Alcoholism research

Drunk as a Rat

WOJCIECH KOSTOWSKI
Scientific Committee of Physiological Sciences
Polish Academy of Sciences;
Institute of Psychiatry and Neurology, Warszawa;
Medical University, Warszawa
kostowsk@ipin.edu.pl

Laboratory animals selectively bred for their preference to alcohol can make a substantial contribution to our understanding of human alcoholism

Vulnerability to alcohol abuse and addiction is conditioned by numerous environmental and genetic factors. The role of genetic predisposition toward excessive alcohol consumption in humans has been widely recognized by researchers. Correlational studies on human populations have been published on the familial and environmental factors influencing alcoholism. Concurrently, experimental studies using laboratory animal models of genetic influences on alcohol preference have also been performed during recent decades. Until the last decades of the 20th century, doubt remained as to whether investigating alcohol consumatory behavior in laboratory animals would make a substantial contribution to our understanding of the human condition of alcoholism. The cause for this skepticism lay in the fact that voluntary consumption of alcohol solutions by animals rarely results in biologically active blood alcohol concentrations, unless special procedures such as weight reduction and conditioning procedures are undertaken. However, laboratory rodents have long been known to exhibit a wide range of alcohol-drinking preferences. Thus, selective breeding of

Wojciech Kostowski

Laboratory rodents exhibits a wide range of alcohol-drinking preferences

laboratory animals, particularly rodents such as rats and mice, for their preference to voluntary alcohol drinking has been recognized as a useful tool for studying the neurobiological basis of alcoholism.

Voluntary drinking

To date, several separate sets of alcohol-preferring and alcohol-nonpreferring lines of rats have been developed. Two sets include the Indiana University (USA) lines: the alcohol preferring/nonpreferring (P/NP) lines and high/low alcohol drinking (HAD/LAD) lines. Three other sets include the alcohol/nonalcohol (AA/ANA) Finland lines, the University of Chile A and B lines and the Sardinian alcohol-preferring/nonpreferring (sP/sNP) lines.

The selection criteria differ somewhat among the various lines. Generally, alcohol preference or avoidance is defined in terms of voluntary alcohol consumption in grams of absolute ethyl alcohol (ethanol)/kg body mass per day, consumed by animals having continuous access to alcohol solutions in the presence of food and water *ad libitum*. Other important criteria include the development of physical dependence (as evidenced by withdrawal symptoms) and attainment of physiologically active blood alcohol concentrations with chronic free-choice drinking.

In our laboratory at the Institute of Psychiatry and Neurology, Warsaw High-Preferring (WHP) and Warsaw Low-Preferring (WLP) rats have been selected from Wistar rats under a breeding program started in 1992. After the first selection procedure, the highest scoring males and females and the lowest scoring males and females were used to initiate upward and downward selection of WHP and WLP lines, respectively. After years of selection a very wide divergence between the lines has been achieved: the alcohol consumption we recently reported for WHP male rats was approximately 8-9 g/kg per day, whereas WLP males drank less than 0.5 g/kg per day. The WHP rats attain pharmacologically active concentrations of blood alcohol and develop visible signs of physical dependence with voluntary oral alcohol intake while in the withdrawal state (such as muscle tremor and spasticity, piloerection, diarrhoea and exophtalmus).

Addicted to alcohol and sweets

The WHP and WLP lines developed in our laboratory have also been demonstrated to differ in a number of other traits. Thus, the WHP rats show a higher preference for, and greater consumption of, solutions of flavored substances such as sucrose solutions. This finding is in line with observations that avidity for sweet solutions is positively associated with high alcohol consumption in other rodent lines and in certain populations of human alcoholics.

We have also showed that there are differences between WHP and WLP lines, with respect to the amounts of brain neurotransmitters (brain chemicals necessary for neural signal transfer). Thus, the WHP line has lower concentrations of brain 5-hydroxytryptamine (serotonin, 5-HT) and dopamine (DA) in some brain areas. This result is generally in line with those reported by others. For example, an abnormality in brain 5-HT and DA systems has been found in the P and HAD lines of rats in association with high alcohol preference.

Wojciech Kostowski

A rat in his home cage during alcohol preference testing. The animal has two fluid sources to choose: water and a 10% ethanol solution

Lines of selectively bred rats with high and low alcohol preference serve as adequate models of alcohol addiction and valuable tools in basic research on alcoholism. Work with our WHP and WLP lines has provided important insight into behavioral and neurochemical phenotypes that may result in abnormal alcohol seeking and alcohol intake. Recently, several laboratories have developed the molecular techniques to begin mapping genes influencing alcohol preference and other related phenotypes in lines of animals selectively bred for high and low alcohol consumption. For example, quantitative trait loci (QTL) influencing alcohol preference have been identified on chromosomes 3, 4 and 8 in the P/NP rats and on chromosomes 5, 10, 12 and 16 in the HAD/LAD lines of rats. Thus, experiments with genetically selected lines of rats offer hope that the neurobiological and genetic basis of alcohol-seeking behavior can be successfully explored in the laboratory. ■

Further reading:

Cicero T. J. (1988) Animal models of alcoholism. In: Eriksson K., Sinclair J. D. and Kiianmaa K. (eds.) *Animal Models of Alcohol Research*, (pp. 99-110). London: Academic Press.

Cloninger C. R. (1987) Neurogenetic adaptive mechanisms in alcoholism. *Science*, 236, 410-416.

Dyr W., Kostowski W. (2004) Preliminary phenotipic characterization of the Warsaw High Preferring (WHP) and Warsaw Low Preferring (WLP) lines of rats. *Polish Journal of Pharmacology* 56, 359-365.