Genes and mechanisms underlying ethanol induced behaviours

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Introduction:
Alcohol is one of the most widely abused drugs in the world. One behaviour found in most of the alcoholics is tolerance. Repeated alcohol consumption causes tolerance which is defined as an increase of resistance to the intoxicating effects of ethanol. However the molecular link between tolerance and alcoholism is not known yet. Therefore we isolate genes and mechanism involved in ethanol tolerance. In long term this research might help to bridge the gap between tolerance and alcoholism. We use the genetic model organism *Drosophila melanogaster* to study ethanol tolerance.

Drosophila is a suitable model system to study ethanol tolerance, because on one hand flies behave under the influence of ethanol similar to humans (Moore et al. 1998, Singh and Heberlein 2000, Scholz et al., 2000). On the other hand genes and molecules are conserved (Heberlein, 2000). In addition the accessibility to genetic analysis, makes *Drosophila melanogaster* an attractive model system to identify genes and mechanisms underlying ethanol induced behaviour.

Project 1:
The mutant AE12 has been isolated in a screen for altered ethanol induced behaviour. The AE12 mutant displays a highly reproducible reduced tolerance phenotype. The mutant carries a transposable element insertion in the *female sterile (1) homeotic* (fs(1)h) gene. The gene encodes a MAP-Kinase-Kinase-Kinase involved in MAPK pathway. This pathway has been shown in cell culture to be altered by ethanol. However the function of the gene has not been investigated during the development of tolerance in animals. Therefore the candidate will use molecular genetic and genetic tools to isolate and characterize the gene altered in AE12 mutants. In addition the candidate will perform anatomical studies to identify the brain region involved in mediating ethanol tolerance and will analyze the behavioural consequences of altered gene function. These different approaches will help to understand the function of the *fs(1)h* gene during the development of ethanol tolerance.

Project 2: Dissection Serotonin function during ethanol induced behaviour
Serotonin (5HT) has an essential role in the development of ethanol tolerance and alcohol dependence. However, it remains elusive how 5HT exerts its function in theses processes. We have shown that increased serotonin signaling impairs the development of ethanol tolerance. The serotonin transporter (SERT) is a key regulator for serotonin signaling. The *Drosophila* SERT (dSERT) is exclusively expressed in all serotonergic neurons throughout the adult brain. By immunolabeling we detected differences in the localization of dSERT and 5HT in adult serotonergic neurons. In addition alterations of SERT function with pharmacological and genetic tools result in reduced ethanol tolerance. However, neither general increase nor decease of 5HT levels affects ethanol tolerance. Our data identify a role for serotonin in the modulation of ethanol tolerance in *Drosophila melanogaster* and suggest that proper

regulation of serotonin signaling during the development of ethanol tolerance is conserved between insects and higher vertebrates. We now want to identify serotonergic neurons that mediate ethanol induced behavior. These questions should be solved by using with neuroanatomical approaches, molecular genetic and behaviour.

Relevant publications:

1. Giang, T, Ritze, Y., Gutierrez, M.O., Rauchfuss, S. and Scholz, H. Serotonin modulates ethanol induced behaviors in *Drosophila* (submitted to *Developmental Neurobiology*).

2. Scholz, H., Franz, M. and Heberlein, U. (2005): The *hangover* gene defines a stress pathway required for ethanol tolerance. *Nature* 436: 845-847.

3. Scholz, H. (2005): Influence of the biogenic amine tyramine on ethanol induced behaviors in *Drosophila*. *J Neurobiol.* 63(3):199-214.

4. Schwaerzel, M., Monastirioti, M., Scholz, H., Friggi-Grelin, F., Birman,S. and Heisenberg, M. (2003): Dopamine and octopamine differentiate between aversive and appetitive olfactory memories in *Drosophila. Journal of Neuroscience* 23(33):10495-10502.

5 .Scholz, H, Ramond, J., Singh, C. M., and Heberlein, U. (2000) Functional ethanol tolerance in Drosophila. *Neuron* 28: 261-271