EUROPEAN BEHAVIOURAL AND NEURAL GENETICS SOCIETY

FIRST ANNUAL GENERAL MEETING
September 29 - October 1, 1997
Orléans, France

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Program

Monday, September 29, 1997

8.00-17.30 Registration

14.00 Symposium "Ethics". Chairs: D.J. Nash (USA) and W.E. Crusio (Orléans, France).
Joint Session with the Third French-American Symposium on Heredity, Nervous System and Behavior.

14.00-14.45 L. Muir (Canada). Wrongful sterilization: A case history.

14.45-15.30 J. Beckwith (Boston, USA). Genetics and human behavior: Lessons from the human genome project.

15.30-16.00 Coffee Break/Poster session

16.00-16.45 W.D. Missouri (USA). Genetic information and society's right to privacy: New challenges for the courts in the twenty-first century.

16.45-17.30 General Discussion

20.00 Banquet

Tuesday, September 30, 1997

8.00-17.30 Registration

8.30-8.40 Opening session

8.40-10.30 Symposium "Practical solutions for the genetic background problem in knockout mice". Chair: H.-P. Lipp (Zürich, Switzerland).

8.40-9.00 H.-P. Lipp (Zürich, Switzerland). Targeted disruption or genetic background: A practical solution to the flanking allele problem in behavioral testing of knockout mice.

9.00-9.20 F. Tronche, C. Kellendonk, Th. Mantamadiotis, K. Anlag, and G. Schütz (Heidelberg, Germany). Analysis of glucocorticoids signaling by conditional mutations of the murine glucocorticoid receptor and CREB genes.

9.20-9.40 R. Gerlai (South San Francisco, USA). Protein targeting: An alternative approach to gene targeting.

9.40-10.00 L. Ricceri, A. Usiello, G. Calamandrei, and J. Berger-Sweeney (Rome, Italy). Methodological caveats for the study of ontogeny of learning in genetically altered mice.

10.00-10.30 Coffee Break/Poster session

10.30-12.00 Symposium "Neurogenetics of Olfaction". Chairs: T. McGuire (Piscataway, USA) and J. Carlson (New Haven, USA).

10.30-11.00 P. Nef (Geneva, Switzerland). Additional role(s) for the odorant receptor proteins?

11.00-11.30 T. Sarafi, S. Daniels, Y. Qian, and P. Sengupta (Waltham, USA). Development and function of the chemosensory system in *C. elegans.*

11.30-12.00 J. Carlson, P. Clyne, and M. deBruyne (New Haven, USA). Olfaction in *Drosophila*.

12.00-12.45 Poster session

12.45-14.00 Lunch break

14.00-15.30 Contributed papers. Neurogenetic bases of behavior. Chair: G. Pflugfelder (Würzburg, Germany).

14.00-14.20 J.-R. Martin and M. Heisenberg (Würzburg, Germany). The effect of mushroom-body on locomotor activity in *Drosophila.*

14.20-14.40 M. Nakajima, A. Inui, and L.C. Samuelson (Kobe, Japan). Anxiety-like behavior is modulated by long-term over-expression or transient administration of neuropeptide Y in the mouse brain.

14.40-15.00 G.O. Pflugfelder (Würzburg, Germany). Genetic lesion in *Drosophila* behavioral mutants.

15.00-15.20 N.K. Popova (Novosibirsk, Russia). Central serotonin and genetically defined strategy of defensive behavior.

15.20-15.30 General Discussion.

15.30-16.00 Coffee Break/Poster session

16.00-17.30 Contributed papers. Neurobehavioral characteristics of genetically modified organisms. Chair: S.G.N. Grant (Edinburgh, UK).

16.00-16.30 L. Webster, S. Nada, and S.G.N. Grant (Edinburgh, UK). Analysis of synaptic plasticity using gene targeting: Interactions between tyrosine kinases and an NMDA receptor multiprotein complex.

16.30-17.00 L. de Acetis, G. dell'Omo, I. Poletaeva, M. Pleskacheva, H.-P. Lipp, and E. Alleva (Rome, Italy). Agonistic encounters in seminaturalistically- and laboratory-housed prionless and wildtype mice.

17.00-17.30 K.M. Frick, L.A. Burlingame, R.L. Neve, and J. Berger-Sweeney (Wellesley, USA). Age- and sex-dependent spatial memory deficits in mice overexpressing the C100 fragment of the amyloid precursor peptide.

17.30-18.00 Break/Poster session

18.00-19.00 Business meeting.

Wednesday, October 1, 1997

8.30-12.05 Symposium "Behavioral and neurochemical responses to stress and drugs of abuse in lines of rats genetically selected for rapid versus poor acquisition of active avoidance". Chairs: O. Giorgi (Cagliari, Italy) and A. Fernandez-Teruel (Barcelona, Spain).

8.30-8.40 O. Giorgi (Cagliari, Italy). Introductory remarks. What can we learn from genetically selected animals?

8.40-9.05 Th. Steimer, P. Driscoll, and P.E. Schulz (Geneva, Switzerland). The Roman High- (RHA/Verh) and Low-(RLA/Verh) Avoidance rat lines/strains as a potential model for studying the etiology and pathophysiology of human anxiety and mood disorders.

9.05-9.30 F.R. Brush (West Lafayette, USA). Adrenal morphology and physiology as genetic correlates of phenotypic difference in avoidance learning in rats of the Syracuse strains.

9.30-10.00 A. Python, Th. Steimer, P. Driscoll, and Z. de Saint Hilaire (Geneva, Switzerland). Roman High-(RHA/Verh) and Low-(RLA/Verh) Avoidance rats differ in 24 hr-EEG sleep patterns: A model for human sleep disorders associated with anxiety and/or depression?

10.00-10.30 Coffee break/Poster session

10.30-10.55 A. Fernandez-Teruel, A. Tobena, and R.M. Escorihuela (Barcelona, Spain). Environmental factors induce dramatic changes in emotionality/ anxiety- and novelty/reward seeking-related behaviors in Roman/Verh rats.

10.55-11.20 F.J. Beaugé (Créteil, France). Ethanol consumptive behavior in Roman High- and Low-Avoidance (RHA/RLA) rats.

11.20-11.45 M.G. Corda, V. Valentini, and G. Piras (Cagliari, Italy). Ethanol intake and preference in Roman High-Avoidance and Low-Avoidance Rats: Behavioral and brain microdialysis studies.

11.45-12.00 O. Giorgi, G. Carboni, and V. Frau (Cagliari, Italy). Recent findings on the behavioral and neurochemical responses to stressors and psychostimulants in Roman High-Avoidance and Low-Avoidance Rats.

12.00-12.05 A. Fernandez-Teruel (Barcelona, Spain). Concluding remarks.

12.05-12.45 Poster session

12.45-14.00 Lunch break

POSTERS

1. R.S. Ackley and D.J. Nash (Greeley, USA). Genetic and acquired cochlear pathologies in laboratory animals.

2. M. Balakireva, R.F. Stocker, N. Gendre, and J.-F. Ferveur (Orsay, France). *Voila*: A new *Drosophila* courtship mutant that affects the nervous system.

3. C. Belzung and A.M. Leguisquet (Tours, France). Flumazenil induces anxiolytic effects in BALB/c and not in C57BL/6 mice.

4. C. Chabert and P.L. Roubertoux (Orléans, France). Correlations between genes included in Down Syndrome Region (human chromosome 21) and learning in transpolygenic mice.

5. F. Cirulli, L. De Acetis, M. Bianchi, V. Poli, A.E. Panerai, and E. Alleva (Rome, Italy). Behavioral analysis of interleukin-6 overexpressing or knock out mice during agonistic encounters.

6. W.E. Crusio and H. Schwegler (Orléans, France). Hippocampal involvement in spatial and non-spatial radial maze learning in inbred mice.

7. S.G. Doronkin and L.I. Korochkin (Moscow, Russia). Molecular analysis of the ecs gene (Ecdysterone Sensitivity) of *Drosophila virilis*.

8. A.L. Doyen, M. Carlier, P.L. Roubertoux, and I. Le Roy (Orléans, France). QTL analysis on exploratory behavior in F_2 mice from two inbred strains, C57BL/6JBy and NZB/BINJ.

9. L. Erlenmeyer-Kimling, V. Hrabak-Zerjavic, V. Folnegovic-Smalc, S. Ivezic, Z. Folnegovic, V. Ljubimir, J. Endicott, C. Gilliam, and J. Knowles (New York, USA). Genetic linkage study of schizophrenia: Croatian-US collaboration.

10. P.-V. Guillot, R. Quinney, P.H. Glenister, S. Kersher, Y. Boyd, and M. Lyon (Harwell, UK). Genetic mapping of the doublefoot *(Dbf)* mutation.

11. R.A. Hensbroek, M. Verhage, and B.M. Spruijt (Utrecht, The Netherlands). Impaired secretion in the *Munc18-1* gene-dose mutant mice leads to changes in open field behavior.

12. D.M. Jackson (Atlanta, USA). Behavior-genetic analysis and the African-American community: Objective science or voodoo genetics.

13. J.-M. Jallon, M. Ait-Said, N. Chamont, A. Komatsu, and S. Birman (Orsay, France). Biogenic amines affect both sexual behavior and cuticular pheromones of *Drosophila melanogaster.*

14. A.I. Kim, L.G. Romanova, N.I. Romanova, and E.A. Soubocheva (Moscow, Russia). Behavioral investigation in Drosophila melanogaster mutant lines (gene *flamenco*).

15. R. Lalonde, M. Dubois, C. Strazielle, and J. Eyer (Rouen, France). Neurobehavioral evaluation of *NFH-LacZ* transgenic mice.

16. I. Le Roy, F. Perez-Diaz, M. Navet, and P.L. Roubertoux (Orléans, France). Co-detection of QTLs for cerebellar patterns of foliation (CPF) and hind limb coordination in mice.

17. I. Le Roy, F. Perez-Diaz, and P.L. Roubertoux (Orléans, France). Quantitative Trait Loci (QTLs) linked to sucrose octoacetate (SOA) consumption in mice.

18. F. Maarouf, P.L. Roubertoux, and M. Carlier (Orléans, France). Substitution of mitochondrial DNA (mtDNA) and laterality in mice.

19. C.C.G. Marican, L.F. Maarouf, F. Sluyter, W.E. Crusio, and P.L. Roubertoux (Orléans, France). Mitochondrial DNA effects on spatial memory and the intra- and infrapyramidal mossy fiber terminal fields of the hippocampus.

20. D. Moechars, I. Dewachter, K. Lorent, and F. Van Leuven (Leuven, Belgium). Expression of mutant and native human amyloid precursor protein in transgenic mouse brain.

21. A.P. Monaghan, D. Bock, P. Gass, A. Schwäger, D.P. Wolfer, H.-P. Lipp, and G. Schütz (Heidelberg, Germany). Aggressive behavior and defective limbic system in mice lacking the *tailless* gene.

22. S. Mortaud, E. Donzes-Darcel, P.L. Roubertoux, and H. Degrelle (Orléans, France). Murine steroid sulfatase gene expression in the brain during postnatal development and adulthood.

23. D.J. Nash, R.S. Ackley, and L. Al-Ani (Fort Collins, USA). Genetic and environmental effects on the incidence of neural tube defects in mice.

24. L. Rondi-Reig, Y. Lemaigre-Dubreuil, D. Müller, A. Lohof, J.C. Martinou, N. Delhaye-Bouchaud, J. Caston, and J. Mariani (Paris, France). Cognitive impairment in Hu-bcl-2 transgenic mice with surnumerary CNS neurons.

25. D. Santucci, E. Alleva, E. Carlson, A. Micera, and L. Aloe (Rome, Italy). Substance P levels in the CNS and peripheral tissue of SOD-1 transgenic mice.

26. D. Santucci, J. Kilbridge, D.M.Holtzman, E. Alleva, W.C. Mobley, and C. Epstein (Rome, Italy). Characterization of the behavior and CNS in partially trisomy 16 mice.

27. O.B. Simonova, S.F. Petruk, I.V. Jagaeva, and L.I. Korochkin (Moscow, Russia). Analysis of a new trans-regulatory locus in *Drosophila*.

28. C.L. Smith, N. Broude, S. Mapel, Y. Shevchenko, M. Lewis, and J. Graber (Boston, USA).Targeted genomic and conventional differential display: analyzing monozygotic twins discordant for schizophrenia.

29. I.A. Spitsyna and T.I. Duka (Dniepropetrovsk, Ukraine). NCAM and GFAP distribution in brains of stressed rats with different alcohol tolerance.

30. S.T. Sweeney, R. Auburn, P. Deak, D.M. Glover, and C.J. O'Kane (Cambridge, UK). Screening for embryonic paralytic mutants.

L. de Acetis[1], G. dell'Omo[1], I. Poletaeva[2], M. Pleskacheva[2], H.-P. Lipp[3], and E. Alleva[1]. Agonistic encounters in seminaturalistically- and laboratory-housed prionless and wildtype mice[4].

Fighting pairs of prionless, heterozygous and wildtype mice housed in two different conditions have been used to investigate possible alterations in aggressive behavior due to genetic background or environment. Twenty experimental male subjects were trapped from a colony containing wildtype mice and animals homozygous and heterozygous for disrupted *PrP* genes, living under semi-naturalistic condition (large outdoor pens, more than 300 m^2, western Russia, Bubonizi). Fifteen male mice came from a control colony of mice housed in a standard laboratory facility at the Univ. Moscow. Matched normal opponents (from the laboratory colony and same-weight) and experimental subjects were isolated for 9 days before being tested for aggressive behavior in clean home cages. Behavior of the mice from both conditions were videotaped during the 1st, 3rd, and 5th of 5 agonistic encounters, lasting 15 minutes. Genotyping had to be done after the experiments.

The number of homozygous prionless mice was too small to make statistical comparisons of aggressive behavior. A clear difference emerged when comparing the former housing condition of the animals. Mice housed in the laboratory showed a significant increase in offensive components of agonistic behavior when compared with mice housed in semi-naturalistic setting. Frequency and duration of elements such as attacks, upright offensive postures, tail rattling, etc., were higher in the first group, while the latter showed a higher frequency of defensive elements (upright defensive posture, and flight) and enhanced social behavior (push under, sniffing, allogrooming and social rest). Moreover, the latency to the first attack was at least four-fold longer in the feralized mice.

The reason for the reduced aggressiveness of the feralized mice remains to elucidated. However, since outdoor pens are dominated by a few aggressive males, it is likely that the random sample included mainly male mice which had already experienced defeat.

[1]Behavioural Pathophysiology Section, Lab. Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanita, Viale Regina Elena, 299, I-00161 Roma, Italy, [2]Biology Dept. Lomonossov Moscow State University, Vorobjevi Gori Street, and [3]Institute of Anatomy, Univ. Zurich-Irchel, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland. [4]Supported by Swiss National Science Foundation 31-46691.96

R.S. Ackley[1] and D.J. Nash[2]. Genetic and acquired cochlear pathologies in laboratory animals.

Study of cochlear pathologies in human patients is limited to indirect observation. Therefore, developing animal models for study of human inner ear disorders provides basic information on the mechanism of hearing loss. To this end, laboratory animals with genetic and acquired cochlear damage were studied.

Genetic Hearing Loss. Microphthalmic white (*Miwh/Miwh*) genetic defect is known to produce deafness, and may be an animal model for study of Waardenburg Type 11 Syndrome. The mechanism of hearing loss is not well understood in either the animal model or the human condition. Twenty-four mice from microphthalmic litters were studied. Auditory evoked potential (AEP) measurements were made to determine normal hearing in normal litter mates (n = 8), moderate hearing loss in heterozygotes (n = 8) and deafness in mutant mice (n = 8). Cochlear histology and scanning electron microscopy (SEM) identified locus of hair cell damage. Interestingly, measurable hearing and intact hair cells occurred in 21-28 day old mutant mice.

Noise Induced Hearing Loss. Guinea Pigs were tested using AEP procedures pre and post noise exposure. Broad-band noise was presented for 30, 45 or 100 minutes. Hearing threshold changes were recorded and SEM studies identified locus of hair cell damage. Results indicate that noise exposure of 100 minutes produces extensive cochlear damage.

Perilymph Fistula. Guinea Pigs were tested using AEP procedures pre and post experimentally induced perilymph fistula, a known cause of Meniere's disease. A change in electrophysiology occurred reliably after decrease in perilymph volume. SEM studies identified hair cell damage pattern which mimics mild noise exposure.

[1]Univ. Northern Colorado, Greeley, CO, USA.[2]Colorado State University, Ft. Collins, CO, USA

M. Balakireva[1], R.F. Stocker[2], N. Gendre[2], and J.-F. Ferveur[1]. *Voila*: A new *Drosophila* courtship mutant that affects the nervous system.

In *Drosophila melanogaster*, the PGAL4 transposon induces the *Voila1* allele with different behavioral phenotypes. Homozygous *Voila1/1* flies of both sexes rarely reach adulthood and die between second instar larva and

late pupa stages. Adult males with a single copy of *Voila1* exhibit a strong bisexual behavior and enhanced locomotor activity while the courtship behavior of *Voila1* females is not affected. When ectopically driving the feminizing transgene *UAS-tra*, *Voila1* drastically decreases male sexual activity without additional behavioral debilitation. These different courtship alterations and the lethality, caused by two copies of *Voila1*, map at the same location as the PGAL4 insertion (86E1-2).

Voila1 is specifically expressed in the nervous system. In the central nervous system, it is expressed mainly in the mushroom bodies and, to a lesser extent, in the antennal lobes. In the peripheral nervous system, GAL4 expression is almost entirely restricted to the gustatory sensilla.

The genetics of the behavioral and lethality phenotypes were dissected by means of chromosomal deficiencies and by the remobilization of PGAL4. The multiple behavioral effects of the complex locus *Voila1* are discussed in light of its expression in the nervous system related to its genetic and molecular basis.

[1]URA CNRS 1491, Bât. 446, Univ. Paris-Sud, 91405 Orsay Cedex, France. [2]Inst. Zool., Univ. Fribourg, CH-1700 Fribourg, Switzerland.

F.J. Beaugé[1]. Ethanol consumptive behavior in Roman High- and Low-Avoidance (RHA/RLA) rats.

The relationship between anxiety disorders and the development of ethanol dependence remains controversial. Roman High-Avoidance and Low Avoidance rat lines which have been selected upon divergent active avoidance behavior seem to display also differential anxiety levels. Anxiety profile of the Roman rats was reevaluated through a punished drinking conflict test and analysis of brain neurotransmitter thought to be involved in anxiety behaviors (such as serotonin) and supported the fact that RLA rats are more emotional and anxious than their RHA counterparts.

To evaluate the possible involvement of emotional reactivity or anxiety in alcohol voluntary intake and emergency of dependence the Roman rats were tested for their alcohol consumption in a free choice situation after or not chronic inhalation of ethanol vapor. This kind of alcoholization is known to induce a craving for ethanol as shown by a large and preferential volitional alcohol intake in heterogeneous populations of regular Wistar rats.

As previously noted, the RHA rats spontaneously consumed more alcohol than the RLA rats. This difference was even enhanced after inhalation which was found totally ineffective to increase significantly alcohol intake in the RLA rats.

Differences between the RHA and RLA rats in general activity, in novelty and sensation-seeking behaviors as well as in adaptation or tolerance to some ethanol effects seem more likely to explain alcohol intake and proneness to dependence divergence than their differences in emotional reactivity. The well established and clear-cut resistance of the RLA line to dependence on ethanol deserves further study.

[1]Centre de Recherche Pernod-Ricard, Créteil, France.

J. Beckwith[1]. Genetics and human behavior: Lessons from the Human Genome Project.

Studies in human genetics have been used to argue for specific social policies. Often, the media, politicians and even scientists have proposed that these studies support a deterministic view of human behavior and aptitudes. Yet the evidence for significant genetic contributions to such traits is still problematic. The traditional twin, family, and adoption studies have not fully explored the role of environment and gene-environment interactions in their findings. More recent molecular genetic studies have failed to provide solid evidence for single genes influencing general behavioral traits and aptitudes or even conditions such as schizophrenia and bipolar manic depressive illness. These failures have led to calls for a new paradigm in the field. In addition, progress in the study of a number of human genetic diseases has revealed unexpected complexity in the expression of disease genes. These findings make even less tenable the deterministic representations of genetics. Because of the unwarranted claims for social policy implications of human behavior genetics, researchers in the field should play a role in public discussion of these issues. Examples to be cited include genetics of homosexuality, aggression, cognitive ability and several well-characterized genetic diseases.

[1]Dept. Microbiol. and Molec. Genet., Harvard Medical School, 200 Longwood Ave., Boston, MA 02115, USA.

C. Belzung[1] and A.M. Leguisquet[1]. Flumazenil induces anxiolytic effects in BALB/c and not in C57BL/6 mice.

In several animal models of anxiety; BALB/c mice have been described as emotional when compared to animals of other strains such as the C57BL/6. This increase of

anxiety may involve benzodiazepine receptors since benzodiazepine agonists abolish the anxiogenesis of these mice. Moreover, compared to C57BL/6, BALB/c mice exhibit a decrease in the number of benzodiazepine receptors.

Recently, it has been suggested that in human pathological anxiety, the benzodiazepine receptor spectrum may shift in such a way that the benzodiazepine receptor antagonist Flumazenil, which does not exhibit any intrinsic activity in normal subjects, may elicit panic symptoms in pathological ones. The scope of this study was to verify this theory in an animal model of anxiety.

BALB/c and C57BL/6 mice were confronted to the light/dark choice situation. Flumazenil (0.001 - 1 mg/kg, IP) did not modify the behavior of C57BL/6 mice. However, in BALB/c mice, the doses of 0.001 and 0.01 mg/kg induced a strong increase of both time spent in the lit area and number of transitions.

So, the benzodiazepine antagonist induce an anxiolytic effect in emotional in BALB/c and not in C57BL/6 mice. A shift in benzodiazepine receptor spectrum may exists, but contrarily to what we expected, this benzodiazepine antagonist shifts toward agonistic and not inverse agonistic properties in anxious subjects.

[1]LEPCO, Fac Sciences, Parc Grandmont, F-37200 Tours, France.

F.R. Brush[1]. Adrenal morphology and physiology as genetic correlates of phenotypic difference in avoidance learning in rats of the Syracuse strains.

Long-Evans rats of the Syracuse High- and Low-Avoidance strains (SHA/Bru and SLA/Bru) differ in adrenal morphology and physiology. Specifically, SHA/Bru animals have small glands that contain and release relatively large amounts of corticosterone, whereas SLA/Bru rats have large and relatively inactive adrenal glands. Several things are known about these unusual relationships: 1) the difference in size is entirely cortical, involving all three layers of the adrenal cortex, 2) the difference in size develops prenatally because it is significant at birth, and 3) the difference in size and physiology cosegregates with the avoidance phenotypes in F_2 and backcross (Bx_H and Bx_L) populations. The experimental results which establish these facts are presented and discussed in terms of possible genetic models.

[1]Purdue University, West Lafayette, IN, USA.

J. Carlson[1], P. Clyne[1], and M. deBruyne[1]. Olfaction in *Drosophila*.

Drosophila has a relatively simple but highly sensitive olfactory system. We have identified a number of genes required for its function and development. Among these is the acj6 (abnormal chemosensory jump) gene, originally identified by virtue of a behavioral defect and subsequently found to have a defect in olfactory physiology.

We have found that acj6 mutants are defective in the response of some, but not all, olfactory neurons. We have characterized, at single neuron resolution, the functional organization of one of the fly's olfactory organs, and have found specific defects in acj6. In some cases, one neuron within a sensillum responds normally while a second neuron in the same sensillum shows no response. In other cases, one neuron in a sensillum shows no response, while the other has acquired a novel response spectrum, as if the neuron has undergone a change of identity. We devised a new behavioral screen and used it to isolate additional alleles of acj6; we found that all alleles have molecular lesions in a POU domain transcription factor gene located at cytogenetic position 13C. Mouse and worm homologs of the gene have been shown to be required in the development of subsets of visual, auditory, or mechanosensory neurons. We propose that acj6 is required in specifying the identity of a subset of olfactory neurons, and thereby in determining the odors to which these neurons respond.

[1]Dept. of Biology, Yale University, New Haven, CT 06520-8103, USA.

C. Chabert[1] and P.L. Roubertoux[1]. Correlations between genes included in Down Syndrome Region (human chromosome 21) and learning in transpolygenic mice[2].

Down Syndrome is due to 3 copies of a short fragment of chromosome 21, the Down Chromosomal Region (DCR). Mental deficiency has been recognized as the clinical major feature of the syndrome although several other abnormalities have been described (body and brain morphology, immune disorders). Chromosomal fragments covering the DCR have been cloned and then incorporated in YACs. These YACs, including a segment of DCR, were transfected into mice (FVB inbred strain). A mouse bearing the YAC that carried one fragment of the DCR was trisomic for this region, due to the homologies between the human chromosome 21 and the murine chromosome 16. Four YACs, covering the DCR region have been selected. Two strains for each YAC were used to control for possible insertion effects. Each group was tested for three learning tasks: water maze, radial maze

and the Krushinsky test. Results confirm those published by Smith *et al*. (1997, *Nature Genetics,* 16, 28-36) showing a contribution of E7 region in latency to escape in the water maze. Our results modulate these conclusions. 1) Mice bearing the G6 region performed poorly in this task compared to both E7 and non transgenic mice. 2) The E7 mice did not exhibit any impairment in the radial maze whereas E6 and E8 did. 3) The 4 regions are involved in lowest performances obtained with Krushinsky task. These results urge to reconsider the concept of mental retardation in Down syndrome

[1]UPR CNRS 9074, Génétique, Neurogénétique, Comportement, Institut de Transgénose, CNRS, 3b rue de la Férollerie, 45071 Orléans Cedex 2, France.
[2]The transgenic mice were generously provided by Dr E. Rubin (Human Genome Center, San Francisco). The authors acknowledge Dr J. Delabar (URA CNRS 1335, Hopital Necker, Paris) for invaluable advice. Supported by CNRS (UPR 9074), Ministry for Research and Technology, Région Centre and Préfecture de la Région Centre. UPR 9074 is affiliated with INSERM and Université d'Orléans.

F. Cirulli[1], L. De Acetis[1], M. Bianchi[2], V. Poli[3], A.E. Panerai[2], and E. Alleva[1]. Behavioral analysis of interleukin-6 overexpressing or knock out mice during agonistic encounters.

Interleukin-6 (IL-6) is a cytokine released by activated immune cells that has been shown to affect brain function. In this experiment aggressive and social behavior exhibited during agonistic encounters by transgenic male mice either not expressing (BIL -/-; strain: BALB/c) or overexpressing (NSE; a cross of C57 and BALB/c strains) IL-6 in the central nervous system was investigated. All subjects were isolated for 24 days before the aggressive encounter and were 52 days old at the time of testing. Subjects were placed in a neutral cage for 15 min with an opponent of the BALB/c strain that had been previously isolated for the same amount of time. All sessions were videorecorded and a number of categories of behavior were later scored by a trained observer. Aggressive behavior: When compared to their controls, BIL -/- showed a higher degree of aggressiveness as indicated by a higher frequency of Upright offensive postures ($p<0.05$). On the contrary, NSE subjects showed a tendency to be less aggressive than their controls. A factorial analysis of variance showed an effect of strain on aggressiveness with C57 crossed with BALB/c subjects being overall more aggressive (e.g. showing a shorter latency to first attack and a higher duration of aggressive grooming) than the BALB/c strain. Social behavior: Overall, NSE mice showed a higher level of social interactions compared to their controls ($p<0.01$) as well as a higher duration and frequency of sniffing ($p<0.01$). Opposite results were found for BIL -/- mice. A factorial analysis of variance showed, once again, an effect of strain on aggressiveness with C57 crossed with BALB/c being overall less social compared to BALB/c. Overall these data suggest that IL-6 exerts complex effects on both aggressive and social behavior. They also indicate that the strain of the animal is an important variable in screening the effects of gene manipulations on behavior.

[1]Section Behav. Pathophysiol., Lab. F.O.S., Istituto Superiore di Sanita, Rome, Italy. [2]Dept. of Pharmacology, Univ. Milan, Milan, Italy. [3]IRBM "P. Angeletti, Pomezia, Italy.

M.G. Corda[1], V. Valentini[1], and G. Piras[1]. Ethanol intake and preference in Roman High-Avoidance and Low-Avoidance Rats: Behavioral and brain microdialysis studies

The contribution of genetic factors to the control of ethanol (EtOH) intake and preference has been investigated in a large variety of selectively bred rodent strains. Moreover, preference for EtOH has been observed also in lines of rats selectively bred for behaviors other than EtOH intake. This is the case of Roman High-Avoidance (RHA) and Roman Low-Avoidance (RLA) rats, two lines bred for rapid versus poor acquisition of active avoidance behavior. RHA and RLA rats show many other behavioral differences related to emotional factors, RLA rats being emotionally more reactive. In addition, a number of differences in dopaminergic (DAergic), serotonergic, and GABAergic function in the CNS have been reported in these two lines. Since these three neurotransmitter systems are involved in the regulation of EtOH consumption, it was considered of interest to investigate the differences in EtOH intake and preference between RHA and RLA rats. Moreover, the effects of EtOH on DA release in the shell compartment of the N. Accumbens were compared in these two lines using brain microdialysis. EtOH solutions were presented on alternate days in a free choice with water. The initial EtOH concentration was 2% and 1% increments were introduced every second day until a final concentration of 10% was reached by day 18. RHA rats consumed significantly larger amounts of EtOH and

displayed higher EtOH preference than did RLA rats. To examine EtOH intake and preference stability, animals were subsequently switched to daily presentations of 10% EtOH for 18 consecutive days. The line-related differences in EtOH intake and preference remained stable throughout the test period. Following chronic exposure to EtOH, the animals were habituated to a restricted access to EtOH schedule (2% EtOH, 2 h per day for 4 consecutive days) before surgical implantation of a dialysis probe in the N. Accumbens. Under these experimental conditions, voluntary EtOH intake (2%, 1h, p.o.) produced a significant increase in accumbal DA release in RHA rats but not in their RLA counterparts. In contrast, voluntary water intake (1 h) failed to change accumbal DA release in either line. These results indicate that RHA and RLA rats can provide a useful model to investigate the neurochemical mechanisms involved in the behavioral responses to EtOH.

[1]Dept. of Toxicology, Univ. Cagliari. Vle. A. Diaz 182, 09126 Cagliari, Italy

W.E. Crusio[1] and H. Schwegler[2]. Hippocampal involvement in spatial and non-spatial radial maze learning in inbred mice.

Three-months old male mice from nine different inbred mouse strains were tested in two different spatial radial maze tasks: one in which the maze was turned by 45° between trials and one in which the maze was always placed in the same way. Only four out of eight arms contained food rewards, permitting simultaneous assessment of working (WM) and reference memory (RM) in both situations. Turning of the maze significantly decreased performance in a strain-dependent manner. Other animals from the same strains were processed histologically to estimate the strain-specific extents of the hippocampal intra- and infrapyramidal mossy fiber projections (IIPMF). The extents of the IIPMF correlated strongly with both WM and RM if the maze was turned between trials. Similar correlations were only found in the early phases of learning in the other condition. We conclude that the IIPMF are involved in spatial learning and that non-spatial within-maze cues may influence learning performance in some inbred strains.

Factor:	I	II	III
Variable			
RM Non-spatial Changed	0.95		
WM Non-spatial Changed	0.93		
RM Non-spatial Not changed	0.84		
WM Non-spatial Not changed		0.79	
RM Spatial Turned Total		1.01	
WM Spatial Turned Total		0.95	
Spatial 8 arms		0.85	
RM Not turned 1st week		0.83	
WM Not turned 1st week		0.82	
Unconfined 8 arm		0.81	
IIP Mossy Fibers		-0.92	
RM Not turned 2nd week			0.90
WM Not turned 2nd week			0.87
Non-spatial 8 arms			0.57

Harris-Kaiser orthoblique rotation; 3 factors with Eigenvalue $\geq$ 1; only loadings $\geq$ 0.40; variance explained: 95%; interfactor correlations < 0.34.

These results were combined with those from previous studies, in which animals from the same inbred strains were tested in other, both spatial and non-spatial radial maze tasks: two spatial tasks in which all 8 arms of the maze were rewarded (one with, one without confinement to the central platform for 5 sec between subsequent arm choices); a non-spatial task in which all 8 arms were reinforced and in which animals had to push open doors in order to enter arms; 2 non-spatial tasks in which only 4 out of 8 arms were reinforced, black-and-white floor patterns identifying individual arms (one in which arms were interchanged between trials, one in which arms remained in the same configuration throughout).

A factor analysis rendered three factors: two representing non-spatial learning (factors I and III), one representing spatial learning (factor II). The IIPMF strongly loaded on the spatial factor only. We conclude that 1) spatial learning, in contrast to non-spatial learning, is a unitary process and 2) individual differences in the extent of the hippocampal IIPMF projection underlie individual differences in spatial learning abilities in the radial maze.

[1]Génétique, Neurogénétique et Comportement, CNRS UPR 9074, Centre de Transgénose, 3b rue de la Férrolerie, 45071 Orléans Cedex 02, France. [2]Institut für Anatomie, Leipziger Strasse 44, Universität Magdeburg, D-39120 Magdeburg, Germany. [3]Supported by CNRS (UPR 9074), Ministry for Research and Technology, Région Centre and Préfecture de la Région Centre. UPR 9074 is affiliated with INSERM and Université d'Orléans.

S.G. Doronkin[1] and L.I. Korochkin[1]. Molecular analysis of the *ecs* gene (Ecdysterone Sensitivity) of *Drosophila virilis*.

The steroid hormone ecdysterone causes radical changes in the genetic program of *Drosophila* metamorphosis, and the *ecs* gene (ecdysterone sensitivity) plays a key role in ecdysterone sensitivity of cells and acts

as a trans-regulator of different genes of *Drosophila melanogaster.*

For a detailed functional analysis of the ecs gene, the *ecs* locus of *Drosophila virilis* was cloned. It occupies a segment of about 100 kb. Resulting map of molecular analysis of this region was obtained. In situ hybridization of the cloned *ecs* locus with mitotic polytene chromosomes shows localization of this gene in the 2C-region of the cytogenetical map in the second chromosome of *D. virilis*. We have used Northern blot analysis of mRNA isolated from different developmental stages *Drosophila virilis* to study the transcription of the *ecs* gene. Our data demonstrate that the *ecs* gene encodes at least six different mRNAs. All transcripts are induced mostly in third instar larvae and medial pupa.

[1]Institute of Gene Biology, Russian Academy of Sciences, 117334 Vavilov st. 34/5 Moscow, Russia.

A.L. Doyen[1], M. Carlier[1], P.L. Roubertoux[1], and I. Le Roy[1]. QTL analysis on exploratory behavior in F_2 mice from two inbred strains, C57BL/6JBy and NZB/BINJ[2].

The GNC QTL program is focused on the genetic map of neuronal and behavioral variants in the mouse. Mice from two inbred strains (C57BL/6JBy and NZB/BINJ), their two reciprocal F_1s and their four F_2s were tested in an exploratory device (in all 395 animals). The device was a small open field (50 x 50 cm) with 3 objects situated at different places (two small cotton balls and a small metal plate). They were recorded by video camera during 5 min. Twenty one behavioral variables were defined covering most possible behaviors in this situation. Twenty eight significant QTLs were mapped for 15 variables using 65 SSLPs (Short Sequence Length Polymorphisms). Two mapping strategies were employed: Kruglyak and Lander's nonparametric method (1995, *Genetics*, 139, 1421-1428) and Lander and Botstein's interval mapping (1989, *Genetics*, 121, 185-199). These QTLs have been located on 12 chromosomes. One QTL (chromosome 7) explained 78% of genetic variance for latency of handling cotton ball. The X chromosome was implicated in 9 variables. Co-localizations were observed in 7 cases at the DXMit25 marker: frequency of sniffing of the cotton, latency of the first rearing, frequencies of rearing, jumping, grooming, digging and pushing.

[1]Génétique, Neurogénétique et Comportement, CNRS UPR 9074, Centre de Transgénose, 3b rue de la Férrolerie, 45071 Orléans Cedex 02, France.

[2]Supported by CNRS (UPR 9074), Ministry for Research and Technology, Région Centre and Préfecture de la Région Centre. UPR 9074 is affiliated with INSERM and Université d'Orléans.

L. Erlenmeyer-Kimling[1-3], V. Hrabak-Zerjavic[4-5], V. Folnegovic-Smalc[5-6], S. Ivezic[6], Z. Folnegovic[4], V. Ljubimir[4], J. Endicott[1,7], C. Gilliam[1-3], and J. Knowles[1,3]. Genetic linkage study of schizophrenia: Croatian-US collaboration.

Croatia was selected for a genetic linkage study, started in 1989 as a collaborative enterprise between US and Croatian investigators, for several reasons, including: (1) the existence of a comprehensive Psychosis Register covering all hospital admissions of psychotic patients in the entire country; (2) an elevated schizophrenia rate in certain parts of the country, which suggested a possibly increased prevalence of high-density families; and (3) comparative genetic homogeneity of the Croatian population, including several small isolate areas.

Despite the recent war in Croatia and other adversities, the study has managed to continue collecting families with at least two schizophrenic or schizoaffective members drawn from the Psychosis Register. Data collected on each family includes: family history interviews; face-to-face SADS-L interviews with each living patient, all "suspect" and as many unaffected relatives as possible; and blood samples for analysis of DNA markers on all interviewed individuals. A family is considered "complete" when all the foregoing information has been obtained.

To date, 35 families have been completed, containing 49 affected sib pairs (both with verified Research diagnostic Criteria, RDC, diagnoses--at least one with schizophrenia). Another 34 individuals have been completed in these families, including 36 with other psychiatric diagnoses. The final linkage sample is expected to include at least 250 sib pairs and over 500 other family members (1,000 individuals at minimum). Additionally, an association study examining approximately 20 candidate genes is planned.

[1]Dept. Psychiatry and [2]Dept. Genetics and Development, College of Physicians and Surgeons, Columbia University, New York, NY, USA. [3]Dept. Medical Genetics, New York State Psychiatric Institute, New York, NY, USA. [4]Croatian National Institute of Public Health, Zagreb, Croatia. [5]Univ. Zagreb School of Medicine, Zagreb, Croatia. [6]Psychiatric Hospital Vrapce, Zagreb, Croatia. [7]Dept. Re-

search and Training, New York State Psychiatric Institute, New York, NY, USA.

A. Fernandez-Teruel[1], A. Tobena[1], and R.M. Escorihuela[1]. Environmental factors induce dramatic changes in emotionality/anxiety- and novelty/reward seeking-related behaviors in Roman/Verh rats.

Roman high- and low-avoidance (RHA/Verh and RLA/Verh) rats, psychogenetically selected for extreme, divergent behavior in two-way, active avoidance acquisition, display several behavioral, physiological and neurochemical line-related differences suggesting higher emotionality/anxiety and lower 'sensation/novelty/reward' seeking in RLA/Verh rats than in their RHA/Verh counterparts. Thus, as compared to RHA/Verh rats, RLA/Verh rats show higher 'sensitivity to punishment' (SP), as indicated by many novelty- or stressor- induced behavioral and hormonal responses, including shock-induced suppression of drinking, fear conditioning, hyponeophagia and other behavioral tests. In these aversive situations RHA/Verh rats display "active coping strategies" whereas RLA/Verh rats behave as "passive copers". Moreover, RHA/Verh rats are more impulsive, and show higher preference for novel and 'stimulus-rich' situations/objects in the hole-board and other tests, as well as for rewarding substances like saccharin and ethanol than RLA/Verh rats. Collectively, these data indicate that RHA/Verh rats display higher "sensitivity to reward" (SR) than RLA/Verh rats. In keeping with the theoretical framework of SP and SR described by J.A. Gray (The psychology of fear and stress, Cambridge University Press, 1987), the results obtained with the Roman/Verh rat lines and with the more recently developed inbred Roman strains indicate that both psychological dimensions can be relatively independent, since they are not correlated with each other and are differentially affected by treatments like neonatal handling (NH) or environmental enrichment (EE). In fact, most of the emotionality (or SP)-related behavioral, and some hormonal, responses of the Roman/Verh rats can be enduringly altered by NH, especially in the direction of a marked reduction of these responses in RLA/Verh rats. On the other hand, responses related to the SR dimension (e.g. hole-board novelty seeking, ethanol intake, etc.) are also enduringly increased in both rat lines after exposing them to a period of EE. Importantly, NH effects are more pronounced on emotionality - related responses, whereas EE appears to mainly affect novelty/reward seeking responses. Thus, the Roman/Verh rats, in conjunction with the study of ontogenetic influences on their behavioral and neurobiological profiles, may be useful as a model to study the psychobiology of behavioral 'inhibition - activation (impulsiveness)' and related disorders.

[1]Medical Psychology Unit, School of Medicine, Autonomous Univ. Barcelona, 08193-Bellaterra, Barcelona, Spain. Partly supported by project PM96-0068. The invaluable collaboration of Dr. Peter Driscoll (Zürich, Switzerland) is gratefully acknowledged.

K.M. Frick[1], L.A. Burlingame[1], R.L. Neve[1], and J. Berger-Sweeney[1]. Age- and sex-dependent spatial memory deficits in mice overexpressing the C100 fragment of the amyloid precursor peptide.

Neuronal degeneration and amyloid plaque deposition are molecular hallmarks of Alzheimer's disease (AD). The C-terminal 100-amino acid fragment of the amyloid precursor protein (APP-C100), which contains the 42-amino acid Aβ peptide, may play a key role in AD neuropathology. Aged mice overexpressing this fragment display severe hippocampal atrophy and degeneration as early as 12 months of age. Furthermore, APP-C100 mice have significant spatial memory deficits, with female transgenics showing a more severe deficit than males.

The present study was designed to examine the age of onset of AD-like cognitive deficits in APP-C100 mice and to correlate these deficits to alterations in cholinergic neurotransmission. Male and female APP-C100 mice and controls were tested at three ages (3-5 months, 8-10 months, and 15-17 months of age). Mice were tested on a battery of cognitive and non-cognitive tasks.

Spatial, reversal, and cued versions of the Morris water maze tested spatial and non-spatial memory. Locomotor activity and basic reflexes were also measured. Choline acetyltransferase (ChAT) activity was measured in the cortex and hippocampus at the conclusion of behavioral testing. Transgenic mice of both sexes performed more poorly in the reversal task, suggesting impaired flexibility in learning a new spatial location. However, the severity of this deficit was inversely proportional to age, such that young transgenics were the most impaired and aged transgenics were the least impaired. ChAT assays are currently being performed.

[1]Dept. of Biological Sciences, Wellesley College, Wellesley, MA 02181; Dept. of Genetics, Harvard Medical School and McLean Hospital, Belmont, MA, USA. Supported by the Whitehall Foundation and NSF IBN9458101.

R. Gerlai[1]. Protein targeting: An alternative approach to gene targeting.

Gene targeting allows the manipulation of single genes. Although powerful and popular, these approaches are not without problems. As discussed previously, homologous recombination in embryonic stem (ES) cells often leads to a hybrid genetic background in the generated mutant animals. Analysis of such animals does not allow one to separate the effects of the introduced mutation from the changes caused by the differences in "background" genes. In addition, the "straight" knock out lacks temporal or spatial control over the introduction of mutation. Therefore, although well defined at the genetic level, gene targeting may lead to non-specific and widespread phenotypical alterations at the anatomy, physiology, or behavioral levels.

Several alternative solutions or control approaches may exist, however. One of them is to use protein targeting. Highly specific molecules, immunoadhesins, that target a particular protein of interest may be used. Immunoadhesins are chimeric fusion proteins generated by recombinant DNA techniques. CHO cells are transfected with a DNA construct encoding, for example, a ligand binding site of a receptor and the Fc portion of the immunoglobulin (IgG). The translated and purified immunoadhesin binds the ligand with high affinity and specificity (the receptor binding site is intact) but is unable to signal as its signaling (catalytic) domain is replaced by the IgG portion. Thus this immunoadhesin is a competitive antagonist for the endogenous receptor. The immunoadhesin comprising of the ligand fused with the IgG often behaves as an effective activator of its endogenous receptor. Thus using immunoadhesins one can impair or facilitate the activation of a receptor. Immunoadhesins are stable and can be delivered to a temporally and spatially controlled way into the brain using osmotic minipumps.

[1]Genentech, Inc., Neuroscience Dept., South San Francisco, California, USA.

O. Giorgi[1], G. Carboni[1], and V. Frau[1]. Recent findings on the behavioral and neurochemical responses to stressors and psychostimulants in Roman High-Avoidance and Low-Avoidance Rats.

The Swiss sublines of Roman high- (RHA/Verh) and low- (RLA/Verh) avoidance rats have been selected and bred since 1972 on the basis of their divergent performance in active avoidance behavior in a shuttle-box. The acquisition of two-way avoidance is strongly dependent upon emotional factors: RHA/Verh rats, which acquire avoidance quickly, do so mainly because they are less emotionally reactive and cope actively with that test in comparison to RLA/Verh rats which, as passive copers, display frequent freezing episodes. Thus, when exposed to a variety of stressors RLA/Verh rats show more pronounced emotional responses (i.e., defecation, freezing episodes, and grooming bouts) and a comparatively higher activation of the HPA axis than do RHA/Verh rats.

The mesocorticolimbic dopaminergic (DAergic) system consists of two major projections, both of which originate in the ventral tegmental area of the brainstem: i) the mesoaccumbens projection terminates in the nucleus accumbens and is involved in the regulation of goal-directed behavior and in the locomotor and reinforcing effects of psychostimulants and other drugs of abuse, and ii) the mesocortical projection mainly innervates the medial prefrontal cortex and plays a pivotal role in the expression of emotion-related behaviors as well as in cognitive and attentional processes. Our results demonstrate that a variety of aversive stimuli increase the cortical DA output in the line of rats showing the less pronounced emotional reactivity to stressors (i.e., RHA/Verh) but not in their more reactive RLA/Verh counterparts. It is proposed that the activation of the mesocortical DAergic pathway by stressors in RHA/Verh rats probably reflects the activation of cognitive processes in an attempt to cope with the stressors. Accordingly, RHA/Verh rats display active coping strategies when exposed to stressors, whereas RLA/Verh rats behave as passive copers. Also the mesoaccumbens projection has proven to be of particular interest in connection with the effects of cocaine and morphine in RHA/Verh and RLA/Verh rats. An acute challenge with low doses of either drug caused significant locomotor activation in RHA/Verh rats only, as well as a significantly larger increase in accumbal DA output in RHA/Verh rats as compared with RLA/Verh rats. Given the central role of the DAergic system in drug reward and the line-related differences in DAergic neurotransmission described herein, it may be proposed that comparative behavioral and neurochemical studies in RHA/Verh and RLA/Verh rats will continue to provide novel information on the biological correlates of anxiety, drug dependence, and drug abuse-related psychiatric disorders.

[1]Dept. of Toxicology, Univ. Cagliari. Vle. A. Diaz 182, 09126 Cagliari, Italy.

P.-V. Guillot[1], R. Quinney[1], P.H. Glenister[1], S. Kersher[1], Y. Boyd[1], and M. Lyon[1]. Genetic mapping of the doublefoot *(Dbf)* mutation.

An F1 offspring male carrying a spontaneous mutation was found in a C3H/HeH x 101/H cross mating. The mutation is characterized by extra toes on all four feet, hence the name doublefoot, *Dbf*. The mutation affects morphology (the long bones are shortened, the skull is broad, the tail is kinked, the feet are twisted), growth (mice are smaller than normal sibs at birth, grow more slowly and remain smaller, the viability is reduced) and reproduction (for the males the testis weights are reduced and for the females the vaginal opening is delayed). Previous work has shown that the mutant allele is dominant and maps on at a new locus on chromosome 1, between fuzzy *(fz)* and leaden *(ln)*.

Linkage tests with microsatellite markers located Dbf between *fz* and *ln* (D1Mit22, D1Mit77, D1Mit24, D1Mit8) carried out on offspring from an interspecific backcross with *Mus spretus* showed that Dbf maps 7.3±1.8 cM away from D1Mit22 and 5.9±1.6 cM away from D1Mit8, and closely to D1Mit24 and D1Mit77 (it does not recombine with both markers, which ought to be about 4 cM distant. This is not an effect of the *Dbf* mutation). Among the genes mapped around *Dbf* locus, *Pax3* might be a candidate gene. However, the analysis of the segregation pattern of 8 mice, known to be recombinant between D1Mit22 and D1Mit8 showed 3 recombinants with *Dbf*, ruling out *Pax3* as a candidate gene for the *Dbf* phenotype.

[1]Mammalian Genetics Unit, Harwell, Oxfordshire, OXII 8UT, England.

R.A. Hensbroek[1], M. Verhage[1], and B.M. Spruijt[1]. Impaired secretion in the *Munc18-1* gene-dose mutant mice leads to changes in open field behavior.

The neuron-specific protein *Munc18-1* is essential for secretion from presynaptic nerve terminals. Mice with a full knockout of *Munc18-1* have no docked vesicles at the active zone, and consequently no evoked secretion and no synaptic activity. The heterozygous mice have lowered expression of the protein *Munc18-1*, fewer docked vesicles at the active zone and less secreted quanta upon afferent stimulation as compared to wildtype litter mates. We have studied the behavioral consequences of this impaired secretion. In pups, there are no differences in the development of a variety of senso-motoric abilities, but the bodyweight of heterozygotes is lower. These differences first occur at the age of 6 days and persist throughout adulthood. Adult heterozygotes show no impairments on the rotorod, indicating that their motorskills are normal. In the open field, heterozygote mice walk twice the distance of wildtypes. Repeated exposures to the open field did not result in a decline in this distance. In addition, heterozygotes showed changes in coping with a novel object in the open field. While all wildtypes displayed object orientated exploration, heterozygotes either ignored the object or explored it very shortly. In the novelty box there was no difference in the latency to enter the novel compartment, indicating that they do not differ in fear for novelty.

In summary, heterozygotes have a heightened general activity in the open field, and they display far less specific exploration. We hypothesize that this is caused by cognitive impairments.

[1]Rudolf Magnus Institute for Neurosciences, Univ. Utrecht, Utrecht, The Netherlands

D.M. Jackson[1]. Behavior-genetic analysis and the African-American community: Objective science or voodoo genetics.

Behavior-Genetic Analysis (BGA) has made major contributions in psychology, especially in clinical psychology, comparative psychology, learning and memory. Despite the contributions made by BGA, the field has received neutral to negative responses from the African-American community. I am an African-American trained in BGA and I have taught in Historically Black Colleges for sixteen years. Two to three weeks of my Animal Behavior course and Introduction to Psychology as a Natural Science course are dedicated to BGA. Students' responses to BGA have varied from indifference to hostility. There are a variety of reasons for this behavior, but the main ones are (1) faulty preconceived notions about the relationship between genetics and behavior, (2) BGA being associated with biological determinism and racism, (3) the race intelligence controversy. The first and to some extent the second reason can be resolved in the classroom. Regarding the race and intelligence issue, there is no clear definition of intelligence nor is there an agreed definition of race. When investigators attempt to deal with ideas that are not clearly defined, and notions that are outside known parameters, my students ask "is this objective science or voodoo genetics."

[1]Dept. of Psychology, Morehouse College, Atlanta, GA 30314 USA.

J.-M. Jallon[1], M. Ait-Said[1], N. Chamont[1], A. Komatsu[1], and S. Birman[1]. Biogenic amines

affect both sexual behavior and cuticular pheromones of *Drosophila melanogaster.*

The *Drosophila melanogaster* pheromonal repertoire comprises female specific cuticular molecules like cis-cis 7,11 heptacosadiene which stimulate male sexual behavior and male rich molecules like cis 7 tricosene which affects female receptivity. Biogenic amines such as dopamine and serotonin are known to have strong effects on a variety of behaviors in vertebrates and invertebrates. Moreover dopamine plays an important pole in the tanning of insect cuticles.

The Ddc gene encodes Dopa decarboxylase, which catalyzes the conversion of Dopa to dopamine and that of 5 hydroxytryptophan to serotonin. Drosophila males homozygous for the temperature sensitive mutation Ddc ts1 and ts4 were much less successful when reared at the restrictive temperature after eclosion (29°C) compared to those reared at a permissive temperature (18°C). Moreover these former males have a markedly reduced level of cis 7 tricosene. Female pheromone levels are also reduced.

The pale gene encodes tyrosine hydroxylase, the rate limiting enzyme in the dopamine biosynthesis. Mutations in this gene also lead to defects in both male sexual behavior and contact pheromone levels. Whichever the allele, males become behaviorally sterile with a reduction of their contact pheromone, 7 tricosene. Female contact pheromones are also significantly modified, although the behavioral correlates seem nul.

[1]Laboratoire des Mecanismes de Communication, URA CNRS 1491, Bât. 446, UPS Orsay, 91405 Orsay Cedex, France and Laboratoire de Neurobiologie Cellulaire et Fonctionnelle, CNRS, Marseille, France.

A.I. Kim[1], L.G. Romanova[1], N.I. Romanova[1], and E.A. Soubocheva[1]. Behavioral investigation in Drosophila melanogaster mutant lines (gene *flamenco*).

Locomotor activity, chemoreception, sexual behavior and learning were tested in *D. melanogaster* lines, which carry the mutant gene *flamenco*. Lines 2 and 3 possessed and line 1 lacked the active genetic element *gypsy*. The line 4, which carries the wild *flamenco* allele, was used as control. Gene *flamenco* is the part of genetic system which controls the genome instability via influencing transpositions of the retrotransposon *gypsy*.

Mutant lines investigated revealed the specific behavioral profiles. In lines 2 and 3 locomotor activity was significantly lower in comparison to lines 1 and 4. Chemosensitivity in response to attracting (acetic acid) as well as to aversive (ethylacetate) odorous was also of characteristic pattern in each line. Sexual behavior was tested in groups and in individuals pairs as well. According to sexual activity lines investigated were ranged as 4>1>3>2. Lines 2 and 3 learned less successfully that lines 1 and 4.

Thus, mutant lines with the *flamenco* gene mutation possessing the retrotransposon *gypsy* active copies and which are characterized by genetic instability demonstrated some peculiarities in behaviors tested in comparison to wild type stable lines. These results suggests that the *flamenco* gene probably influences the development of behavioral functions.

[1]Dept. of Biology, Moscow State University, Moscow, Russia.

R. Lalonde[1], M. Dubois[1], C. Strazielle[2], and J. Eyer[3]. Neurobehavioral evaluation of *NFH-LacZ* transgenic mice.

NFH-LacZ transgenic mice are characterized by an early accumulation of a neurofilament of high molecular weight (NFH) in the cell bodies of neurons and a slower progression of Purkinje cell degeneration in the cerebellum. By comparison to normal littermate controls, irrespective of age (3 and 12-20 months), *NFH-LacZ* transgenic mice had a lower number of rears in an open field, lower latencies before falling on a large steel beam, longer movement times on a coat-hanger, and a higher number of quadrant entries and escape latencies in the visible platform version of the Morris water maze. Aged *NFH-LacZ* transgenic mice were disproportionately impaired on spontaneous alternation rate and latencies before falling on the coat-hanger and on the rotorod. No transgene effect was observed for horizontal motor activity in two open fields, choice latencies during spontaneous alternation, and distance traveled on the stationary beam tests. These results indicate selective defects of vertical motor activity, equilibrium, and visuomotor performance in a transgenic mutant with cerebellar degeneration.

[1]Univ. Rouen, Fac. Sciences, Lab. Neurobiol. Apprentissage, 76821 Mont-Saint-Aignan Cedex France. [2]Univ. Nancy1, France. [3]INSERM U 298, Angers, France.

I. Le Roy[1], F. Perez-Diaz[1], M. Navet[1], and P.L. Roubertoux[1]. Co-detection of QTLs for cerebellar patterns of foliation (CPF) and hind limb coordination in mice[2].

The NZB/BlNJ (N) and C57BL/6JBy (B6) inbred strains of mice exhibit large differences for CPF and hindlimb coordination. A

joint QTL detection was performed for these traits employing 260 F_2 male and female mice. Sixty five SSLPs (average distance 22.5 centiMorgans) were individually typed. Variation of intraculminate fissure is linked to three genes: *Cpfi-1* (Chr. 1), *Cpfi-2* (Chr. 4, corresponding to the previously mapped *Cfp-1*, Neumann *et al*., 1990, *Brain Res*., 524, 85-89) and *Cpfi-3* (Chr. 19). The presence or absence of the uvula fissure is determined by a single genetic locus (*Cpfu-1*) which is located on Chromosome 1. Four genes are implicated in declival fissure: *Cpfd-1* (Chr. 1), *Cpfd-2* (Chr. 5), *Cpfd-3* (Chr. 9) and *Cpfd-4* (Chr. 13). The *Cfp-2* and *Cfp-3* genes (Garretson *et al*., 1993, *Brain Res*., 630, 221-225) do not contribute to CPF variation between N and B6. The abnormal coordination of the hind limbs (measured by the number of slips on the carved bar, generously provided by H.-P. Lipp, Zürich) is linked to five QTLs. *Cpfd-1, Cpfu-1* and one QTL (contributing 17% of the genetic variance) of the motor coordination are located on the telomeric part of chromosome 1. This result suggests a functional link between uvula and declival fissures and hindpaw coordination.

[1]UPR CNRS 9074, Génétique, Neurogénétique, Comportement, Institut de Transgénose, CNRS, 3b rue de la Férollerie, 45071 Orléans Cedex 2, France.
[2]Supported by CNRS (UPR 9074), Ministry for Research and Technology, Région Centre and Préfecture de la Région Centre. UPR 9074 is affiliated with INSERM and Université d'Orléans.

I. Le Roy[1], F. Perez-Diaz[1], and P.L. Roubertoux[1]. Quantitative Trait Loci linked to sucrose octoacetate (SOA) consumption in mice[2].

NZB/BlNJ (N) and C57BL/6JBy (B6) mice differ in two-bottle preference tests for sucrose octoacetate (SOA) at two concentrations (0.1 mM SOA and 1 mM) *vs.* water. The N strain is considered as demitaster and B6 as non-taster. We took advantage of large DNA polymorphisms measured by Short Sequences of Length Polymorphisms (SSLPs) between N and B6, to map the QTLs implicated in SOA consumption at these two concentrations. Two hundred sixty four male and female mice from the F_2 generation were individually phenotyped then genotyped using 65 SSLPs (average interval length 22.5 centiMorgans). Four methods were used for mapping because different assumptions underlie the mathematical models used to map QTLs, 1) Nonparametric method, 2) interval mapping method (Lander and Botstein, 1989, *Genetics* 121:185-189) 3) Zeng's model 3 (Zeng, 1993, *PNAS* 90:10972-10976) and 4) Zeng's model 6 including the interval mapping and cofactors markers (Zeng, 1993, *PNAS* 90:10972-10976). QTLs co-detected with the four methods are reported here. Three QTLs were mapped for 0.1 mM SOA concentration: chromosomes 11, 2 and 19 (15, 9 and 4,1% of genetic variance, respectively). Three other QTLs were detected for 1 mM SOA concentration: chromosomes 6, 11 and 19 (30, 8 and 4% of genetic variance, respectively). A locus on chromosome 6, mapped at 62 cM from the centromere (Capeless *et al*., 1990, *Behav. Genet*. 22:655-663) may be the same as the locus that we have mapped on the same chromosome between 54.5 and 58.5 cM. This QTL cosegregates with *Prp* (prolin-rich protein), *Ldr-1* (lactate dehydrogenase regulator-1), *Rua* (raffinose undeca-acetate aversion) and Qui (quinine aversion). Two QTLs are common to consumption at 0.1mM and 1 mM SOA concentration, suggesting that sensitivity (low concentration) and aversion (high concentration) have partially identical genetic correlates.

[1]UPR CNRS 9074, Génétique, Neurogénétique, Comportement, Institut de Transgénose, CNRS, 3b rue de la Férollerie, 45071 Orléans Cedex 2, France.
[2]Supported by CNRS (UPR 9074), Ministry for Research and Technology, Région Centre and Préfecture de la Région Centre. UPR 9074 is affiliated with INSERM and Université d'Orléans.

H.-P. Lipp[1]. Targeted disruption or genetic background: A practical solution to the flanking allele problem in behavioral testing of knockout mice[2].

Some of the behavioral effects attributed to targeted disruptions might be due behavioral background rather than to the mutation itself (Gerlai, TINS 19: 177-181, 1996). Many targeted mutations have been done using stem cells derived from various 129 mouse substrains known as poor performers in learning tasks. Yet, any targeted locus is flanked by an unknown number of alleles derived from the 129 stem cell donor, even after backcrossing to another strain. Such linkage may then fake an impaired learning phenotype due to the presence of behaviorally confounding 129 alleles.

In practice, the problem is not so relevant for mouse samples consisting of a mixed background (commonly 129 x C57BL/6) because the 129 derived problems are canceled by hybrid vigor, that is, even those mice carrying targeted disruptions perform better than

the original C57BL/6 mutation, at least in swimming navigation learning.

A practical and theoretical solution is possible for recessive targeted mutations, using congenic backcrosses to 129 and C57BL/6. Crossing 129 and C57BL/6 congenics (each one carrying one chromosome with the targeted 129 segment) with the pure inbred lines will result in 3 genotypes of F1 mice with one set of alleles from 129 and the other from C57BL/6.: an ordinary F1 hybrid 129 x C57, one sample which is homozygous for the flanking segment, one of the segments containing the targeted deletion, and one sample in which the flanking segment with the mutation matches a C57 flanking segment. When the groups heterozygous for the targeted mutation are compared, one should observe no phenotypical differences. If the groups behave differently, it must be due to homozygosity of flanking 129 alleles.

[1]Inst. Anatomy, Univ. Zürich, Winterthurerstrasse 190, CH-8057 Switzerland. [2]Supported by SNF 31.46691.96 and the Human Frontier Science Programme.

F. Maarouf[1], P.L. Roubertoux[1], and M. Carlier[1]. Substitution of mitochondrial DNA (mtDNA) and laterality in mice[2].

The mtDNA makes up less than 0.2% of the total DNA in mouse. It is entirely transmitted by the mother. The laboratory strains of inbred mice share mtDNA from *Mus musculus domesticus* origin except NZB which has mtDNA from *M. musculus brevirostris* origin. Two congenic strains for mtDNA have been developed: NZB with mtDNA from CBA/H and CBA/H with mtDNA from NZB. The congenic strains have now reached the 25th and 26th backcross generations, respectively. The mtDNA transfer was checked by PCR amplification and Alu1 digestion. The primers (from Dr. Yonekawa) are specific of the D. loop region of the mtDNA, that presents polymorphisms between NZB and CBA/H. The quartet of congenic strains for mtDNA was tested for laterality in four independent conditions involving fore- and hind-paw preference or performance and body orientation. Substitution of mtDNA was related to the direction of laterality for the hind paws as well as direction and degree of laterality of the body orientation.

[1]UPR CNRS 9074, Génétique, Neurogénétique, Comportement, Institut de Transgénose, CNRS, 3b rue de la Férollerie, 45071 Orléans Cedex 2, France. [2]Supported by CNRS (UPR 9074), Ministry for Research and Technology, Région Centre and Préfecture de la Région Centre. UPR 9074 is affiliated with INSERM and Université d'Orléans.

C.C.G. Marican[1], L.F. Maarouf[1], F. Sluyter[1], W.E. Crusio[1], and P.L. Roubertoux[1]. Mitochondrial DNA effects on spatial memory and the intra- and infrapyramidal mossy fiber terminal fields of the hippocampus[2].

To investigate possible genetic effects of mitochondrial DNA (mtDNA) on spatial memory, two strains of laboratory mice NZB and CBA/H, having different mtDNA, and their reciprocal congenics for the mtDNA ($N^{mtDNA.H}$ and $H^{mtDNA.N}$) were used. Per genotype, 12-16 male mice were tested in an 8-arm radial maze. Total numbers of errors and the numbers of correct entries in the first eight arm sampled on days 2-5 were analyzed. The results show an effect of the origin of both the genetic background and the mtDNA with the background and mtDNA of strain H increasing spatial learning ability. In addition, the sizes of the intra- and infrapyramidal mossy fiber (IIPMF) terminal fields, known to be correlated with spatial memory, were quantified. The mtDNA of an N origin decreases the size of the IIPMF of mice with an H background. We conclude that non-pathological variations in mtDNA may influence complex neural and behavioral characters.

[1]Génétique, Neurogénétique et Comportement, CNRS UPR 9074, Centre de Transgénose, 3b rue de la Férrolerie, 45071 Orléans Cedex 02, France. [2]Supported by CNRS (UPR 9074), Ministry for Research and Technology, Région Centre and Préfecture de la Région Centre. UPR 9074 is affiliated with INSERM and Université d'Orléans.

J.-R. Martin[1] and M. Heisenberg[1]. The effect of mushroom-body on locomotor activity in *Drosophila.*

The search for the basic functional organization of insect brains has suggested that the mushroom bodies (MBs) play a role in the processing and storage of chemosensory information (e.g. olfactory learning). In an attempt to correlate the motivation process with different brain structures we have developed a new paradigm of spontaneous locomotor activity by measuring free walking behavior. We have investigated the role of the MBs in this paradigm using three different and independent approaches: by chemical ablation, by mutations affecting MB gross anatomy, and by toxigenetic interruption of MB neuron activity.

Drosophila MBs are a paired neuropil each consisting of about 2500 parallel Kenyon cell fibers derived from four neuroblasts. Feeding hydroxyurea (HU) to newly hatched larvae nearly exclusively deletes these cells, resulting in near complete MB ablation in the

adult. In measuring the total walking activity of HU-treated MB-less flies, there was not significant difference from untreated control flies. However, the pattern of activity or the distribution of activity as a function of time was significantly different. While control flies had a level of activity that decreased to almost zero as a function of time, the HU flies had a level of activity that only slightly decreased with time. This finding, implicating the MBs in a general inhibition of motor activity is consistent with previous work on crickets (Huber, 1960).

These results were reinforced by the measurement of walking activity in two MB mutations, mushroom-body-deranged *(mbdKS65)* and mushroom-body-miniature *(mbm1*). Both mutations showed the same defects as the HU flies. That is, a change in the distribution of activity compared to wild-type flies. Recently, the GAL4 enhancer-trap technique allowed us to specifically target the MBs with expression of a transgene encoding the tetanus toxin light chain, which is known to block synaptic transmission. The behavioral defects in locomotor activity were also observed in three different GAL4 enhancer-trap lines which drove the tetanus-toxin expression specifically in the Kenyon cells of the MB.

Thus, similar results were obtained by three different approaches and strongly suggest a regulation of locomotor behavior by the MBs. It also argues that the MBs, in addition to the previously determined role in olfactory processes, could be implicated in a more general process organizing temporal and spatial patterns of behavior. Importantly, the consistency of results with the three techniques implies that the tetanus toxin (depending on GAL4 expression) is sufficiently specific to be useful for the structure-function mapping of the brain.

F. Huber, 1960. *Z. vergl. Physiol.,* 44, 60-132.

[1]Theodor-Boveri-Institut für Biowissenschaften, Lehrstuhl für Genetik, Am Hubland, D-97074 Würzburg, Germany.

D. Moechars[1], I. Dewachter[1], K. Lorent[1], and F. Van Leuven[1]. Expression of mutant and native human amyloid precursor protein in transgenic mouse brain.

Alzheimer's disease (AD) is a devastating neurodegenerative disorder affecting an increasing fraction of the elderly population. Clinically, AD is a progressive disease beginning with diffuse deterioration of short term memory and mental functions. Neither effective treatment, nor specific clinical diagnosis is available. The definite diagnosis of AD is only reached by post-mortem pathological analysis of the brain, i.e. by microscopical demonstration of senile plaques, neurofibrillary tangles, vascular amyloid deposits, neuronal damage and astrogliosis. The slow course of the disease, the late age of onset, the physical condition of the patients, the fact that the brain is the target organ and the lack of direct methods to study the disease process in humans are all compelling arguments to search for an experimental animal model. A model is also needed to clarify the mechanistic cause and the pathological evolution of the disease process itself and would serve as a test-system for potential therapeutic strategies and screening drug libraries available.

The knowledge that different mutations in the Amyloid Precursor Protein (APP) gene cause early-onset, familial and very aggressive forms of AD, was the incentive to use transgenic mouse technology for the purpose of developing models. Using the neuron specific elements of the mouse thy1 gene as a promoter, we have generated transgenic mice that overexpress in brain, wild type and clinical mutants of APP.

Wild type and mutant APP tg mice become progressively hyperactive, aggressive, display seizures and die prematurely, reminiscent of observations in AD patients. In addition, neurodegeneration in the hippocampus and in the cortex of the tg mice is concordant with areas that are severely affected in AD brain. In the brain of older transgenic mice b-amyloid deposits become apparent throughout the hippocampus and cortex. Astrogliosis, disturbed behavior, learning deficit and neophobia are all evidenced. Pharmacologically, disturbed glutamatergic changes are most noticeable with overt de-sensitization towards NMDA and increased sensitivity towards kainic acid. Many of phenotypic traits are dependent on the expression levels in different transgenic strains and are more severe in homozygous animals.

[1]Experimental Genetics Group, Center for Human Genetics, Leuven, Belgium.

A.P. Monaghan[1], D. Bock[1], P. Gass[1], A. Schwäger[1], D.P. Wolfer[2], H.-P. Lipp[2], and G. Schütz[1]. Aggressive behavior and defective limbic system in mice lacking the *tailless* gene.

Tailless is a member of the nuclear receptor gene superfamily of transcription factors, and is expressed in the invertebrate and vertebrate brain. In mice, its transcripts are restricted to the periventricular zone of the forebrain (4), the site of origin of neurons and glia. We generated mice lacking functional protein from this gene by homologous recombination. At birth, homozygous mutant mice

are viable indicating that tailless is not required for prenatal survival. However, adult mutant mice show a reduction of rhinencephalic and limbic structures, including the olfactory, infrarhinal and entorhinal cortex, amygdala and dentate gyrus. Disruption of proliferation events is first observed in the ventricular zone of E14.5 day embryos. Homozygous mutant males exhibit an extremely aggressive behavior and are sexually aggressive toward females. Forty-five percent of mutant females are also aggressive and lack normal maternal instincts. These animals therefore provide a molecular approach to understand the genetic architecture and morphogenesis of the forebrain and to identify structures and connections involved in aggression.

[1]Div. Molec. Biol. Cell I, German Cancer Research Centre, Im Neuenheimer Feld 280, Heidelberg, Germany. [2]Institute of Anatomy, Univ. Zürich-Irchel, 8057 Zürich, Switzerland.

S. Mortaud[1], E. Donzes-Darcel[2], P.L. Roubertoux[1], and H. Degrelle[2]. Murine steroid sulfatase gene expression in the brain during postnatal development and adulthood[3].

The microsomal enzyme steroid sulfatase (STS, E.C.3.1.6.2) has a central function in the neurosteroid activity. It determines the switch between the sulfated forms and the free forms of steroids. These two forms of steroids have opposite effects. The expression of STS in the brain during development was investigated in mice. An enzyme linked immunoabsorbent assay (ELISA) was used, employing polyclonal mono-specific antibodies (Mortaud *et al.*, 1995, *J. Ster. Bioch. Mol. Biol.* 52:91-96). The results show that STS was present in the brain. The STS concentration was higher at birth than in adult brains and higher in males than in females as a general rule. The pattern of expression of STS in the brain was strain dependent.

[1]UPR CNRS 9074, Génétique, Neurogénétique, Comportement, Institut de Transgénose, CNRS, 3b rue de la Férollerie, 45071 Orléans Cedex 2, France. [2]Laboratoire d'Endocrinologie, UFR Biomédicale, Université Paris V-René descartes, 45 rue des Saints Pères, 75270 Paris Cedex 06. [3]Supported by CNRS (UPR 9074), Ministry for Research and Technology, Région Centre and Préfecture de la Région Centre. UPR 9074 is affiliated with INSERM and Université d'Orléans.

L. Muir[1]. Wrongful sterilization: A case history.

The Government of Alberta in Canada at one time believed that childhood learning and behavior problems arose entirely from defects of heredity. It passed the Sexual Sterilization Act in 1928, and then 2832 people were surgically sterilized by order of its Eugenics Board until 1972 when the Act was repealed. The Board believed intelligence was fixed by heredity and used IQ tests to justify its directives. In reality, many children capable of normal intelligence and a full life were confined in institutions, poorly educated, and then forcibly sterilized. Leilani Muir will tell of her experiences with eugenics in Alberta and appeal to scientists to oppose any recurrence of this practice.

[1]Alberta, Canada.

M. Nakajima[1,2], A. Inui[1], and L.C. Samuelson[2]. Anxiety-like behavior is modulated by long-term over-expression or transient administration of neuropeptide Y in the mouse brain.

Neuropeptide Y (NPY), one of the most abundant peptide transmitters in the mammalian brain, is assumed to play an important role in behavior and its disorders. These studies examined the effects of exogenous NPY administration as well as NPY overexpression in transgenic mice. The long-term effects of NPY overexpression were studied in transgenic mice carrying the neuron-specific promotor of the human Thy-1 gene linked to mouse NPY cDNA. These transgenic mice displayed signs of anxiety in the elevated plus-maze, which was different from the anxiolytic effects of NPY reported previously. To further investigate anxiety-like behavior in normal mice, we tested the effects of NPY peptide agonists with specificity for Y1- or Y2-type receptors using the same paradigm.

Anxiety levels were assessed 10 minutes after intracerebroventricular administration of various doses of NPY, [Leu31, Pro34]NPY (Y1 receptor specific) or NPY13-36 (Y2 receptor specific). NPY has both an anxiolytic and an anxiogenic effect at 0.7 nmol/brain and 7 pmol/brain, respectively. The anxiolytic effect was reproduced at 70 pmol/brain of [Leu31, Pro34]NPY and the anxiogenic effect at 20 pmol/brain of NPY13-36. The results indicate that NPY produces not only an anxiolytic effect via Y1-type receptors, but also an anxiogenic effect via Y2-type receptors at low doses. The anxiogenic effect of NPY could no longer be observed 30 minutes after administration. These experiments suggest the involvement of NPY in anxiety physiologically as well as pathologically.

[1]Second Dept. of Internal Medicine, Kobe University School of Medicine, Japan. [2]Dept. Physiol, Univ. Michigan, USA.

D.J. Nash[1], R.S. Ackley[2], and L. Al-Ani[1]. Genetic and environmental effects on the incidence of neural tube defects in mice.

The objectives of this study were to explore further the relationship between teratogens and genetic factors in the causation of neural tube defects and to document genetic and phenotypic parameters. A single dose of hydroxyurea (HU), retinoic acid (RA), or mitomycin-c (MM-C) was administered intraperitoneally (IP) to pregnant females on day 7, 8, or 9 of gestation at a dosage of 100, 200, 300, or 400 mg/kg (HU); 5, 10, 15, or 20 mg/kg (RA); or 0.75, 1.5, 2.5, or 3.5 mg/kg (MM-C) respectively. Mice were sacrificed at day 17 of gestation and their fetuses were examined for NTDs and other abnormalities.

Results indicated wither synergistic or curative effects of the treatments with (HU), (RA), or (MM-C) depending upon the day of the injection, drug, and the dosage. The penetrance of the tail zigzag Tz gene was decreased significantly on day 9 of gestation compared with controls groups for (HU), and (RA). No beneficial or curative effect on NTDs was obtained by (MM-C) treatments on day 8 or 9 of gestation. Fetal mortality was significantly increased in all doses tested. The highest proportions were 0.48, 0.48 for tail zigzag fetuses at dose 400 mg/kg (HU) on day 8, and random fetuses at dose 20 mg/kg (RA) on day 7 of gestation respectively.

Maternal age, mutation, drug, day of injection, dose/drug, and drug x mutation contributed significantly to the variation in neural tube defects. Heritability estimates were calculated by paternal half-sibs methods. Using all data the heritability estimates were 0.29 – 0.08, - 0.01 – 0.03, 0.22 – 0.07, - 0.10 – 0.02, and 0.04 – 0.06 for body weight, tail length, body length spina bifida and exencephaly.

[1]Colorado State University, Fort Collins, CO, USA. [2]Univ. Northern Colorado, Greeley, CO, USA.

P. Nef[1]. Additional role(s) for the odorant receptor proteins?

The detection of a myriad of odor molecules takes place on a restricted nasal surface composed of sensory neurons. What is the biological mechanism allowing the detection and discrimination of thousand different smells? Several hypotheses have been proposed since the beginning of the century. However, only recently, a model for the perception of odors is supported for the first time by experimental data. These studies illustrate not only how the nose may smell, but also suggest additional roles for the odor receptors within and outside the olfactory system. Here, I will review recent experiments on i) the putative odor receptor gene family, ii) the three models for olfaction, and iii) the potential roles for the odor receptors during development in tissues unrelated to olfaction. In conclusion, olfaction allows the study of a sensory neural coding scheme responsible for the conscious perception of chemical stimuli within the context of other environmental signals.

[1]Dept. of Biochemistry, University of Geneva, 30, quai Ernest-Ansermet, CH-1211 Geneva 4, Switzerland.

G.O. Pflugfelder[1]. Genetic lesion in *Drosophila* behavioral mutants.

Over the last 30 years, several hundred behavioral mutants were isolated in Drosophila. Only a fraction of these are well characterized genetically, behaviorally, and structurally. From six areas of behavior a set of 24 well studied mutants was chosen in which the behavioral defect is probably caused by a central dysfunction and not by an impairment of sensory input or motor output. In all cases, the affected genes can be mutated to more than just a behavioral phenotype. Most genes in the sample are essential. Phenotypic specificity thus is caused by the specificity of the mutation and not by the gene being a "behavioral gene". It is asked how partial functional inactivation in these loci is brought about genetically. In particular, I attempt to discern whether behavioral mutations affect part of a protein´s functional repertoire, a subset of protein isoforms, or the spatio-temporal expression of a gene. Not unexpectedly, in view of the predominant use of ethyl methanesulfonate (EMS) as mutagen, the majority of sampled mutations fall into the first two categories. The potentially richest source of genetic versatility, the spatio-temporal modulation of promoter activity by enhancers and silencers, has thus been insufficiently exploited for obtaining behavioral mutants. Various mutagens are reviewed as to their suitability in inducing selective regulatory mutations.

[1]Lehrstuhl für Genetik, Biozentrum, Theodor-Boveri-Institut, Univ. Würzburg, Germany

N.K. Popova[1]. Central serotonin and genetically defined strategy of defensive behavior.

Aggression as an active response to threatening stimuli and freezing (catalepsy) as passive reaction represent two principal kinds of fear-induced defensive behavior. Significant

differences in brain serotonin metabolism and serotonergic receptors was found in animals genetically predisposed to different kinds of defensive behavior. Increased activity of tryptophan hydroxylase, the key enzyme in serotonin biosynthesis, was shown in the striatum but not in the midbrain of rats selected for many generations for predisposition to catalepsy. In contrast to genetic cataleptics, the decreased tryptophan hydroxylase activity in the midbrain as well as decreased serotonin and its major metabolite 5-HIAA in some brain regions of aggressive Norway rats in comparison to rats selected for many generations for the lack of aggressive behavior towards man was found. At the same time, specific binding of [3H]8-OH DPAT in some brain regions was decreased both in rats with a manifest active fear-induced aggression, indicating the decreased density in 5-HT1A-like serotoninergic receptors.

The data suggest the involvement of 5-HT1A-like serotonergic receptors in the mechanisms of anxiety and fear inducing various kinds of defensive behavior, while the strategy of defense seems to be determined by genetically defined serotonin metabolism in some brain regions, *i.e.,* genetic predisposition to freezing is associated with increased serotonin metabolism in the striatum, while a decreased serotonin metabolism in the midbrain makes animals highly aggressive.

[1]Inst Cytol and Genet, Siberian Branch Russian Acad Sci, Novosibirsk, Russia.

A. Python[1], Th. Steimer[2], P. Driscoll[3], and Z. de Saint Hilaire[1,4]. Roman High-(RHA/Verh) and Low-(RLA/Verh) Avoidance rats differ in 24 hr-EEG sleep patterns: A model for human sleep disorders associated with anxiety and/or depression?[5]

The role of genetic factors in determining psychological traits, social and non-social behaviors, physiological and behavioral adaptation to the environment, and their relationship to sleep disorders is still unclear. Psychogenetically-selected Roman High- (RHA/Verh) and Low- (RLA/Verh) Avoidance rats differ in the way they respond to environmental stimuli and in several neuroendocrine and neurochemical parameters. Because of their high emotional reactivity and relatively passive coping style, RLA/Verh rats are more anxious and more susceptible to stress. Thus, behavioral and physiological changes resembling human depressive symptoms can be more easily induced in RLA/Verh rats by repeated exposure to moderate stressors. As a preliminary step towards a more detailed analysis of the impact of stress on sleep patterns, EEG-sleep recordings were obtained from adult males over 24 hours under stress-free conditions, in order to determine how the particular behavioral and/or neuroendocrine/ neurochemical characteristics of each line could influence the sleep-wake cycle. During the light phase, total sleep time was increased in the hyperemotional RLA/Verh rats as compared to the hypoemotional RHA/Verh rats, due to a shorter sleep latency and longer slow wave sleep (SWS) duration. During the dark phase, RLA/Verh rats showed less paradoxical sleep (PS), fewer sleep cycles and PS episodes, with a longer PS latency, whereas RHA/Verh rats showed a more discontinuous sleep/activity pattern. The results of the present study indicate that there are marked differences in the sleep-wake patterns and sleep stages of psychogenetically selected RHA/Verh and RLA/Verh rats. These may be due to genetically-determined differences in neurotransmitter system activity and/or reactivity or, alternatively, to the way rats from each line react to, and cope with environmental stimuli, including day length. These two lines may therefore provide an interesting animal model for further investigations on the biological and behavioral correlates of sleep disorders associated with anxiety and depression. Moreover, because of the neurochemical differences known to exist between RHA/Verh and RLA/Verh rats, these two genetically-selected lines may prove useful for further investigations into the neurobiological mechanisms underlying sleep regulation.

[1]Division of Neuropsychiatry and [2]Clinical Psychopharmacology Unit, University Institute of Psychiatry, HUG, CH-1225 Chêne-Bourg, Switzerland. [3]Institut für Nutztierwissenschaften, Physiologie und Tierhaltung, ETHZ, CH-8092 Zurich, Switzerland. [4]Neurobiologie des Régulations, Collège de France, Paris, France. [5]Work supported in part by grant No 31.36485.92 from the FNSRS.

L. Ricceri[1], A. Usiello[1], G. Calamandrei[1], and J. Berger-Sweeney[2]. Methodological caveats for the study of ontogeny of learning in genetically altered mice.

There has been a growing interest in methods for assessing learning and retention capabilities in mice, primarily because genetically altered mice have made it possible to investigate the molecular basis of learning and memory.

Most of the studies with transgenic mice, however, have investigated hippocampal-related cognitive functions in adulthood, using a very limited number of behavioral tests. Recently, we assessed short- and long-term effects of

neonatal immunolesions of different cholinergic nuclei in the CNS. Our findings, based on comparisons of the effects of the same treatment in neonatal and adult rodents, suggest strongly that:
i) It is useful to examine the behavioral repertoire of the animal throughout its life-span; behavioral effects can change over the animal's life.
ii) The task chosen should not only be appropriate for mice but also be designed to discriminate associative versus non-associative factors.
iii) A modified version of an open field test, with different patterns of objects to explore, is an effective way to examine spatial behavior and may be more sensitive than a water maze task to subtle alterations in spatial performances.

[1]Section of Comparative Psychology, Lab. FOS, Istituto Superiore di Sanità, Rome, Italy. [2]Dept Biological Sciences, Wellesley College, Wellesley, MA, USA.

L. Rondi-Reig[1], Y. Lemaigre-Dubreuil[1], D. Müller[2], A. Lohof[1], J.C. Martinou[3], N. Delhaye-Bouchaud[1], J. Caston[4], and J. Mariani[1]. Cognitive impairment in Hu-bcl-2 transgenic mice with surnumerary CNS neurons.

During central nervous system (CNS) development, many neuronal cell types undergo a period of naturally occurring cell death. Overexpression of the Hu-bcl-2 under the control of the neuron specific enolase promotor in transgenic mice decreases the extent of naturally neuronal occurring cell death with subsequent increase in many neuronal populations. For instance, in the NSE73a mouse line with embryonic overexpression of Hu-bcl-2, the average number of cerebellar Purkinje cells is increased by 43% when compared to controls (Zanjani et al, 1996), and the mean number of granule cells and olivary neurons are increased by 28% and 29% respectively (Zanjani et al., 1997). Our aim was to study the capabilities for learning and memory in these mice, in order to assess the consequences of surnumerary neurons on such cognitive processes. For this purpose we used two experimental protocols, the rotarod test for motor learning, and the Morris water maze for spatial learning. Our results show that Hu-bcl-2 transgenic mice are not ataxic but exhibit motor-synchronization learning impairment. Spatial learning is also impaired in Hu-bcl-2 as they show a delay in the acquisition of the task. Electrophysiological studies show that long-term potentiation of the hippocampus is reduced by 35 % in these transgenic mice. These results demonstrate that surnumerary neurons provoke cognitive deficits.

[1]CNRS URA 1488, 75005 Paris, France. [2]1228 Geneva, Switzerland. [3]Institut Glaxo, 1228 Geneva, Switzerland. [4]Neurobiologie de l'apprentissage, 76821 Rouen, France.

D. Santucci[1], E. Alleva[1], E. Carlson[2], A. Micera[3], and L. Aloe[3]. Substance P levels in the CNS and peripheral tissue of SOD-1 transgenic mice.

Motor neuron diseases include a number of different sporadic and inherited disorders involving degeneration or death of motor neurons in the spinal cord and in the brain. In recent years a possible therapeutical approach for motor neuron diseases has emerged from studies on neurotrophin actions. Neurotrophins are polypeptides known to play a role in promoting and maintaining survival of motor neurons. It is conceivable to hypothesize that, during motor neuron disorder, peripheral sensory nerves are also affected. However, very few studies has taken into consideration the possible contribution of these polypeptides in maintaining sensory functions during motor neuron diseases and/or reducing peripheral sensory deficit. Nerve Growth Factor is a neurotrophin which is known to play a role in regulating neuropeptide synthesis and release, and in particular that of Substance P (SP), in sensory neurons and primary afferent nerves. In the present study, we used SOD-1 transgenic mice, a relevant model of motor neuron disease, to evaluate the level of SP in peripheral tissue such as the forepaws and the bladder, and in the central nervous system (cortex, hypothalamus and spinal cord). We also investigated the profile of spontaneous activity of these mice. Our results showed no changes in SP concentration in the central nervous system whereas SOD-1 mice had higher SP levels in the bladder when compared to controls. Moreover, a modification in locomotor activity was observed in two-months SOD-1 mice. Our biochemical and behavioral data will be discussed in the context of current knowledge about SOD expression and basal neuropeptide levels.

[1]Lab. di Fisiopatologia di O.S., Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Roma, Italy. [2]Dept. Pediatrics, Univ. California, 505 Parnassus Ave., San Francisco, CA 94143, USA. [3]Istituto di Neurobiologia, Consiglio Nazionale delle Ricerche, Viale Carlo Marx 15, 00185 Roma, Italy.

D. Santucci[1], J. Kilbridge[2], D.M.Holtzman[2], E. Alleva[1], W.C. Mobley[2], and C. Epstein[3]. **Characterization of the behavior and CNS in partially trisomy 16 mice.**

Partially trisomic mice (Ts 1716) may provide a new and reliable model for mental retardation in children, since they genetically and phenotypically resemble the trisomy for chromosome 21 in humans, have good viability at birth, and show a moderate impairment in memory and learning performances.

The neurobehavioral profile of pTs16 animal was characterized by several tests both during the early development and at the adulthood. A delay in the appearance of several sensorimotor reflexes, an impairment in performing the homing test, and changes in locomotor activity were evident throughout the first week of life. Moreover, the ultrasonic vocalization pattern recorded on pnd 3, 5, 7, 9, 11, and 13 confirm a delay in the developmental profile. At adulthood, pTs16 mice showed an alteration in locomotor activity and were slightly impaired in both the Morris maze test and in the acquisition of the passive avoidance task. TrkA-immunoreactive neurons of the basal forebrain from adult pTs16 appear to be fewer in number and smaller in size when compared to that of control littermates.

[1]Behavioural Pathophysiology Section, Lab. Fisiopatologia di Organo e di Sistema, Istituto Superiore di Sanita ,Viale Regina Elena, 299, I-00161 Roma, Italy. [2]Dept. Neurol, and [3]Pediatrics, Univ. California, San Francisco, USA.

T. Sarafi[1], S. Daniels[1], Y. Qian[1], and P. Sengupta[1]. **Development and function of the chemosensory system in *C. elegans.***

The nematode *C. elegans* responds to many chemicals using a few defined chemosensory neurons. Using behavioral screens we and others have previously identified several genes required for the sensory functions of these neurons. These include *odr-10* (olfactory receptor), *odr-3* (G protein subunit), *osm-9* (putative calcium channel) and *tax-2* (subunit of a cyclic nucleotide gated channel). Analysis of the data from the genome sequencing project has also led to the identification of several large families of putative chemosensory receptors.

Unlike vertebrates, each chemosensory neuron in *C. elegans* expresses multiple receptors. Different neurons also appear to use different second messenger systems for transducing the sensory signals. Therefore, diversity of function arises from both the expression of particular subsets of receptors as well as appropriate signal transduction genes in different neurons. We are exploring the mechanisms that generate this functional diversity. We have shown that the nuclear receptor gene *odr-7* specifies the functions of an olfactory neuron type by regulating the expression of cell-type specific signaling genes. We have recently shown that several *odr-7*-related genes are expressed in restricted subsets of olfactory neurons and thus may also play roles in the specification of their sensory functions. In additional genetic screens, we have identified mutants where the expression of cell-type specific olfactory genes is altered. These screens have also led to the identification of mutants with altered axonal and dendritic morphologies as well as mutants with cell migration defects. Mutants with altered olfactory behavior but normal cellular morphology have also been identified and these genes may define additional signaling components. We expect that the molecular identification of these genes will allow us to understand the mechanisms that result in the appropriate development and function of the different chemosensory neurons in *C. elegans*.

[1]Dept. Biol., Brandeis University, Waltham, MA 02254, USA.

O.B. Simonova[1], S.F. Petruk[1], I.V. Jagaeva[1], and L.I. Korochkin[1]. **Analysis of a new trans-regulatory locus in *Drosophila*.**

A novel regulatory sex-linked semilethal mutation of *Drosophila melanogaster* has been obtained in a system of genome instability, induced by transpositions of two mobile elements: *mdg Stalker* and P- element. Phenotypically it appears to be the set of distortions of many parts of the *Drosophila* body including a slice homeotic arista transformation into tarsus. New gene was named *leg-arista-wing-complex (lawc).*

Ten week *lawc*-alleles were obtained using P-M hybrid disgenesis. One of them *(lawcp1)* was found to be temperature-sensitive. From the genetic analysis of the interaction of *lawcp1* and different *achaete (ac)* and *scute (sc)* mutations (the alleles of two proneural genes which control the bristle pattern formation) it was concluded that the *lawcp1* bristle-phenotype is mediated by the *ac-sc* expression depending on temperature.

The *ctn* mutation of the proneural homeobox containing the *cut* locus, strongly enhances the *lawcp1* wing phenotype. This interaction is fully suppressed by *H1* - the mutation of the *Hairless* gene which suppresses the cut-wing phenotype of mutations in the other neurogenic locus *Notch*.

It was shown that EMS-induced embryonic lethal l(1)EF520 not complement *lawcp1*.

Cuticle preparations of l(1)EF520 and *lawcp1* embryos will be presented.

The *lawcp1* mutation has been cloned and a *lawc* gene fragment was isolated. *lawcpdel* flies display an unusual morphological phenotype of the thorax. In addition, they have poor survival and three times longer embryonic stage of development. DNA blotting analysis revealed a 950 bp deletion of the gene region. Apparently, this deletion is the cause of the drastic *lawcpdel* phenotype.

lawc cDNA was isolated. Northern blot analysis revealed 9 kb mRNA in all stages of development but mostly at the embryonic stage.

[1]Institute of Gene Biology, Russian Academy of Sciences, 117334 Vavilov st. 34/5 Moscow, Russia.

C.L. Smith[1], N. Broude[1], S. Mapel[1], Y. Shevchenko[1], M. Lewis[1], and J. Graber[1]. Targeted genomic and conventional differential display: Analyzing monozygotic twins discordant for schizophrenia.

Conventional differential display (DD) is difficult and a widespread lack of success has led some to call it "differential dismay". We have developed a genomic differential display (GDD) and an targeted differential display (TDD) methods which allows differences between samples to be identified. Our methods use interspersed repeat sequences to target particular classes of genes and DNA sequences. In GDD, genomic restriction fragments containing the target sequence are isolated, PCR amplified, and displayed by size on an automatic DNA sequencing device. In enhanced TDD, cDNA containing the target sequence are displayed. Restriction fragment length polymorphisms may be due to insertions, deletions and rearrangments are detected as well as some single base pair differences. Using GDD we have identify differences between monozygotic discordant for Schizophrenia. Monozygotic twins were choosen to minimize irrelevent differences between samples. One goal of our work is to improve our analytical computational methods so that we will be able to apply this approach to analyze pools of affected vs non-affected individuals. This method is an alternative to positional cloning and is applicable potentially to a large number of neurodegenerative diseases.

[1]Center for Advanced Biotechnology and Depts Biomedical Engineering, Biology, and Pharmacology, Boston University, Boston, Mass 02215, USA.

I.A. Spitsyna[1] and T.I. Duka[1]. NCAM and GFAP distribution in brains of stressed rats with different alcohol tolerance.

An attempt was made to find out some details of the relationships between anxiety and alcohol disorders and the contents of neural adhesion molecule (NCAM) and glial fibrillar acidic protein (GFAP) as determined by ELISA in brains of stressed rats with different alcohol tolerance. Rat groups predisposed and non-predisposed to alcohol consumption were divided using an ethanol narcosis duration test. A model of chronic emotional maladaptation based on probable confirmation of audio and luminous stimuli by electric irritation was chosen for stress procedures. Distinct endocrine and neurochemical differences were initially found between the two groups. Strong increase of relative adrenal weight (1.5 times) and of the NCAM content (1.5-3 times) in cerebellum, striatum, and hippocampus with a simultaneous decrease in cerebral cortex were found in predisposed rats under chronic emotional maladaptation. Moreover, GFAP content was up-regulated in hippocampus and down-regulated in cerebral cortex. In the case of non-predisposed rats we have found only decreased levels of GFAP in hippocampus (in contrast to predisposed rats) and cerebral cortex. So, more obvious stress alterations were observed in the group of rats predisposed to alcohol consumption. We believe that strong expressed NCAM change in this group may be connected with developing anxiety.

[1]Dept. Biophysics and Biochemistry, State University, 72 Gagarin Ave., Dniepropetrovsk, 320625 Ukraine.

Th. Steimer[1], P. Driscoll[2], and P.E. Schulz[1]. The Roman High-(RHA/Verh) and Low-(RLA/Verh) Avoidance rat lines/strains as a potential model for studying the etiology and pathophysiology of human anxiety and mood disorders.[3]

Roman high-(RHA/Verh) and low-(RLA/Verh) avoidance rats are selected and bred for rapid vs. poor acquisition of two-way, active avoidance. Divergent genetic selection has produced two lines/strains which differ in emotional reactivity and coping style. Thus, when exposed to unfamiliar environments, RLA/Verh rats are more emotionally reactive and less active copers than their RHA/Verh counterparts, showing signs of increased anxiety. These behavioral differences are associated with particular neuroendocrine and neurochemical characteristics, including enhanced hypothalamo-pituitary-adrenocortical (HPA) axis activation and increased prolactin secretion in the more emotional RLA/Verh rats

following exposure to moderate stressors, as well as several differences in neurotransmitters systems. These divergent psychobiological characteristics can be used to investigate the role of emotional reactivity and coping style in behavioral and physiological adaptation to environmental and psychosocial challenges, as well as the underlying neuroendocrine/ neurochemical mechanisms. Emotional reactivity and coping style, as constitutive personality "traits", certainly play an important role in the etiology of human anxiety and mood disorders. It has been shown that the basic behavioral and neuroendocrine reactivity traits which characterize each of the Roman lines are genetically determined, but that their phenotypic expression is also influenced by environmental factors, e.g. postnatal handling. These psychogenetically-selected lines/ strains therefore provide a valuable model to study the respective roles of genetic and epigenetic factors in determining individual psychobiological profiles (e.g. neuroendocrine and behavioral reactivity vs. coping style), in connection with stress and adaptation. Moreover, recent experiments carried out in our laboratory indicate that sensitization may occur more easily in RLA/Verh rats after repeated exposure to moderate stressors. This differential sensitivity to the effects of prior stress could also provide a useful model to investigate the "sensitization" theory of affective disorders (Post, 1992). In summary, these psychogenetically-selected rats seem to offer a unique opportunity to investigate complex interactions between genes and the environment with respect to the development of particular biopsychological profiles which may predispose each individual's response to "the stress of life". They may contribute to a better understanding of the biobehavioral mechanisms involved in the occurrence of maladaptive syndromes such as human anxiety and affective disorders.

[1]Clinical Psychopharmacology Unit, HUG, University Dept. Psychiatry, Geneva, Switzerland. [2]Institut Nutztierwissenschaften, Physiologie und Tierhaltung, ETHZ, Zürich, Switzerland. [3]Work supported by grant No 31.36485.92 from the Fonds National Suisse de la Recherche Scientifique.

S.T. Sweeney[1], R. Auburn[1], P. Deak[2], D.M. Glover[2], and C.J. O'Kane[1]. Screening for embryonic paralytic mutants.

Muscle movements of late *Drosophila* embryos include coordinated contractions of body wall muscles, gut muscle contraction, and heartbeat. We have previously shown that inhibition of synapse function abolishes coordinated body wall movements (1), although more general defects in neuromuscular development or function will also cause this phenotype. To identify further mutants with synaptic defects, we are screening embryonic lethal P element insertions for mutants with impaired body wall motility. Out of 500 lines screened, about 80 show severely impaired body wall motility. In most cases, heart and gut movements are not seriously affected, demonstrating that the phenotypes observed are not usually due to general cellular debilitation.

To identify some of the genes affected, we have sequenced DNA flanking 25 of the insertions. About 12 have an insertion in a known gene. In vindication of the rationale of the screen, most of these are genes with known or likely roles in neuronal development or function *(pros, ming, svp, cpo),* muscle development or function *(who, Tropomyosin II, Paramyosin),* neuromuscular connectivity *(Tl)* or genes affecting the number and properties of differentiated cells *(stg, cycA).* Two of the mutants have an insertion in an identified gene, not previously associated with the phenotype we are screening for. These are an insertion in a protein phosphatase subunit gene, and in a gene encoding a small heat shock protein. Neither of these mutants has a severe anatomical defect. The remaining insertions have not yet been identified as lying in any identified gene.

[1]Dept. of Genetics, Univ. Cambridge, Downing Street, Cambridge, CB2 3EH, UK. [2]Dept. of Anatomy and Physiology, Univ. Dundee, UK.

F. Tronche[1], C. Kellendonk[1], Th. Mantamadiotis[1], K. Anlag[1], and G. Schütz[1]. Analysis of glucocorticoids signaling by conditional mutations of the murine glucocorticoid receptor and CREB genes.

Glucocorticoids are involved in the regulation of numerous physiological processes. Most of the effects are thought to be mediated by the glucocorticoid receptor (GR) via activation and repression of gene expression. To analyze the molecular mechanisms that underlie glucocorticoid effects, mutations in the GR gene were generated in the mouse and analyzed. Mice with a disrupted glucocorticoid receptor gene die shortly after birth due to respiratory failure indicating an important role of the glucocorticoid receptor in lung function. Transcription of genes encoding gluconeogenic enzymes in liver is decreased. Proliferation of erythroid progenitors and ontogenesis of the adrenals are impaired. However, since all mice with a mutated GR die shortly after birth, the function of the receptor

in physiological processes could not be assessed in living animals.

Using the *Cre-loxP* system we have generated a conditional mutant of the murine glucocorticoid receptor gene. The third exon of the *GR* gene was flanked by two *loxP* DNA sites. By crossing *GR-loxP* mice with mice expressing the *Cre* recombinase in T-lymphocytes or in the nervous system we obtained mutant mice lacking the *GR* gene in the corresponding cells. We also developed a strategy controlling *Cre* recombinase activity in order to obtain inducible mutations in mice. This was achieved by fusing the recombinase to the hormone binding domain of a mutated progesterone receptor that responds to RU486 but not to the progesterone. By expressing this fusion protein under the control of the CamKIIa promoter, we obtained inducible recombination in mice hippocampus.

[1]Molecular Biology of the Cell I (0115), DKFZ, INF 280, 69121 Heidelberg, Germany.

L.C. Webster[1], S. Nada[1], and S.G.N. Grant[1]. Analysis of synaptic plasticity using gene targeting: Interactions between tyrosine kinases and an NMDA receptor multiprotein complex.

The NMDA receptor detects patterns of synaptic activity and signals long-lasting synaptic potentiation or depression that is instructive during brain development and in the adult where it contributes to learning and memory. We have characterized a multiprotein complex associated with the NMDA receptor which changes in composition and phosphorylation during the developmental period of synaptic plasticity, is regulated by mutations in genes required for long-term potentiation and learning, and is dephosphorylated by NMDA receptor activation. We propose that this complex represents the core machinery for initiating NMDA receptor signaling and that ion-channel associated proteins play a physiological role in establishing the threshold for forms of synaptic plasticity.

[1]Center for Genome Research and Center for Neuroscience, Univ. Edinburgh, West Mains Road, Edinburgh, EH9-3JQ, UK.