Acquisition, maintenance and relapse-like alcohol drinking: Lessons from the uchb rat line

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This review article addresses the biological factors that influence: (i) the acquisition of alcohol intake; (ii) the maintenance of chronic alcohol intake; and (iii) alcohol relapse-like drinking behavior in animals bred for their high-ethanol intake. Data from several rat strains/lines strongly suggest that catalase-mediated brain oxidation of ethanol into acetaldehyde is an absolute requirement (up 80%?95%) for rats to display ethanol?s reinforcing effects and to initiate chronic ethanol intake. Acetaldehyde binds non-enzymatically to dopamine forming salsolinol, a compound that is selfadministered. In UChB rats, salsolinol: (a) generates marked sensitization to the motivational effects of ethanol; and (b) strongly promotes binge-like drinking. The specificity of salsolinol actions is shown by the finding that only the R-salsolinol enantiomer but not S-salsolinol accounted for the latter effects. Inhibition of brain acetaldehyde synthesis does not influence the maintenance of chronic ethanol intake. However, a prolonged ethanol withdrawal partly returns the requirement for acetaldehyde synthesis/levels both on chronic ethanol intake and on alcohol relapse-like drinking. Chronic ethanol intake, involving the action of lipopolysaccharide diffusing from the gut, and likely oxygen radical generated upon catechol/salsolinol oxidation, leads to oxidative stress and neuro-inflammation, known to potentiate each other. Data show that the administration of N-acetyl cysteine (NAC) a strong antioxidant inhibits chronic ethanol maintenance by 60%?70%, without

inhibiting its initial intake. Intracerebroventricular administration of mesenchymal stem cells (MSCs), known to release anti-inflammatory cytokines, to elevate superoxide dismutase levels and to reverse ethanol-induced hippocampal injury and cognitive deficits, also inhibited chronic ethanol maintenance; further, relapse-like ethanol drinking was inhibited up to 85% for 40 days following intracerebral stem cell administration. Thus: (i) ethanol must be metabolized intracerebrally into acetaldehyde, and further into salsolinol, which appear responsible for promoting the acquisition of the early reinforcing effects of ethanol; (ii) acetaldehyde is not responsible for the maintenance of chronic ethanol intake, while other mechanisms are indicated; (iii) the systemic administration of NAC, a strong antioxidant markedly inhibits the maintenance of chronic ethanol intake; and (iv) the intra-cerebroventricular administration of anti-inflammatory and antioxidant MSCs inhibit both the maintenance of chronic ethanol intake and relapse-like drinking.

Acetaldehyde

Catalase

Ethanol

Inflammation

Reactive oxygen species

Reinforcement (psychology)

Relapse

Stem cells

acetaldehyde

acetylcysteine

alcohol

catalase

dopamine

salsolinol

alcohol consumption

alcohol withdrawal syndrome

aversion

binge drinking

drinking behavior

mesenchymal stem cell

nervous system inflammation

nonhuman

oxidative stress

rat

rat strain

reinforcement

relapse

Review