exhibit behavioural abnormalities and some impairment of learning and memory that requires the integration of visual and spatial information. These abnormalities may be due to the fact that there are 30% less asymmetric synapses in the temporal cortex of aged TS65Dn than in diploid controls and synaptic opposition zones are significantly larger in Ts65Dn mice. These results may also have a bearing on the cognitive deficits in DS, but the brains of aged Ts65Dn mice do not show the Alzheimer's disease (AD) pathology characteristic of the brains of DS individuals from middle age. A central feature of the neuropathology of AD is the deposition of β-amyloid (Aβ). Aβ is formed by cleavage of the amyloid precursor protein (APP), which is coded for by a gene in the obligate DS region of HSA21. A number of transgenic murine models of AD have been developed. One of the best to-date, carries APP and presenilin 1 (PS1) transgenes. These APP/PS1 mice develop large numbers of fibrillar Aβ deposits in the cortex and hippocampus. They also exhibit cerebrovascular Aβ deposits and degenerating neurites and perikarya, which are characteristic of AD. However, although hyperphosphorylated tau deposits are present in the brains of APP/PS1 mice, their distribution is different from that in AD and paired helical filaments resembling neurofibrillary tangles are rare. Despite the severe pathology in the brains of these mice, the behavioural and cognitive deficits that they exhibit are relatively mild. Therefore, although the murine models described above mimic features of the pathology of DS and AD, they do not exhibit the mental retardation and/or dementia associated with these conditions and the relationship between the neuropathology and functional deficits remains to be explained.
Department of Anatomy and Developmental Biology, St George's Hospital Medical School, London, SW17 0RE, UK.

Deleted:

Mara Dierssen, Ruth Benavides-Piccione, Carmen Martínez-Cué, Carmela Baamonde, Cristina Fillat, María Martínez de Lagrán, Xavi Altafaj, Guy Elston, Javier DeFelipe, Jesús Flórez, Xavier Estivill
Genotype-phenotype neural correlations in trisomy 21

Down syndrome (DS) is the most common genetic cause of mental retardation. Subjects with DS present brains smaller than normal, with disproportionately smaller cerebellar and frontal lobe volumes, and the depth and number of sulci are reduced. Neuronal density is decreased and abnormal neuronal morphology is observed, especially in the neocortex. In foetuses, a reduction in the width of the cortex and abnormal cortical lamination patterns, altered dendritic

arbors and dendritic spines, altered electrophysiological properties of membranes, reduced synaptic density and abnormal synaptic morphology have been described. Despite intense investigation of the pathology, biochemistry and physiology of DS, it is still not known how the individual genes on HSA21, either singly or in concert produce the alterations associated with the trisomy. The molecular mechanisms underlying the DS phenotype remain largely unknown. Even knowing the molecular defect, it is difficult to decipher the complex pathophysiology of the disease, the developmental consequences of the trisomy and the impact on behavior and cognitive function. The generation of animal models that provide ready access to cells and tissues from different developmental stages of the disease is a powerful tool to help us understand the role of individual genes in DS and some of the clinical alterations observed in DS. They also allow the study of the consequences of therapeutic strategies. Several useful mouse models of DS have been generated, and new strategies are being initiated.

Exposure to an enriched environment enhances performance in learning, memory and visual acuity tasks, suggesting that circuits are modified in order to optimize multiple levels of information processing and storage. Our previous study showed that exposure to complex environments has the capacity to modulate behaviour and spatial memory of Ts65Dn and euploid mice. In the present study these functional effects are shown not to be correlated with modifications in the morphology of the pyramidal neurons, either in the dendritic arborization or in the number of spines in the enriched trisomic mice. On the contrary, the euploid mice presented an increase in their arbor complexity and spine number that may account for the better performance observed in some behavioral tasks. These results suggest that the molecular pathways that mediate neuronal reinforcement in the early stages of pruning might be affected by the partial trisomy of MMU16, resulting in different behavioral and cognitive abilities. Thus, the behavioral consequences of enrichment observed in the Ts65Dn mice may not be dependent on the structural reorganization of the pyramidal cells of the frontal cortex.

F. Crestani.

GABAA receptor subtypes: dissecting their pharmacological functions.

The enhancement of GABA-mediated synaptic transmission underlies the pharmacotherapy of various neurological and psychiatric disorders. GABAA receptors are pluripotent drug targets that display an extraordinary structural heterogeneity. In order to identify the functional significance of defined GABAA receptor subtypes, we introduced histidine to arginine point mutations into the mouse a1, a2, a3 and a5 subunit genes, respectively, by homologous recombination in embryonic stem cells. These point mutations abolish diazepam binding and thus render the respective GABAA receptor subtype silent to diazepam. Behavioural studies revealed that while the sedative action and the anterograde memory impairing effect of diazepam are mediated by the a1-GABAA receptors, its anxiolytic-like action (as determined in the light-dark choice and the elevated X-maze) is mediated by the a2-GABAA receptors. In addition the muscle relaxing properties of diazepam involve spinal a2-, a3- and a5-GABAA receptors. Thus, the behavioural effects of diazepam result of the activation of specific GABAA receptor subtypes in distinct neuronal circuits, which is of interest for drug design. In addition, the high density of the a2 subunit on somata and axon initial segments of principal cells in cerebral cortex, hippocampus and amygdala may outline the neuronal circuit that mediates anxiolytic activity.

Institute of Pharmacology and Toxicology, University of Zürich, Winterthurerstrasse 190, CH-8057 Zürich.

Crabbe, J.C.

Phenotypical complexities of behavioral studies targeting single proteins

Individual differences in behavior represent the integrated output of genetic influences as modulated by the environmental conditions in which genes act. With the recent dramatic advances in availability of information regarding human and non-human animal genomes, it is becoming possible to advance beyond making purely statistical inferences about genetic contributions. As specific genes are identified or targeted for experimental manipulation, it is increasingly clear that precision in behavioral analysis is crucial to the interpretation of how genes express their effects to influence behavior. Environmental interactions with specific genes' effects is pervasive, and a more sophisticated understanding of these interactions is essential to avoid inaccurate inferences of genetic determinism. This paper discusses examples of the complexity of phenotypic assessment relevant for assessment of the effects of gene targeting studies in mice.

Portland Alcohol Research Center, VA Medical Center, Dept. of Behavioral Neuroscience, Oregon Health & Science Univ., Portland, OR 97201 USA.

Supported by the VA, NIAAA and NIDA.

F Tronche

Abstract missing

Catherine Belzung

Involvement of 5-HTa receptors in the anti-depressant effects of fluoxetine: evidence that gene invalidation does not mimick the effects of a pharmacological antagonism.

Fluoxetine is believed to induce its anti-depressant effects by blocking the serotonin (5-HT) transporter, thus elevating the level of 5-HT in the synaptic cleft. However, few is known about the precise target of this action. Indeed, this elevated 5-HT can bind to a wide range of receptors. The 5-HT1a receptors may a potential target, for two principal reasons: a)because of their localisation in the limbic system; b)because it has been observed that co-administration of fluoxetine and of a 5-HT1a receptor antagonist accelerates the onset of the fluoxetine's clinical action. The hypothesis of the involvement of 5-HT1a receptors in the anti-depressant action of fluoxetine has been tested in two experiments, using either pharmacological blockade of the 5-HT1a receptor by injection of the 5-HT1a antagonist WAY 100635 or by using 5-HT1a receptor KO mice. Both experiments were undertaken in mice subjected with the chronic mild stress (CMS), a murine model of depression. The effects of CMS were evaluated using two variables: the fur state index and the number of new object exploration. Results clearly show that CMS induce a worsening of the fur state and a lack of interest for the novel object, in non treated mice of the two experiments. Chronic treatment with fluoxetine (in tap water, 0.24 mg/day during 14 days) completely reversed the worsening of fur state and the lack of interest for the object in the wild type mice, an effect accelerated by administration of WAY 100635. However, fluoxetine had surprisingly no effect in the KO mice. A possible explanation id related to effects of developmental modification occurring in 5-HT1a KO mice.

EA3248, Tours, France

P.J. Kahle1, M. Neumann2, L. Ozmen3, H.A. Kretzschmar2, C. Haass1.

Transgenic mouse models of neuronal and oligodendroglial alpha-synucleinopathy.

Fibrillar aggregates of the presynaptic protein alpha-synuclein form Lewy bodies and Lewy neurites that are diagnostic for Parkinson's disease and pathologically related diseases (dementia with Lewy bodies, neurodegeneration with brain iron accumulation type 1 (formerly known as Hallervorden-Spatz disease), and pure autonomic failure). Moreover, (oligodendro)glial cytoplasmic inclusions composed of alpha-synuclein characterize multiple system atrophy. In order to generate transgenic mouse models for these diseases collectively referred to as alpha-synucleinopathies, we have expressed wild-type

and the Parkinson's disease associated A30P mutant alpha-synuclein throughout the central nervous system neurons (Thy1 promoter), selectively in catecholaminergic neurons (tyrosine hydroxylase promoter), and in oligodendrocytes (proteolipid protein promoter). Abnormal accumulation of insoluble transgenic alpha-synuclein in neuronal cell bodies and swollen neurites occurred in young mice. This early pathology aggravated in a strictly time and gene dose dependent manner. Argyrophilic, thioflavin-positive and electron-dense inclusions of pathologically phosphorylated and misfolded alpha-synuclein became abundant in >1.5 year old hemizygous and >0.5 year old homozygous mice. Pathology was predominant in the brain stem, where astrogliosis developed in mice that eventually became paralyzed. Transgenic alpha-synuclein expressed in oligodendrocytes also accumulated in an insoluble, pathologically phosphorylated form. Thus, misfolding and (hyper)phosphorylation of alpha-synuclein may cause dysfunction of affected brain regions, as reflected in transgenic mouse models of human

Department of Biochemistry, Adolf Butenandt Institute and 2Department of Neuropathology, Ludwig Maximilians University of Munich, Germany, and 3Pharma Research, Hoffmann – La Roche Ltd, Basel, Switzerland.

H.-P. Lipp (1) & Dell'Omo, G.(1,2)

Functional correlates of neurodegeneration in mice by continuous in-cage monitoring: analysis of circadian activity differentiates between prion strains

Mice inoculated with transmissible spongiform encephalopathies (TSE) show behavioural abnormalities well before the appearance of clinical signs. TSE strains are obtained by serial re-infection of infectious brain homogenates in laboratory rodents. They are characterised by strain-typical brain lesion profiles, which implies that they might be differentiated behaviourally as well. Seventy female C57 BL/6 were tested, 14 per group. Controls received no or sham inocula, two other groups scrapie strains adapted to mice (139A, ME7) and one group a mouse-adapted BSE strain (301C). From week 7 until the end of the incubation period, 8 mice per group were subjected bi-weekly to open-field and hot-plate tests. Assessment of clinical signs, and measuring of body weight, food and water consumption were carried out weekly on the remaining animals kept in single cages. In addition, in these mice locomotor activity was recorded continuously by means of infrared detectors. Monitoring of circadian activity revealed early significant TSE strain differences, most pronounced during the nocturnal active phase of mice. Behavioural changes in open-field tests occurred equally before the appearance of clinical signs, and differences in rearing, wall rearing and sniffing were strain-specific. However, such differences varied according to the period of testing. Pain latencies increased equally in all infected mice after week 19, together with the appearance of clinical signs. These data imply that automated assessment of circadian activity in mice is a powerful and economical tool for early behavioural typing of TSE strains including differentiation between scrapie and BSE.

Institute of Anatomy, University of Zürich &
Laboratory of Veterinary Medicine, Istituto Superiore di Sanita, Rome

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Thomas A. Bayer, Stephanie Schäfer, Oliver Wirths, Christoph Schmitz, Gerd Multhaup

Molecular events in the aging brain of transgenic mouse models for Alzheimer disease

Neuropil deposition of beta-amyloid peptides Abeta40 and Abeta42 is believed to be the key event in the neurodegenerative processes of Alzheimer's disease (AD). Numerous studies have demonstrated that intraneuronal and extracellular Abeta can induce neurotoxity. Additionally, APP has a neurotrophic capacity,

which may be lost in the course of the disease process. The recent discovery of transport signal domains required for axonal and transcytotic sorting of beta-amyloid precursor protein (APP), the precursor of Abeta, implicated that missorting of APP may be a key event in AD pathology. Transgenic mouse models proved to be an ideal animal system to model some aspects of AD pathology. A marked neuronal cell loss was found in the CA region of the hippocampus, which was most obvious in optical dissectors with plaques. In addition to neurotoxicity induced by amyoid plaques, the loss of density of CA neurons at the margin of the pyramidal layer suggests retrograde neurodegeneration as an additional event. Immunohistochemical staining revealed that intraneuronal Abeta40 and Abeta42 staining preceded plaque deposition. Abeta was observed in the somatodendritic and axonal compartments of many neurons. Interestingly, the striatum, which lacks transgenic APP expression harbored many plaques at later stages. This is most likely due to an APP/Abeta transport problem and may be a model region to study APP/Abeta trafficking as an early pathological event. The APP copper binding domain (CuBD) has been shown to reduce Cu(II) to Cu(I) and to modulate oxidative stress in primary neuronal cultures. Copper inhibits amyloid Aß production and stimulates the non-amyloidogenic pathway of APP. To study the effects of APP overexpression and APP-Cu complexes in vivo, we have treated APP23 transgenic mice and controls with Cu-supplemented drinking water. We measured the levels of Cu in brain, liver and blood, analyzed the copper-zinc superoxide dismutase (SOD)1) activity and quantified the plaque load in brain. This animal model for AD revealed three different effects associated with APP overexpression. (1) Whereas the survival rate of untreated APP23 mice was significantly decreased compared with littermate controls in aged mice, Cu-treatment rescued the premature death phenotype in APP23 mice. (2) In APP23 mice having received a long-term treatment with Cu-sulfate, significant copper accumulation was found in brain of plaque containing APP23 mice. (3) A significant decrease of the SOD1 activity was found in APP23 mice possibly due to a mis-metallation of the antioxidant enzyme. Conversely, APP23 mice supplemented with copper successfully reversed the deleterious effect caused by APP overexpression on SOD1 activity. Changes in plaque load were associated with a sexual dysmorphism with female mice having significantly more plaques.

P. F. Chapman, P. Barnes, A. Falinska, and M. Good

Learning, memory and synaptic function in Alzheimer's disease model mice

Genetic models of Alzheimer’s disease (AD) have developed with astonishing speed over the past ten years. The utility of these models in developing treatment strategies has been a source of tremendous excitement, but equally exciting is the opportunity to use these models to develop a greater understanding of the basic mechanisms of AD. We have used the Tg2576 model to examine the development of impairments in trial-dependent spatial memory and determine their relationship to changes in synaptic function. We find that deficits in the forced-choice alternation task in the T-maze develop at approximately eight months of age in transgene-positive mice. Long-term potentiation in the dentate gyrus is deficient in the aged, but not young, transgenic mice when measured in vivo, and in vitro LTP is reduced in a way that correlates with T-maze performance. Chronic (dietary) administration of the non-steroidal anti-inflammatory drug ibuprofen, beginning at three to five months of age, prevents the onset of behavioural deficits at eight months of age. Thus, it is possible to produce age-related, AD-like behavioural and physiological deficits in transgenic mice, in the absence of detectible neurodegeneration, and to prevent those changes with ibuprofen.

Cardiff School of Biosciences and 2School of Psychology, Cardiff University, Cardiff, Wales, United Kingdom. Supported by N.I.H. (PFC) and the Wellcome Trust (PFC,MAG).

C. Janus, L. Lovasic, S-H. Johnson, S. Mathews

Impaired short-term spatial memory in APP-transgenic mice

Transgenic (Tg) mice (TgCRND8) encode a double mutant genes of human amyloid precursor protein (APP), (Swedish; KM670/671NL + Indiana;V717F), which are implicated in Alzheimer's Disease (AD). These mice show increased levels of amyloid-b (Ab) in the brain, as well as Ab plaque deposition from 3 months onwards, and they manifest cognitive impairment on several measures of spatial reference (long-term) memory as evaluated in a Morris water maze paradigm. In this study, we extended our focus to short-term spatial memory and memory retention in TgCRND8 mice. To test our hypothesis that TgCRND8 mice should show impairment in short-term spatial memory, we compared the Tg mice with their non-transgenic (non-Tg) littermates in a 6-arm radial water maze paradigm. In our paradigm, a freely swimming mouse had to find a submerged escape platform located each day in a different arm of the maze. Each day a mouse was given four consecutive acquisition trials (ITI=10 s) followed by a retention trial 30 min later. The number of errors (an entry into an arm not containing the escape platform) was used as a measure of short-term spatial memory, while the sequence of arm entries during each trial was used to distinguish spatial from non-spatial search strategies. Since extensive evidence exists that stress and glucocorticoids influence cognitive function, we measured plasma corticosterone levels before, during, and at the end of the experiment (work in progress). The obtained results showed that: (1) non-Tg mice successfully learned the task and significantly improved their performance over the 10 days of training; (2) TgCRND8 mice showed significantly slower acquisition of learning and their performance never reached the level of the non-Tg mice; but their retention of acquired information did not deteriorate over the 30 min time period. In conclusion, the TgCRND8 mice showed an impairment in short-term spatial memory as evaluated in the radial arm water maze paradigm when a mouse was allowed freely explore the maze during a trial. These results further validate the use of TgCRND8 mice as an animal model of Alzheimer's Disease.

1Centre for Research in Neurodegenerative Diseases, 2Department of Physiology, University of Toronto, Toronto, Canada.

Fred Van Leuven

Transgenic mice: incomplete as models for Alzheimer's disease ?

The exact mechanisms behind the amyloid- and tau-pathology, and their interplay that is evident in all AD patients, remain largely elusive. For effective early diagnosis and therapy it is imperative to understand the processes that fail or go wrong in the earliest clinical stages. The multi-disciplinary and invasive analysis that needs to be done in vivo is only possible in experimental model systems. Single and multiple transgenic mouse strains are successfully generated and analysed to define how "clinical" phenomena relate to each other and to fundamental mechanisms particularly in the processing and control of APP and protein tau.

Successful models are mice that overexpress mutant APP, eventually in combination with PS1. Our APP[V717I] transgenic mice robustly display early behavioural defects (at 3-9 months) with disturbed behaviour, reduced exploration, neophobia, increased aggression, excitotoxicity, and with defective cognition and decreased LTP. The mice develop later in life (>10 months) the typical amyloid plaque pathology and the angiopathy which is very similar to the pathology in the brain of AD patients. Co-expression of mutant PS1 exacerbates this phenotype considerably and brings it forward in time (>6 months).

Model-building for tau-pathology is less advanced, partially because mutations in the tau gene are not linked to AD but to a group of diverse forms of fronto-temporal dementia. At this moment in time expression of mutant forms of tau

and co-expression of APP and tau appears to be most promising, although no models genuinely recapitulate the typical intraneuronal paired helical filaments and neuro-fibrillary tangles in combination with extracellular amyloid pathology. Such a model would be most welcome in this field of research, for fundamental, clinical and therapeutic purposes alike.

Finally, we need to understand the epidemiological observation of the "ApoE4-allele" effect in AD, particularly how it links up with molecular changes of the amyloid- and/or tau-pathology. Again, much fundamental work needs to be done to fully understand the normal role of ApoE in brain, and how it relates to lipid and cholesterol metabolism in the CNS, and to its lipoprotein receptors, essentially LRP1 and ApoER2 (LRP8). That neuronal expression of ApoE4 leads to hyper-phosphorylation of protein tau could provide a novel model in this, respect.

Experimental Genetics Group (LEGT_EGG), K.U.Leuven-Campus Gasthuisberg, B-3000 Leuven, Belgium

A. Ferrus, A. Acebes and J.M. Devaud
The role of synapse number in sensory perception in Drosophila

Synapses are in a exceedingly large number considering their accepted biological role, to excite or inhibit the postsynaptic cell. Although it is generally accepted that the number ofsynapses changes as a consequence of behavior, the actual data to illustrate this assumption are difficult to obtain. We have taken advantage of the feasible experimental manipulations of Drosophila to carry out : a) an increase in the number of synapse to study potential changes of behavior, b) to change behavior in order to study potential changes in the number of synapses, and c) to functionally silence specific subsets of synaptic inputs to study potential effects in behavior. All these manipulations have been carried out in sensory systems of various modalities under quantitative conditions of both, behavior and synapse number. Taken toghether, the results clearly demonstrate that synapse number is a relevant biological parameter that serves to determine the level of sensory perception and the strength of the ellicited behavioral response. Among the molecular mechanisms involved, cAMP metabolism plays a critical role.

Jean-René Martin
Neuroendocrine control of a sexually dimorphic behavior by few neurons of the pars intercerebralis in Drosophila

In Drosophila, locomotor activity is sexually dimorphic and the brain area controlling this dimorphism has been mapped. The neurons of the pars intercerebralis (PI) have been suggested to participate in such differences between males and females. However, the precise physical nature of the dimorphism, the identity of the PI neurons involved, and the nature of the neuronal signal coding the dimorphism remain unknown. We have used a new video-tracking paradigm to characterize further the pattern of locomotor activity in Drosophila. We show that the number of activity/inactivity periods (start/stop bouts) is also sexually dimorphic, and that it can be genetically feminized in males. Moreover, the transplantation of PI neurons from a female, or of feminized PI neurons from a donor male into a receiver wild-type male is sufficient to induce the feminization of locomotor behavior, confirming that this tiny cluster of about 10 neurons is directly responsible for the sexual dimorphism in locomotor activity. Finally, feeding males with fluvastatin, a juvenile hormone inhibitor, also led to start/stop feminization, suggesting the existence of a neuroendocrine control of such behavioral dimorphism.

Henrike Scholz
Genetic dissection of ethanol-induced behavior in *Drosophila*

Tolerance is a common phenomenon associated with chronic drug abuse and it is partially mediated by adaptations of the brain. To identify the molecular genetic and neuronal basis underlying these adaptive processes we

established *Drosophila melanogaster* as a model system. Wild-type flies develop tolerance to the effect of ethanol on postural control and sedation after a previous exposure to ethanol vapor. These behavioral changes require the functional and structural integrity of the brain as determine by targeted expression of tetanus toxin and the analysis of EMS-induced mutants carrying lesions in the brain. The behavioral and phenotypical analyses of different behavioral mutants demonstrated that at least two different mechanisms contribute to tolerance. One mechanism is revealed by the analysis of a mutant unable to synthesize the neurotransmitter, octopamine; thought to be the functional analogue of noradrenaline in insects. This mechanism shares similarities to mechanism underlying learning and memory. The second mechanism of ethanol tolerance is based on cellular integrity. This was discovered by the analysis of the transposon-induced mutant *hangover*^{AE10NT}, one among several isolated in a behavioral screen. *hangover*^{AE10NT} mutants are impaired in cellular stress responses.

Lehrstuhl Genetik und Neurobiologie,
Biozentrum, Am Hubland, 97074 Würzburg

O'Dell KMC, Toivonen JM, Alziari S and Jacobs HJ.

Drosophila as a model of mitochondrial deafness.

Mutations that perturb human mitochondrial protein synthesis lead to a variety of phenotypes, the most common of which are short stature, antibiotic sensitivity and deafness. To date very little is known about the pathogenesis of the disorder, and we have been investigating the suitability of Drosophila melanogaster as an appropriate model organism. One potentially interesting Drosophila gene is technical knockout (tko) which encodes the mitoribosomal protein S12, a well-characterised component of the ribosomal accuracy centre. In the one viable tko mutation, tko25t a conserved leucine residue is mutated to histidine (L85H) resulting in a bang-sensitive mutant phenotype. The mutant protein appears to affect mitoribosomal assembly or stability, and as a consequence there is a marked reduction in mitochondrial redox enzyme activity. We have recently undertaken a more detailed study of the tko25t mutant phenotype to reveal developmental delay (the fly equivalent of short stature), antibiotic sensitivity and deafness. Therefore disruption of mitochondrial protein synthesis in flies and humans leads to apparently similar phenotypes. We are now using tko25t mutants to reveal the molecular events that enable a quantitative deficiency in mitochondrial translational capacity to cause the complex phenotype described. Shah et al. (1997) Gene 204: 55-62 Toivonen et al. (2001) Genetics 159: 241-254.

Kretzschmar1, J. A. Tschaepe1, E. Asan2, and G.O. Pflugfelder1.

Behavioural deficits in polyglutamine-expressing flies.

In the last years, Drosophila has been used as a model system to study human neurodegenerative disorders. In one of these approaches, the effect of expanded polyglutamine stretches was analyzed in transgenic Drosophila flies, expressing (human) polyglutamine-containing proteins or protein fragments. Expression in the fly eye causes accumulation of protein aggregates in the nucleus followed by degeneration. In human patients, the deleterious proteins accumulates, however, in the central nervous system. We, therefore, investigate the effects of expressing polyglutamine-containing SCA 3 protein fragments in either neurons or glia. Expression in both cell types leads to a reduced life span, or pre-adult lethality, even though we could not detect degeneration upon neuronal expression. Glial expression, on the other hand, caused progressive CNS degeneration and early death of the flies. The severity of the phenotype correlated with the length of the polyglutamine tract and to the protein expression level. A shortened life span and degeneration is observed even in flies expressing a polyglutamine stretch whose length in humans does

not elicit pathogeny.The first signs of the human diseases often are subtle changes in motor behaviour, generally before cell death occurs. To assess whether this is also the case in the fly model system we tested the reaction of different transgenic flies to light. This assay showed that behavioural defects preceded degeneration. Neuronal expression, which did not lead to histological defects, also caused an age-dependent decrease in the phototaxis reaction. Drosophila, therefore, offers the possibility to study early steps of polyglutamine induced pathogenesis which may still be susceptible to treatment before degeneration and cell death may lead to incurable defects.

1Lehrstuhl für Genetik und Neurobiologie, Biozentrum, and 2Anatomical Institute Universität Würzburg, Germany. Supported by SFB581 (Molecular Models of Diseases of the Central Nervous System) of the Deutsche Forschungsgemeinschaft.

Free communications

L. Lewejohann1, H. Prior2, J. Brosius3, N. Sachser1, B. Skryabin3

Behavioural phenotyping of mice lacking BC1, a non-protein coding gene

Genes that do not code for proteins are still outside the scope of many genome oriented projects. The gene BC1 ("Brain Cytoplasmic 1") encodes a small non-messenger RNA and is expressed in a unique pattern in the nervous system of rodents. The RNA coding region of the gene is - in contrast to the flanking region - highly conserved indicating that BC1 is under selective pressure. To begin dissecting a functional role of BC1, the gene was eliminated in vivo. Three different knockout lines from three separate embryonic stem cells, yet with the identical BC1 gene deletions were established. Additionally, a control group was established by backcrossing the heterozygous founder colonies into a homozygous line, carrying the BC1 gene.

To assess a behavioural phenotype, a wide-ranging battery of behavioural tests was performed with numerous male and female mice from all three lines and control-mice, respectively. The test battery incorporated a general health check, activity rhythm, various tests on exploratory and anxiety related behaviours and tests on spatial memory.

Results of the health check and the test on activity indicated that there were no general physiological or behavioural disturbances caused by gene knockout. Differences in spatial memory could, however, not be detected. However, findings from the different behavioural tests revealed differences between control- and knockout-mice in exploratory behaviour, with knockout-mice exploring less than control-mice. Although the degree of this effect varied between the different knockout-lines and between the sexes, this is the first time that a behavioural phenotype could be attributed to a non-protein coding gene.

1Department of Behavioural Biology, University of Münster, Germany,2Department of Biopsychology, University of Bochum, Germany3Institute of Experimental Pathology, University of Münster, Germany

Dae Jong Jeon, Yu-Mi Yang, Myung-Jin Jeong, Kenneth D. Philipson, Hyewhon Rhim, and Hee-Sup Shin

Enhanced Long-Term Potentiation, Learning, and Memory in Mice Lacking Na+/Ca2+exchanger 2

Plasma membrane Na+/Ca2+exchanger (NCX) plays an important role in Ca2+ homeostasis by extruding Ca2+ out of the cell. Because a proper regulation of intracellular Ca2+ level is important in synaptic transmission, NCX has been proposed to be involved in the regulation of synaptic transmission. However, direct evidence in vivo to support this hypothesis has been lacking. To address this question, we generated mice deficient for NCX2, the major isoform in the brain. Hippocampal neurons of the mutant mice exhibited significantly reduced NCX currents and delayed clearance of elevated Ca2+ following depolarization. Electrophysiological analysis in the CA1 region of the hippocampal slices of the mutant mice revealed facilitated short-term plasticities and enhanced long-term potentiation (LTP), but the absence of long-term depression (LTD). Behaviorally the mutant mice showed enhanced performance in hippocampus-dependent learning and memory tasks. These studies demonstrate that NCX2-mediated Ca2+ homeostasis is critical for the control of synaptic plasticity and hippocampus-dependent learning and memory.

National CRI Center for Learning and Memory, Korea Institute of Science and Technology, 39-1 Hawolgok-dong Seongbuk-ku, Seoul 136-791 Republic of Korea

Marco Angelo and Karl Peter Giese

Forebrain-restricted overexpression of p25 improves learning and increases aggression

The onset and progression of cognitive deficits associated with Alzheimer’s disease (AD)

correlate best with tangle formation. Recently, an abnormal accumulation of p25, a degradation product of p35, has been discovered in brains of AD patients. p25 increases the activity of cyclin-dependent kinase 5, which phosphorylates tau. Thus, the accumulation of p25 was hypothesized to cause hyperphosphorylation of tau, resulting in tangle formation and cognitive deficits. To test this hypothesis we have generated a transgenic mouse line in the C57BL/6 genetic background, overexpressing p25 in forebrain under the control of the alphaCaMKII promoter. Surprisingly, the p25 mutants have improved reversal learning in the water maze, indicating that p25 accumulation in AD patients is a compensatory mechanism to maintain cognitive abilities. However, the p25 mutants are aggressive: In about one-third of male sibling cages injuries are observed. Thus, p25 accumulation may cause the aggression associated with AD.

Wolfson Institute for Biomedical Research, University College London, UK. This work is supported by the British Medical Research Council.

Josh Dubnau, Scott Gossweiler, Lori Grady, Jodi Barditch, Pat Smith, Jim Dezazzo, Ulli Certa, Clemens Broger, Rod Scott, Ann-shyn Chiang and Tim Tully.

DNA chips reveal the involvement in memory of multiple components mRNA localization machinery

One evolutionarily conserved feature of long-term memory formation (LTM) is a requirement for gene expression. A key regulator in both vertebrate and invertebrate species of LTM and of long-lived synaptic plasticity, is the cAMP responsive transcription factor, CREB. In Drosophila CREB-dependent LTM normally is formed after spaced training but not after massed training. Using a novel statistical method optimized to detect small-magnitude effects with DNA chips, we have identified 141 candidate memory genes (CMGs) whose transcripts are differentially expressed after spaced versus massed training. Among these CMGs are multiple components of the cellular machinery used to localize mRNAs and to regulate their translation. Using genetic manipulations of several of these genes, we demonstrate an acute requirement during memory consolidation for this genetic pathway. These data suggest a plausible model to explain synapse specific modifications underlying memory

O. Roussot1 , F. Pitel1, A. Vignal1, J.M. Faure2, A.D. Mills2, D. Guémené2, C. Leterrier2, S. Mignon-Grasteau2, P. Le Roy3, M. Perez-Enciso4 and C. Beaumont2

QTL research on the duration of tonic immobility in quail

A QTL (Quantitative Trait Loci) research was initiated to identify the genome regions involved in the control of duration of tonic immobility (DTI), a catatonic-like state of reduced responsiveness to external stimulation. A total of 1048 animals were obtained from a second generation cross (F2) between two quail lines divergently selected for more than 25 generations for or against DTI trait. The difference (DIFF) between DTI and the number of inductions (NI) necessary to induce tonic immobility (both centered and reduced) was analyzed. Segregation analysis led to suspect the existence of a gene explaining more than one standard deviation of DIFF. As no genetic map of quail was available yet, a first set of 432 AFLP™ markers was developed. Significant effects were observed for alleles of several markers belonging to one linkage group so that the existence of a QTL within this group is highly suspected

1INRA, Laboratoire de Génétique Cellulaire, 31326 Castanet-Tolosan, France, 2 INRA, Station de Recherches Avicoles, 37380 Nouzilly, France. 3 INRA, Station de Génétique Quantitative et Appliquée, 78352 Jouy-en-Josas, France. 4 INRA, Station d’Amélioration Génétique des Animaux, 31326 Castanet-Tolosan, France.

S. Richard1, D. C. Davies2, A. D. Mills1, D. Guémené1, C. Leterrier1, J. M.Faure1.

A genetic model to investigate the mechanisms of fear behaviour in birds.

Genetic selection for behavioural traits has been employed in an attempt toimprove the adaptation of poultry to intensive rearing conditions.Moreover, it has proved to be a useful tool for investigating the mechanisms underlying avian behaviour. Two lines of Japanese quail have been divergently selected for long (LTI) or short (STI) duration of tonic immobility, which is positively correlated with other measures of fear.Thus, LTI quail display significantly higher levels of fear than STI quail,as demonstrated by a variety of classical behavioural indices. LTI and STI quail also diverge in their physiological responses to fear, measured by changes in plasma corticosterone concentration and heart rate.The extreme divergence in fear responses between the two lines has facilitated investigation of the neural bases of fear behaviour. The forebrain of LTI quail contains less d opioid receptors and exhibits reduced benzodiazepine receptor binding affinity compared to STI quail, suggesting that these receptors may play a role in fear behaviour. In addition, bilateral lesions of the archistriatum (a telencephalic structure considered to be a partial homologue of the mammalian amygdala) impair the expression of fear behaviour in LTI, but not STI quail. Moreover, preliminary data suggest that there are morphological differences between the two lines within the archistriatum. Further work is in progress to characterise the neural differences between LTI and STI quail. It is hoped that these studies will lead to a better understanding of the neural mechanisms underlying avian fear behaviour.

1Station de Recherches Avicoles, INRA, 37 380 Nouzilly, France and 2Dept.of Anatomy and Developmental Biology, St George's Hospital Medical School, London SW17 0RE, UK.

POSTER SESSION

Arabo, A.*, Costa, O., Tron, F.**, Caston, J.* Impairment of spatial cognition in the lupus-prone NZW/BXSB mice**

The lupus-prone mice NZW/BXSB (F1) are an animal model of Systemic Lupus Erythematosus, a human disease. They displayed severe immune disorders and a loss of immune system tolerance associated to numerous auto-antibodies production directed against the Central Nervous System (CNS) and more particularly against areas involved in spatial cognition i.e. the hippocampus, the cerebellum and the associative parietal cortex. The pathology is present in both sexes, but a Y chromosome factor derived from the SB/Le male, known as the autoimmune accelerator (Yaa), leads to an earlier onset and greater severity of autoimmune disease in males NZW/BXSB. In contrast, females, which lack the Yaa gene are to a great part protected. Thus, 4-5 month-old males are affected whereas females are not yet. Spatial learning and memory have been studied in these animals by means of a device derived from the Morris water maze.Two groups have been constituted: an experimental group made of 4-5 month-old males (n=11) and a control group of females of the same strain and age (n=15).

Our results, based on water escape latency, number of crossed quadrants and strategy used, clearly show that, compared to females, males display severe deficits in acquisition and retention of spatial task. However, none of the animals, whatever their sex, present motor, visuo-motor and motivational disorders. The poor results of males can therefore be interpreted as an important deficit of spatial cognition. We can hypothesise that cognitive abnormalities observed in NZW/BXSB lupus-prone male mice are linked to hippocampical disorders, resulting themselves from the auto-antibodies action on this structure. Immunological and neuro-anatomo-pathological studies will allow a possible correlation between behavioural, neurological and immune disorders.

*UPRES EA1780, IFRMP 23, Neurobiologie de l'Apprentissage, Rouen ; **INSERM U519, IFRMP 23, Rouen

Arguel, E.*, Costa, O., Tron, F.**, Caston, J.***
Anxious-like behaviors in the NZW/BXSB lupus-prone mice.

Lupic mice suffer from auto-immune pathology similar to Human Systemic Erythematosus (SEL). Neurologic manifestations in this mice, as in patient affected by SEL, are related to auto-anticorps action, in particular against hippocampal areas. NZW/BXSB lupic males carry Yaa gene leading to an early onset and great severity of auto-immune disorders. Females, lacking this gene, are protected a longer time. So, 4-6 month-old males develop the disease whereas females of the same age are still healthy. Anxious-like behaviors have been studied in this animals since the limbic system is particularly involved in this behavior. Two groups have been constituted : an experimental group made of 4-6 month-old males (n=11) and a females group, not yet affected at the same age, used as control group (n=15). Two anxiety tests have been used to study trait-anxiety (constitutional anxiety) : emergence in an open-field and emergence in a lighted compartment. Two other tests have been used for state-anxiety (related to anxiogenic situation where mice are placed) : exploration of an open-field and of an elevated +-maze. Motricity, exploratory behavior, and discrimination abilities are not different in males and females. On the other and, anxious-like parameters show that state-anxiety is more important in males than in females, whereas trait-anxiety is similar in both sexes.

We can suggest the existence of two differents neurobiologic substrates for the two anxiety types. Moreover, these results suggest the existence of a correlation between state-anxiety, hippocampal functions and auto-immunity

*UPRES EA1780, IFRMP 23, Neurobiologie de l'Apprentissage, Rouen ;**INSERM U519, IFRMP 23, Rouen

V.Besson1, V.Blanquet1, A.Puech2, Y.Hérault1.

An ENU-induced mutagenesis screen for recessive mutation affecting basic behaviour.

The mouse is the most commonly used animal model to study and understand human genetic diseases. Models are generated thought genetic approach, including Knock-out, conditional approaches, etc. and more historically by selecting mutant animals, the phenotypic approach. Recently, such an approach was reinforced by the used of Ethyl-nitroso-urea (ENU), a powerful mutagen which induces point mutations in the mouse genome, that leads to null, hypomorphic or hypermorphic allele. Such a phenotypic approach leads recently to the identification of various dominant mutations (Hrabe de Angelis, 2000; Justice, 1999; Nolan, 2000). We decide to start a new program of ENU-induced mutagenesis in the "Institute of Transgenose", called PhenoMut, in order to provide new mouse models for human recessive pathologies.Mutations are selected though a screening procedure looking for phenotypic alterations in a wide range of parameters including basic behaviour. This program does not require any knowledge on the identity of the genes since ENU induced mutations are selected by their phenotype. This is more rather a functional approach, complementary to the genetic approach, in which remains the candidate gene hypothesis.
In this meeting, we will present the degree of advancement of the PhenoMut project and we will focus our attention to some behavioural and neuromuscular mutants already isolated.
1Génétique Expérimentale et Moléculaire, CNRS FRE 2358, Institut de Transgénose, Orléans, France. 2Centre National de Génotypage, Evry, France.Hrabe de Angelis, et al. (2000). Genome-wide, large-scale production of mutant mice by ENU mutagenesis. Nat Genet 25, 444-447.Justice, M. J., et al., (2000).Effects of ENU dosage on mouse strains. Mamm Genome 11, 484-488.Nolan, P.,et al.(2000). A systematic, genome-wide, phenotype-driven mutagenesis programme for gene function studies in the mouse. Nat Genet 25, 440-443.

Bichler Z.1, Migliore-Samour D.1, Gonzalez M-C.1, and Branchi I.2.

Neurobehavioural alterations in YAC transgenic mouse model of Down syndrome: a possible implication of DYRK1A gene, the human homologue of Drosophila minibrain

Down syndrome (DS) or trisomy 21 is the most frequent genetic cause of mental retardation (1:700 live births). To investigate the genetic bases and pathogenesis of central nervous system in DS, four transgenic mouse lines have been phenotyped, each one bearing a Yeast Artificial Chromosome (YAC) which embodies a specific fragment of the human Down Chromosomal Region-1 (DCR-1; Smith D.J. et al, 1995, Genomics). The DCR-1 contains genes involved in the development of several DS features including mental retardation. We have performed immunohistochemical and behavioural analysis of the four mouse lines to understand the role played by each fragment in DS. Specific neuroanatomical and cognitive alterations were observed only in the 152F7 line, which bears the fragment containing the DYRK1A gene. In particular, an altered developmental pattern of basal forebrain cholinergic neurons and an abnormal increase of brain weight during the entire lifespan were found. Furthermore, these mice showed a clear learning impairment in a passive avoidance task on PND (post-natal day) 16-17, and a hyperactive locomotor profile in an open-field test on PND 18. We suggest that the DYRK1A gene, the human homologue of Drosophila minibrain, is implicated in the neurobehavioral alterations found in the 152F7 line. Thus, this gene could play a crucial role in the pathogenesis of Down syndrome.
1Institut de Transgenose, CNRS, FRE 2358, 3b Rue de la Ferollerie, 45071 Orleans Cedex 02, France.2Laboratorio di Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanita, Viale Regina Elena 299, 00161 Roma, Italy.

J.A. Bouwknecht and R. Paylor

Mice lacking the BETA-4 subunit in nicotinic acetylcholine receptors show reduced anxiety on the elevated plus maze

Nicotine is seen as the addictive component in tobacco and causes a variety of behavioural and cardiovascular responses via activation of nicotinic acetylcholine receptors (nAChR). The nAChRs are ligand-gated ion channels, consisted of five subunits with different compositions that are expressed in muscles and neurons. One of these subunits is the beta-4 subunit that forms heteromeric nAChRs.We studied mice lacking the beta-4 subunit (beta-4 KO) in an extensive behavioural test battery as recently described. Acoustic startle habituation, prepulse inhibition, conditioned fear and hot plate responses were similar in wildtype (WT) and beta-4 KO mice. Also performance on the rotarod and in the Morris swim test was unaffected in beta-4 KO mice. The anxiety paradigms that were tested were the light-dark exploration (LD) test, the open-field activity (OF) test and the elevated plus maze (EPM). The anxiety measures in the LD test (number of LD-transitions and time spent in the dark area) showed similar levels in both lines. The anxiety measure in the OF test (i.e. ratio center/total distance) was not different for the two genotypes either. However, beta-4 KO mice showed reduced anxiety levels in the EPM paradigm: both the number of open-arm entries as well as time spent on the open arms was increased in beta-4 KO mice compared to wildtype mice. In addition, the frequency of nose pokes over the edge of the open arms was significantly higher in mutant mice. Overall, the role of the beta-4 subunit in behavioral responses appears to be rather limited. Whereas nicotine is thought to have a role in anxiety-related processes, our data suggest that the beta-4 receptor subunit is probably involved in only certain aspects of anxiety. Future studies focusing on other nAChR subunit knockout mice, both classic and inducible knockouts as well as double knockout mice will hopefully lead to a better understanding of the complicated interaction between different subunits and their involvement in behavioral responses, like anxiety-related processes. (supported by NIDA grant P01 DA12661).

Richard E. Brown, Lianne Stanford, Martin Williamson, Krista Luedemann and Christianne Hawken

Strain and sex differences in rotarod performance in mice are confounded by body weight

The rotarod is commonly used to assess strain, sex, and age differences in motor learning and motor co-ordination and is used to examine neuromotor ability in mutant mice and the effects of drugs and brain damage on motor coordination. We observed that smaller animals performed better than larger animals on the rotarod, thus we correlated body weight and rotarod performance and used analysis of covariance with body weight as the covariate to re-analyze differences in rotarod performance that were significant with ANOVAs. We found strain and sex differences in rotarod performance between C57BL/6J, 129S1, and HS mice. Body weight was correlated with rotarod performance ($r = -.38$, $n = 66$, $p = 0.0015$) and ANCOVA indicated significant effects of body weight on rotarod performcance but no strain or sex effects. In study 2, Molf/ei mice reached almost 70 rpm on the rotarod, while A/J and Balb/cByJ mice reached only 16-17 rpm, but even this large strain difference was due to body weight. Likewise in other studies with different strains of mice in our lab: significant strain, sex and age differences in rotarod performance were all confounded by body weight. The majority of published papers using the rotarod (18 of 27 reviewed) do not report the body weight of their animals and only 2 studies that we reviewed used body weight as a covariate when analyzing strain and sex differences in rotarod performance. We conclude that studies using the rotarod to test for differences in motor learning and motor coordination must remove the confound of body weight before concluding that the results are due to genetic, sex, or age differences or to drug or brain damage effects on motor learning and co-ordination.

Psychology Department, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4 J1

P. Chapillon1; C. Belzung2 and C. André3

Behavioural effects of b2-adrenergic receptor over-expression in mice.

Mice over-expressing the human beta2-adrenergic receptor (2-AR) gene were generated and compared to C57BL/6 mice. As the transgene transcripts were detected in total brain extracts, we examined the expression of the 2-ARs in different brain areas including the cerebral hemispheres, the mesencephalon, the brain stem and the cerebellum. We evidenced a 9 fold over-expression of 2-ARs cerebellum of the transgenic mice and slighter increases (1.7-1.9 fold) in the cerebral hemispheres, the mesencephalon and the brain stem. We therefore investigated the behaviour of these mice in paradigms constructed to evaluate cerebellar function, such as the wooden beam, the suspended string, the unstable platform and the rotarod test. Finally, in order to assess the consequences of 2-AR over-expression in other brain regions, we compared the behaviour of the mice from the two genotypes in mice models of anxiety (openfield and free exploration test) and of learning and memory (passive avoidance and radial arm maze). Results show that transgenic mice display an impairment of performance in all the models of cerebellar function, which suggest a very severe deficit. Furthermore, mice display increased anxiety in the free exploratory test. Finally, simple learning such as habituation or emotional learning, was not modified while learning in complex task such as the radial maze was impaired. Taken together, these results suggest that 2-adrenergic receptor over-expression may be an animal model of the cerebellar cognitive affective syndrome.

1LNBA Faculté des Sciences, EA 1780 "PSY.CO", Université de Rouen, 76821 Mont Saint Aignan Cedex. 2 EA 3248 "Psychobiologie des émotions", UFR Sciences et Techniques, Parc Grandmont, 37200 TOURS. 3 ICGM, U380 INSERM, 22 rue Mechain - 75014 PARIS.

J.S. Chen, G. Preston, J.M. Pickel^, B.S. Kolachana, J.W. Nagle, M.F. Egan and D.R. Weinberger

DEVELOPMENT OF INDUCIBLE TRANSGENIC MICE CARRYING HUMAN CATECHOL-O-METHYLTRANSFERASE VAL AND MET ALLELES.

Dysfunction of prefrontal cortex is a prominent feature of schizophrenia and has been associated with genetic factors including the Val108/158 Met polymorphism in the catechol-O-methyltransferase (COMT) gene. It has been hypothesized that the higher enzyme activity of COMT encoded by the Val allele impairs frontal function by increasing prefrontal dopamine catabolism, and by this mechanism increases risk for schizophrenia. To test this hypothesis, we developed inducible transgenic mice carrying the membrane bound form of human COMT Val and Met genes. The membrane bound form of COMT is predominant in all brain regions, and is hypothesized to play an important role in the catabolism of dopamine in postsynaptic neurons, especially in prefrontal cortex. To achieve inducible and tissue-specific expression in transgenic mice, the human COMT Val and Met cDNAs were subcloned into the inducible vector, pTet-splice, and placed under the control of tetracycline-regulated promoter. The inducible COMT-Val and COMT-Met constructs were microinjected into mouse oocytes. Seven founder lines of inducible COMT-Met transgenic mice and five founder lines of inducible COMT-Val transgenic mice have been identified by regular PCR-based genotyping, and confirmed by single nucleotide polymorphism (SNP) genotyping and DNA sequencing. To test the effect of the human Val and Met polymorphism on mouse COMT, human Met and Val mutations were introduced into the mouse COMT gene to replace the corresponding amino acid residue Leu. Since there is only 76% homology in nucleotide sequences and 80% homology in amino acid sequences between human and mouse COMT genes, the transgenic mice carrying human COMT genes may serve as a better animal model for

study the effect of novel human COMT inhibitors on the improvement of prefrontal-type cognitive function for the potential treatment of schizophrenia and other disorders involving frontal dysfunction.
Clinical Brain Disorders Branch, Laboratory of Genetics, NIMH, NINDS, NIH, Bethesda, MD 20892.

Cécile Ducottet and Catherine Belzung
DIVERSITY IN THE RELATIONSHIP BETWEEN ANXIETY LEVEL AND SENSIBILITY TO SUB-CHRONIC UNPREDICTABLE STRESS AMONG EIGHT STRAINS OF MICE

A large inter-strain variability has been observed in mice subjected to animal models of anxiety such as the elevated plus-maze. According to some theories, an elevated anxiety can be a risk factor as to the development of depressive symptoms by inducing increased susceptibility to psychological stressors which are putative etiological factors in depression.
To test this hypothesis, we subjected mice from eight strains (FVB/NA, BALB/cByJ, C57BL/6J, DBA/2J, 129/SvJ, C3H/HeJ, CBA/J and BA) first to two anxiety-related tests: the elevated plus-maze (EPM) and the free exploratory paradigm (FEP), then, to a 2-week period of sub-chronic unpredictable mild stress (SCUMS), which is a model of depression. Sucrose preference and a physical state index were observed before and after SCUMS. Data were analysed by a hierarchical cluster analysis that revealed a separation of the population in two clusters. In the first, mice that deteriorated physically after SCUMS appear to be highly anxious in the two tests and display both a lack of variation of their sucrose preference and a body weight gain (i.e. 129/SvJ and C3H/HeJ). The second cluster shows that physically unchanged mice are low or mildly anxious animals that decrease their preference for the sucrose solution and exhibit a body weight loss. Specific strains of mice do not characterise one of these two clusters however some strains appear more resistant to the procedure with no physical changes (i.e. the C57BL/6J and CBA/J strains) while others exhibit a high sensitivity to SCUMS (i.e. physical deterioration in FVB/NA, BALB/cByJ, DBA/2J, C3H/HeJ, and BA).
EA 3248, Tours, France

Galaeva I.P., Garibova T.L., Voronina T.A., Krajneva V.A., Borlikova G.G., Makarenko A.M.
NOOGLUTYL CORRECTS HEMORRHAGIC STROKE-INDUCED NEUROLOGICAL DISTURBANCES IN THE RAT

A novel nootropic agent Nooglutyl is a positive regulator of AMPA glutamatergic system receptors. Its cerebroprotective properties were evaluated in rats with experimentally produced hemorrhagic stroke. The model of local cerebral hemorrhage was made in outbred white male rats. The brain tissue was destroyed within internal capsule area using the stereotaxis with the following under-language blood injection into damaged region. The rats with hemorrhagic stroke (HS) developed state and behavior disorders: neurological deficit (McGrow’s scale), movements coordination disturbances (rotating rod test), impairments of simple reflexes performance (hole), learning and memory deficits (passive avoidance reflex PAR). Rats also demonstrated behavioral impairments in EPM test, which indicated their anxiety. Dynamics examination showed the exacerbation of changes and death of animals with HS to the 14th. Nooglutyl given as single dose of 10 mg/kg after operation was found to attenuate the neurological deficit in rats, restore movement coordination, diminish learning and PAR retrieval disturbances. Besides, Nooglutyl was capable of preventing completely the death of animals with hemorrhagic stroke. In HS rats group animal survival made 80% on Day 1st of observation and 50% on Day 14th, whereas while on Nooglutyl administration at a dose of 10 mg/kg no rat death was observed. Thus, it can be concluded that Nooglutyl exerts a marked neuroprotective effect, the mechanism of

its action is probably associated with the glutamatergic system
Institute of Pharmacology, Moscow, Russia

M. Labbe, L. Magnol, A. Duchon and Y. Herault.
Creation and phenotypic analysis of a new mouse model for Down Syndrome

Down Syndrome (DS) is the most frequent form of trisomy in human and corresponds to a complete trisomy of the human chromosome 21 (HSA21). This increase in gene-dosage induces many developmental defects including mental retardation and other pathophysiological alterations. Genes of HSA21 have murine homologues located in syntenic region on mouse chromosomes 16, 17 and 10 (MMU10). Mouse models available until now correspond to entire or partial trisomy of MMU16. The most commonly used models display some features of the human syndrome, including some behavioral phenotypes but, it does not resume the whole phenotype that should be expected. The most telomeric part of the HSA21 is not amplified in the models whereas 1) it carries a large number of genes and 2) this region contains genes involved in the DS features according to the human genetic studies. In orde! r to understand and to further characterise the features of DS, more improved mouse models should be developed for the HSA21 telomeric part. Thus, we are engineering duplication of the corresponding homologous chromosomal regions in the mouse, in order to further study the developmental and physiological defects associated with DS. For this purpose, we develop ES cell technology combined with either the in vitro Hprt selection system or the in vivo TAMERE strategy, to engineer duplication inside the MMU10 homologous region. Such a new mouse mutant line, carrying a partial duplicated chromosome of the homologous region for the telomeric part of HSA21, will be studied in order to address the aetiology of DS through a wide phenotypic analysis.
Institut de Transgenose, CNRS GEM FRE 2358, Orleans, France.

L. Liu1, C. Fernandes1, M. J. Galsworthy1, J. L. Paya-Cano1, S. Monleon2, R Plomin1 and L. C. Schalkwyk1.
Constructs of Exploratory Activity and Anxiety in Heterogeneous Stock (HS) Mice

Anxiety and related exploratory activity are complex traits with a genetic contribution likely to be equally complex. A large variety of mouse tests of anxiety have been developed and attempts have been made to define the trait within, and across, different models. However, it is unclear whether a common underlying phenotype of anxiety can be extracted from these multiple tests or whether each test measures distinct situation specific anxiety and/or other exploratory behaviours. We will present data we have collected from 170 heterogeneous stock (HS) mice (outbred mice derived from an 8-way cross of inbred strains) in a battery of anxiety tests (open field, elevated plus maze, light/dark box, SHIRPA primary screen, approach behaviour and response to handling). Using principal component factor analysis, we obtained two major factors accounting for 25% and 18% of the total variance respectively, with exploratory activity measures highly loaded on the first factor, and the second factor representing classical anxiety measures. Sibling correlations were between 0.2-0.4 ($p<0.05$, $n=85$ sib pairs) for individual measures, while between the factors, sibling correlations were greater (0.2-0.5, $p<0.05$), suggesting that there is a strong familial basis for the phenotypic data. Our results suggest that phenotypes assessed in this way will make good targets for molecular genetic research to identify associated genes and for functional genomic research to investigate gene-behaviour pathways.
1 Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK.
2 Area de Psicobiologia, Facultad de Psicologia, Universitat de Valencia, Avda, Blasco Ibanez, Valencia, Spain.

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R. Madani, S. Kozlov, A. Vyssotski, G. Dell'Omo, A. Akhmedov, J. Kinter, H-P Lipp, P. Sonderegger, D.P. Wolfer.

Altered expression of the extracellular protease inhibitor neuroserpin interferes with exploratory behavior and reaction to novelty.

Available evidence suggests that the balance between antiproteases and their target proteases in the extracellular space may be critical for neuronal function and pathology. Neuroserpin, a member of the serpin family of serine protease inhibitors, is expressed in the central nervous system and is an inhibitor of tissue type plasminogen activator (tPA) and plasmin. Mice genetically made deficient in neuroserpin (NsKO) have been generated. Homozygous NsKO mice lack Ns protein completely, whereas heterozygous mice express a reduced amount. Interestingly, zymographic analysis of NsKO brain did not reveal increased tPA activity, suggesting that other inhibitors contribute to the regulation of tPA and may compensate for the defect. These mice, together with transgenic mice which overexpress neuroserpin in neurons under the control of Thy1.2 promoter (Thy/cNs) have been subjected to analysis of activity in their home cages and to a battery of behavioral tests. Both NsKO and Thy/cNs mutants show normal levels and circadian patterns of home cage activity. However, homozygous NsKO mice exhibited reduced exploratory activity in novel environments, in particular they were reluctant to investigate the open zones of an elevated maze, as well as a novel object introduced into a familiar arena. A milder form of this phenotype was observed also in heterozygous mice. Thy/cNs mice showed normal activity in most of these tests but displayed a neophobic reaction towards the novel object. These results implicate neuroserpin in the regulation of emotional behaviour through a mechanism that is at least in part independent of tPA activity and they shed new light on the role of extracellular proteolysis in the brain. University of Zurich, Institutes of Anatomy and Biochemistry, CH-8057 Zurich.

B. Martin 1,2, D. Rinaldi 1,2,3 and A. Depaulis 2

A common genetic mechanism involved in GABA- and glutamate-induced seizure susceptibility revealed by a mouse model for absence-epilepsy.

Two selected mouse lines BS/Orl and BR/Orl - were derived from the BS and BR progenitor lines initially selected for susceptibility to seizure induced by methyl-beta-carboline 3-carboxylate (ß-CCM: an inverse agonist of the GABA-A receptor). These selected lines represent the first genetic mouse model for human absence-epilepsy with both epileptic (BS/Orl) and non-epileptic (BR/Orl) animals. Whether the genetic mechanism for ß-CCM-induced seizures shares common genes with convulsions induced by GABAergic and glutamatergic ligands was addressed in this study. Using the BR/Orl and BS/Orl lines, significant genetic correlations were found, which were positive for DMCM (methyl6,7-dimethoxy-4-ethyl-ß-carboline-3-carboxylate) and PTZ(pentylenetetrazol), and negative for NMDA (N-methyl-D-aspartate) and KA(kainic acid) ($p<0.0001$, $p<0.0001$, $p<0.003$ and $p<0.0001$ respectively).Because any genetic correlation analysis necessitates a confirmation using another genetic approach to avoid any genetic drift, we have tested BR/OrlxBS/Orl F2 and F3 segregating populations. Similar correlations were found ($p<0.03$, $p<0.0001$, $p<0.004$ and $p<0.0004$ respectively).
Altogether, these results suggest a major common genetic factor responsible for the susceptibility/resistance to the GABA and glutamate convulsants. Interestingly this major genetic factor has opposite effects: seizure prone mice for GABA ligands are resistant for the glutamatergic ones and vice versa.

1. Laboratoire de Metabolisme Cerebral et Neuropathologies,U.P.R.E.S. E.A. 2633 Universite d'Orleans, B.P. 6759, 45067 Orleans

Cedex 2, France. 2. U 398 INSERM : Neurobiologie et Neuropharmacologie des Epilepsies Generalisees, Faculte de Medecine - Universite Louis Pasteur, 11, rue Humann, 67085 Strasbourg Cedex, France. 3. Centre Hospitalier Regional d'Orleans, 1 rue de la porte Madeleine, 45000 Orleans, France.

Yann S. Mineur1, Daniel J. Prasol1, Wim E. Crusio1 and Paul R. Dobner2.
What role does Neurotensin play in D-Amphetamine sensitization?

Neurotensin (NT) produces a wide range of behavioral and neurochemical effects after central administration that are similar to those produced by psychostimulant and antipsychotic drugs (APDs). There is increasing evidence that NT can both augment and antagonize dopamine (DA) signaling, depending on the site of administration. Thus, NT microinjection in the VTA increases locomotor activity and this response becomes sensitized upon repeated administration. This behavioral activation is accompanied by increased DA release in the nucleus accumbens (NAc) and prefrontal cortex, most likely due to the direct stimulation of DA neurons by NT acting at NT receptors (NTR-1). This contrasts with the APD-like effects of NT administered in the NAc. Psychostimulants and APDs induce NT expression in distinct striatal regions in medium spiny neurons in either the direct or indirect pathways, respectively. These observations taken together indicate that NT could mediate at least a subset of the effects of these drugs. Recent evidence that non-peptide NT antagonists attenuate amphetamine sensitization and the effects of APDs on prepulse inhibition and latent inhibition support a role for endogenous NT in both psychostimulant and APD drug action. However, the available NT antagonists have agonist activity at a second NT receptor subtype, NTR-2, and may display partial agonist activity at NTR-1. We have taken a genetic approach toward understanding NT signaling functions by generating NT knockout (NTKO) mice and have used these mice to examine amphetamine induction of locomotor activity.

We investigated the behavioral effects of acute and chronic D-amphetamine injection in the open field. NTKO mice exhibited lower locomotor activity when compared to their wild type (WT) littermates. Moreover, the behavior of NTKO compared to WT mice showed a different temporal pattern. These data suggest that NT plays a role in the behavioral response to amphetamine. Preliminary results indicate that NTKO mice are also defective in amphetamine sensitization.

1Brudnick Neuropsychiatric Research Institute, University of Massachusetts Medical School, 303 Belmont Street, Worcester, MA 01604, USA. 2Department of Molecular Genetics and Microbiology, University of Massachusetts Medical School, 55 Lake Ave. North,

J. L. Paya-Cano1, M. J. Galsworthy1, C. Fernandes1, L. Liu1, S. Monleon2, L. C. Schalkwyk1 and R. Plomin1
General cognitive ability does not vary with brain, cerebellum or hippocampus weights in heterogeneous (HS) mice

Recently, human research aimed at identifying brain mechanisms that are correlated genetically with general cognitive ability (‘g’) have shown that individual differences in brain volume are highly heritable and that genetic factors appear to mediate substantially the phenotypic correlation of about 0.40 between brain volume and ‘g’ (Pennington et al. 2001). Although brain weight has been found to have functional correlates with behaviour in mice, as yet there have been no reports of investigations on genetic mediation of brain weight and behaviour in mice. Here we analysed brain weight and cognitive data from 72 sibling pairs of outbred HS mice (n=144). Total brain weight as well as cerebellum and hippocampus weights were obtained for all mice. The cognitive tests included T-maze, Hebb-Williams test, Puzzle box and Morris water maze. Consistent with human data

suggesting substantial genetic influence on brain volume, total brain, cerebellum and hippocampal yielded high positive sibling correlations. Also similar to human data, general factor ('g') extracted from the cognitive measures yielded a significant sibling correlation. These sibling correlations suggest that the brain weight and 'g' measures are reliable. However, unlike the human data, brain weight measures did not correlate with 'g'. The present sample size has greater than 99% power to detect an association between brain weight and 'g' if the effect size of the association in mice is comparable to human research (correlation of .40). Thus, despite the evidence for 'g' in mice, it appears as though total brain weight does not contribute to explain the individual differences found in general cognitive functioning in this sample.

1 Social, Genetic and Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF,UK. 2 Area de Psicobiologia, Facultad de Psicologia, Universitat de Valencia, Avda, Blasco Ibanez, Valencia, Spain.This work was supported by an MRC Career Development Award (LCS)

W.PINOTEAU, L.NICOLAS, S.ROUTIER, D.MIGLIORE-SAMOUR, P.ROUBERTOUX and S.MORTAUD

Postnatal administration of COUMATE, a STEROID SULFATASE inhibitor, affect behavioral development in CBA/H mice

Over the past decade, it has become clear that the brain is a steroidogenic organ. Furthermore the steroid sulfatase (STS) is an important enzyme in steroid metabolism. In fact, it plays a central function in the neurosteroid mode of action, since it is responsible for the switch between the sulfated and the free forms of steroids wich have opposite effects. Generally dehydropiandosterone sulfate (DHEAS) and pregnenolone sulfate (PREGS) are considered to be GABAA antagonist. The unsulfated forms (PREG but not DHEA) are classified as GABAA agonists. Moreover, DHEAS, PREGS and their unconjugated forms are positive allosteric modulators of the NMDA receptor. Several studies have equally demonstrated that DHEA, DHEAS regulate the motility and /or growth of neocortical neurons in vitro and that PREG, PREGS regulate microtubule lattice formation and dynamics, which determine shape and control the balance between rigidity and plasticity in neuronal processes.At birth, the STS level was clearly higher than in adults. This level increased regularly until day 30. Then it decreased until day 45, where the concentration observed corresponded to the adult brain level. The high level of STS concentration in the brain during pups development could be responsible for a regulation of the sulfated to free steroids ratio. So, in this study we assessed whether COUMATE (an STS inhibitor) modulate behavioral development in pups CBA/H mice. Coumate (10mg/kg) was daily administred orally during 15 days after birth and pups were tested for sensorial and motor responses. A single dose of coumate produced a significant inhibition of the STS activity both in brain (70.57%) and liver (87%) 24h fallowing administration. Furthermore, we investigated brain anatomy at P5, P10, P15 during the treatment. The behavioral tests showed that COUMATE damaged behavioral development in pups CBA/H mice. These results demonstrate that STS could be involved in brain maturation probably by a modification of the sulfated and free forms of steroids ratio.

a FRE 2134 CNRS Génétique, Neurogénétique, Comportement, 3B rue de la Férollerie, 45071 Orléans La Source, France.b UMR 6005 CNRS Institut de Chimie Organique et Analytique, BP 6759, 45067 Orléans cedex 2, France.c CNRS Laboratoire de Neurophysiologie cognitive, Chemin Joseph-Aiguier 13402 Marseille cedex 20, France.d Université d'Orléans La Source, UFR Sciences, 45067 Orléans La Source Cédex 2, France.

Claudia F. Plappert, Peter K. D. Pilz, H.-U. Schnitzler

Prepulse inhibition and prepulse facilitation of the acoustic startle response is variably

influenced by stimulus parameters and stimulus habituation in different mouse strains

Changes in the sensory environment called prepulses administered before the startle stimulus change the acoustic startle response (ASR). The interpulse interval (IPI) between prepulse and startle stimulus is decisive whether the ASR is decreased (prepulse inhibition, PPI) or increased (prepulse facilitation, PPF). In rats, IPIs of 10-500 ms evoke PPI, IPIs of 0-10 ms PPF. Aim of the present study was to investigate PPI and PPF in several inbred mouse strains (C57BL/6J, 129/SvHsd, AKR/OlaHsd) and a hybrid strain between NMRI mice and wild mice (M. musculus domesticus). Exp 1: 12 mice (6 females, 6 males) of each strain were given prepulses (14 kHz, 65 dB SPL) at different IPIs (6.25, 12.5, 25, 37.5, 50, 100, 200, 400 ms) before the startle stimuli (noise, 110 dB SPL). Prepulses evoked differently strong PPI in all inbred strains (129>C57>AKR) at all IPIs which was maximal at 37.5 ms IPI and decreased at shorter or longer IPIs. In hybrids, however, prepulses caused PPF at IPI up to 37.5 ms while PPI occurred only at longer IPIs (50-400 ms). Exp. 2: At lower prepulse intensities (45 and 35 dB SPL), PPF was observed in all mouse strains with a maximal ASR decrease at 12.5 ms IPI, while PPI at IPI = 37.5 ms was decreased. Exp. 3: When repeating Exp. 1 with naïve mice over several days, PPI and PPF changed over the days depending on genotype: PPI increased over the days in C57. In hybrids, PPI increased and PPF decreased over the days. In 129 mice, both, PPI at longer IPIs and PPF at short IPI increased. We conclude that the genotype of the mice determines PPI and PPF in all examined aspects: differences in influence of prepulse intensity and IPI, and in long-term changes over days were found. We deduce there fore, that PPI and PPF are independent processes which are genetically determined.

1Animal Physiology, University of Tuebingen, Morgenstelle 28, 72076 Tuebingen, Germany. This work was supported by the Deutsche Forschungsgemeinschaft (DFG, Schn 23/1-4), hybrids were provided by Prof. G. Ehret, University of Ulm.

S. Pothion, C. Belzung, JC. Bizot.

Effect of chronic unpredictable mild stress on anhedonia and memory in two strains of mice.

Anhedonia, the loss of pleasure or interest, is one of the core symptoms of human depression. In depressive patients, anhedonia is often associated with memory deficits, particularly in old patients which are more sensitive to stressful events. In rat, chronic exposure to a variety of mild stressors has been found to cause a reduction of sucrose consumption that is consistent with a loss of responsiveness to reward.Using a mouse-adapted version of this model, we investigated the effect of chronic unpredictable mild stress (CUMS) on both anhedonia and memory in two strains of mice (C57BL/6 and CBA/H). Mice were submitted to 7 weeks of CUMS and anhedonia was weekly assessed using a sucrose consumption test, the evaluation of the physical state and the measurement of body weight. Results were compared with the ones non-stressed animals, housed in a separated room. Following 4 weeks of stress exposure, mice were tested for spontaneous alternation in the Y-maze, for spatial memory in the water-maze, and for social recognition for a juvenile. Results show that the effects of CUMS on the measured parameters are different according to the mouse strains.

1Key-Obs SA, Orleans. 2Laboratoire Psychobiologie des Emotions, Tours.

Laetitia Prut; F. Crestani; R. Keist; J.-M. Fritschy; D. Benke;; H. Blüthmann; H. Möhler; U. Rudolph

TRACE FEAR CONDITIONING INVOLVES HIPPOCAMPAL α_5 $GABA_A$ RECEPTORS

The heterogeneity of $GABA_A$ receptors contributes to the diversity of neuronal inhibition in the regulation of information processing. While most $GABA_A$ receptors are located synaptically the small population of α_5GABA_A receptors is largely

expressed extrasynaptically. To clarify the role of the α_5GABA_A receptors in the control of behavior a histidine-to-arginine point mutation was introduced in position 105 of the murine α_5 subunit gene which rendered the α_5GABA_A receptors diazepam-insensitive. Apart from an incomplete muscle relaxing effect, neither the sedative, anticonvulsant nor anxiolytic-like activity of diazepam was impaired in α_5(H105R) mice. However, in hippocampal pyramidal cells, the point mutation resulted in a selective reduction of α_5GABA_A receptors which altered the drug-independent behavior. In line with the role of the hippocampus in certain forms of associative learning, trace fear conditioning, but not delay conditioning or contextual conditioning, was facilitated in the mutant mice. Trace fear conditioning differs from delay conditioning in that the conditioned and the unconditioned stimulus is separated by a time interval. Thus, the largely extrasynaptic α_5GABA_A receptors in hippocampal pyramidal cells are implicated as control elements of the temporal association of threat cues in trace fear conditioning.
Institute of Pharmacology and Toxicology, University of Zurich and Department of Applied Biosciences, Swiss Federal Institute of Technology (ETH), Zurich, Switzerland; F. Hoffmann-La Roche Ltd., Pharma Research Gene Technology, Basel, Switzerland. Supported by: Swiss National Science Foundation

Daisy Rinaldi 1,2,3; Antoine Depaulis 2 and Benoit Martin 2,3
BS/Orl and BR/Orl, two genetic mouse models for absence epilepsy

Absence-epilepsy is characterized by non convulsive seizures associated with bilateral synchronous spike-wave discharges (SWDs) recorded on the electroencephalogram in both cortex and thalamus. The genetic mechanism underlying absence-epilepsy is not known in human or in animals. However a possible involvement of the gene encoding the gamma2 subunit of the GABA-A receptor has been suggested. We have derived two mouse lines (BS/Orl and BR/Orl) from the BS and BR progenitor lines initially selected for differential susceptibilities to seizures induced by methyl-beta-carboline 3-carboxylate (beta-CCM), a ligand of the GABA-A receptor benzodiazepine site. Since it has been shown that the beta-carboline compounds are involved in aggravation of absence seizures, the possibility of spontaneous occurrence of SWDs was examined in these two lines BS/Orl and BR/Orl. In BS/Orl mice, spontaneous SWDs (8±1 Hz) occurred regularly (about 1/min) and lasted for up to 8 s, when animals were awake and inactive, in both cortex and lateral thalamus. No SWDs were recorded in the dorsal hippocampus. Injections of ethosuccimide (200 mg/kg) or valproate (200 mg/kg) suppressed SWDs whereas injections of carbamazepine (30 mg/kg) enhanced the total duration of seizures in these mice. No SWDs were recorded in BR/Orl mice either spontaneously or after beta-CCM injection (4 mg/kg). These data suggest that the BS/Orl and BR/Orl lines constitute a genetic model of human absence-epilepsy relevant for studying the mechanisms underlying both the genesis of SWDs and the resistance to this form of seizures.

Thomas S., Thiery E., Aflalo R., Vayssettes C., Verney C., Berthuy I., Créau N.
The expression of PCP4 (PEP19), the chromosome 21 camstatin, is regulated during early development and aging

PCP4 belongs to a family of proteins involved in calcium transduction signals. It binds calmodulin as neuromodulin and neurogranin via a IQ motif, but it is not regulated by PKC and therefore belongs to another regulation pathway (Slemmon et al. 1996, J Biol Chem 271, 15911). More recently it has been shown in a transfection model that it regulates the CaMKII which mediates the transduction of apoptotic signal (Johanson et al. 2000, J. Neurosci 20, 2860). PCP4 has been identified in the mouse before human and the aminoacid homology between the two species is 98%. Its expression has been described post-natally and in adult in many brain

regions with a neuronal pattern, where its function is still not understood. A reduction of its expression has also been shown in degeneration diseases such as Huntington and Alzheimer (Utal et al. 1998, Neuroscience, 86, 1055).The gene is localized on human chromosome 21 and is in three copies in Down syndrome patients. In the mouse it is localized on MMU16 and present in three copies in the mouse trisomic models Ts65Dn and Ts1Cje. We therefore try to determine in the mouse if the gene expression begins earlier in development and if it is restricted to the neuronal lineage. Moreover the level of this expression was analyzed during normal aging. Mouse were studied from embryonic day 7.5 p.c. to P0. PCP4 was found expressed in ectoderm at E7.5 p.c. and later in some surface ectoderm and neuroectoderm derivatives, particularly in post-mitotic neurons. During adult life the expression level in the brain showed a decrease with age which was analysed in the cerebellum by quantification of in situ hybridization signals on Purkinje cells and real time RT-PCR. In the adult trisomic mouse Ts1Cje, PCP4 was found overexpressed in all adult brain regions. These results are particularly relevant to evaluate the role of PCP4 during embryogenesis and the consequences of its overexpression in trisomy 21 patients during development and aging.

EA3508, Université Denis Diderot, Paris France.

V.V.Voznessenskaya1, C.J.Wysocki2

Mammalian Model of Aggression and Smell

In many species odors are involved in initiation and cessation of aggressive activities; however, it is unclear wheather these two complex behavioral traits have an overlapping genetic basis. Inour research we take adventage of the discovery that two inbred strains of mice, CBA (CBA/J) and NZB (NZB/B1NJ) serve as animal models for both extreme olfactory variation and for aggression. The phenotypes are sensitivity to androstenone(5a-androst-16-en-3-one) and the level of inter-male aggression. The androstenone-sensitive and low-aggressive CBA strain and the androstenone-anosmic and highly-aggressive NZB strain were used. In a classical genetic analysis we tested sensitivity to androstenone in both types of F1 hybrids and in segregating F2 mice (n=104) using a "buried cookie test". Differences in sensitivity to AND between CBA and NZB mice were estimated to be at least 2,000-fold. Analysis of the results of AND sensitivity tests of the segregating F2 generation indicated the polygenic nature of this trait. The level of aggressiveness was quantified using a standard test with castrated male intruders serving as target mice. 93% of CBA mice did not attack the intruder. Of the NZB males, 88,2% exhibited high levels of aggression. Only 23% of CBA(female)xNZB(male) F1 were aggressive; however, 92% of the males from the reciprocal, NZBxCBA, cross revealed high levels of aggression. In the F2 generation, the level of sensitivity to AND is correlated with the level of male aggressiveness (r=0.78). A strong correlation between these two phenotypes in the segregating F2 generation suggests either linkage of genes controlling these behavioral traits or pleiotropy.

1A.N.Severtzov Institute of Ecology & Evolution RAS, Moscow, Russia. 2Monell Chemical Senses Center, Philadelphia, USA

Wolfer DP (1), Plath N (2), Kuhl D (2), Mohajeri MH (3), Minichiello L (4), Drescher I (1), Madani R (1), Lipp HP (1)

Spatial and non-spatial deficits in the watermaze distinguished by automatic identification and classification of swimming strategies

Water-maze navigation is frequently used to assess spatial learning of mutant mice. However, learning the task is a multistage process that requires complex adaptive responses and involves multiple memory systems. During learning, mice explore many strategies. Initial wall hugging (thigmotaxis) is soon followed by random exploration of the pool. More systematic scanning of the pool then increases the chance of hitting the platform. After learning that the platform is at a constant distance from the wall, mice adopt a circular swim pattern (chaining). Eventually, they realize that the goal has a fixed

position in space and focus their search on successively smaller areas, until precise navigation leads them directly to the platform from any release point. Because manipulations can interfere with any learning stage and do not necessarily disrupt spatial navigation per se, it must be verified that learning progressed normally to a stage where processing of spatial information becomes limiting. We have implemented an automatic software algorithm that combines new and previously published variables with empirical thresholds in order to classify video-tracked trials according to the predominant swimming strategy. The algorithm revealed characteristic differences of strategy choice between commonly used mouse strains. Furthermore, it showed that pilocarpine induced hippocampal lesions and genetic ablation of forebrain TrkB receptors disrupt early stages of watermaze learning that are largely independent of the processing of spatial information. In arg3.1-null mice, by contrast, the algorithm revealed a selective impairment of spatial navigation during advanced learning stages.

(1) University of Zurich, Institute of Anatomy, CH-8057 Zurich, Switzerland(2) ZMNH, D-20251 Hamburg, Germany(3) University Hospital, Centre of Psychiatric Research, CH-8008 Zurich, Switzerland@(4) EMBL, Mouse Biology Programme, 00016 Monterotondo-Rome, Italy
@Supp. SNF and NCCR Neural Plasticity and Repair