Alcoholism: the molecular basis of addiction and deprivation

Scientists at the Central Institute of Mental Health in Mannheim use rats and mice to study the genetic basis and neurobiological mechanisms of alcohol addiction, the changes that occur during alcohol deprivation and the factors that favour a relapse. In translational research, the results from animal experiments are reviewed using alcohol-dependent patients in order to turn them quickly into preventive strategies and therapies.

Figure Alcohol consumption per capita in litres of pure ethanol.

Per capita alcohol consumption worldwide.

In Germany and many other parts of the world, alcoholism can be regarded as one of the most prevalent neuropsychiatric diseases afflicting our society. Two and a half million deaths per year are due to the harmful effects of alcohol. Almost four percent of all deaths worldwide are attributed to alcohol, greater than the deaths caused by HIV/AIDS, tuberculosis or violence (Global status report on alcohol and health, World Health Organization, 2011). Prof. Dr. Rainer Spanagel from the Central Institute of Mental Health (ZI) in Mannheim defines alcoholism as a pathological behavioural syndrome that is characterised by a compulsive desire (i.e. craving) for alcohol and by repeated

relapses that can occur even after many years of alcohol abstinence - despite the obviously devastating or even fatal consequences for the individual affected.

Prof. Dr. Rainer Spanagel
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There is no doubt that the social environment plays a crucial role in whether or not someone becomes addicted to alcohol. The major influence of genetic factors is supported by epidemiological studies on twins and adopted children. Children whose biological parents are alcohol addicts but who grow up in foster families without alcohol abuse have a three to four times higher risk of becoming addicted to alcohol than other adopted children.

The hereditary component is obviously based on different effects and complex interactions of different genes; there is no single "alcohol addiction gene". Funded by the German National Genome Research Network (NGFN and NGFNplus), the cooperative project "Genetics of Alcohol Addiction" brings together basic researchers, clinicians, geneticists and other researchers who use animal experiments, genome-wide association studies and neurological examinations of humans to better understand the genetics and environmental factors that can lead to alcohol addiction. One goal of this interdisciplinary approach is to find new ways for the prevention and improved medicinal therapy of alcoholism. Prof. Spanagel is the spokesperson of the research consortium.

Reaching for the bottle after a stressful day?

Rats or mice can easily be made dependent on alcohol and are therefore popular models for studying alcohol use and dependence as well as deprivation and relapse. Spanagal and his colleagues have shown that stress - conditioned stimuli as well as small alcohol samples - led to relapses in alcohol-dependent mice following a period of alcohol deprivation. The researchers used the bottle choice method to show an increase in alcohol intake when alcohol is again made available: after a period of successful alcohol deprivation, rats that were allowed an unrestricted choice between bottles of pure water and of alcohol solutions of differing strengths would always choose the water bottle. However, under stress (harmless but unpleasant electric shocks), the rats would always choose the strongest alcohol solution. The injection of a tiny amount of alcohol into the blood (an amount similar to a liquor chocolate, which would be enough to make a dry alcoholic reach for the bottle again), or a light or sound signal that was previously associated with the provision of alcohol, makes abstinent animals "reach for the bottle again".

The researchers from Mannheim used transgenic mice with a defective CRHR1 gene for studying the causes of stress and alcohol dependence. The CRHR1 gene codes for the corticotropin-releasing hormone (CRH) receptor 1. CRH is secreted by the hypothalamus and activates a signalling chain that is involved in the synthesis and secretion of glucocorticoids (e.g. cortisol). Under normal conditions, CRHR1 mutants as well as healthy control animals consumed alcohol every now and then, and chose water rather than alcohol when they had the choice. However, under stress, the CRHR1 mutants had a three times higher alcohol consumption than the healthy mice. The control

Laboratory mouse and alcohol.
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animals showed no change in their drinking behaviour.

Investigations carried out with alcoholic-dependent people by Prof. Dr. Gunter Schumann (now at the King's College, London, UK) and his team at the ZI suggest that the CRHR1 gene also influences human drinking behaviour. Two CRHR1 gene variants are common in the human population. Although people with one of the two variants did not drink more than other people on average, they drank considerably more when they did drink.

In their recent publication, Spanagel and his team reviewed the current state of knowledge on stress-induced alcohol abuse: glucocorticoids in the nucleus accumbens (which plays a key role in the brain's reward system, the so-called mesolimbic system) have been shown to be important messengers for the craving for alcohol under stress. The enhanced activation of CRH in the amygdala (which is also part of the mesolimbic system) seems to be responsible for stress-induced alcohol relapse.

Alcohol problems and day-night cycle

It has long been known that the activity of the corticoid hormone system underlies a circadian rhythm. The PER2 ("period circadian clock 2") gene is one of the clock genes that govern the day-night rhythm. Focussing on the involvement of PER2 in the modulation of alcohol-induced behaviour, Spanagel and his team have established a link between PER2 and the circadian rhythm of mice. They showed that a defective PER2 gene affects the sleep-wake rhythm in mice. PER2 mutant mice that had the choice between water and alcohol consumed a lot more alcohol than healthy control animals. The link between PER2 and excessive alcohol consumption in mice has also been shown to exist in humans. "We know that young people with specific PER2 mutations drink more alcohol than their healthy peers," says Spanagel. "In addition, shift workers, airline staff and other people with disordered circadian rhythms have been shown to suffer more frequently from alcohol problems than other people (RP Online, 18th May 2005).

The researchers found high glutamate concentrations in the brain of PER2 mutant mice. Glutamate is a neurotransmitter that increases a person's excitability. Excited mice consumed more alcohol than normal. The researchers were able to control the elevated glutamate level as well as the increased alcohol consumption of the mutant mice with acamprosate and found that it effectively reduced alcohol consumption in PER2 mutant mice. Acamprosate, the calcium salt of N-acetyl homotaurinate, is used in clinics as an anti-craving drug for treating alcohol dependence and for relapse prevention. Unfortunately, the drug only reduces the relapse rate by around 14%.

Spanagel and his colleagues performed studies on rats with the aim of improving the efficiency of the

drug, and they made a sensational discovery: they found that acamprosate did not interact with glutamate receptors and does not seem to be an active psychotropic drug either. Instead, they found that the observed effects were exclusively due to calcium and were also able to show that the drug can be replaced with other calcium compounds and achieve the same effect. They believe that the anti-craving effects in humans are most likely due to the elevated calcium concentrations in the blood of people undergoing acamprosate treatment and conclude that "N-acetyl homotaurinate is a biologically inactive molecule and that the effects of acamprosate described in more than 450 published original investigations and clinical trials and 1.5 million treated patients can possibly be attributed to calcium".

Prof. Dr. Alexander Sartorius, Translational Imaging, Central Institute of Mental Health

Researchers in the Translational Imaging group led by Prof. Dr. Alexander Sartorius at the ZI studied the effect of glutamate and its metabolic products, including glutamine and γ-aminobutyric acid, in live mice. The researchers used a high-field animal MRI scanner adapted to the tiny brain volumes of mice. The found elevated glutamate levels in alcohol-dependent mice immediately after the mice had been deprived of alcohol. Elevated glutamate levels have been linked with the nervousness and hyperexcitability of patients during the acute alcohol deprivation phase. The glutamate levels returned to normal within three weeks of alcohol deprivation. It has also been shown that alcohol-dependent patients had elevated glutamate levels during the period of acute alcohol deprivation. The glutamate levels coincided with the severity of the alcohol deprivation symptoms: the higher the glutamate levels, the worse the patients' symptoms.

The studies impressively demonstrate the effectiveness of the translational approach pursued by the NGFN project "Genetics of Alcohol Addiction" which is attempting to close the gap between preclinical and clinical research. Spanagel highlighted that the establishment of a research group focused on translational addiction research at the Institute of Psychopharmacology and the close cooperation with the Hospital for Dependent Behaviour and Addiction Medicine at ZI has enabled the rapid validation of the animal experiment findings in humans and the rapid implementation of research achievements into clinical application.

Publications:

Spanagel R, Vengeliene V, Jandeleit B, Fischer W-N, Grindstaff K, Zhang X, Gallop MA, Krstew EV, Lawrence AJ, Kiefer F: Acamprosate produces its anti-relapse effects via calcium. Neuropsychopharmacology (2014) 39, 783-791.

Spanagel R, Noori HR, Heilig M: Stress and alcohol interactions: animal studies and clinical significance. Trends Neurosci. 2014 Apr; 37(4):219-227.
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Article

19-May-2014
EJ
BioRN

The article is part of the following dossiers

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