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Review

Operant self-administration of ethanol in infant rats

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HIGHLIGHTS

- The infant rat is highly sensitive to appetitive motivational effects of ethanol.
- Operant response to ethanol in infancy is enhanced by exposure to ethanol in utero.
- Operant response to ethanol in infancy is mediated by opioid transmission.
- Operant response to ethanol can facilitate subsequent ethanol intake.

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ABSTRACT

The review focuses on operant self-administration of ethanol in immature, infant rats. Several methods for the analysis of ethanol intake in infants are available, yet only oral self-administration models the typical pattern of ethanol consumption found in humans. The study of ethanol intake in infants is important for our understanding of how early alcohol experiences facilitate subsequent engagement with alcohol. It seems that sensitivity to ethanol-induced operant reinforcement is found very early in life, a few hours after birth, and throughout the first three weeks of life. Most of the studies reviewed complied with most, albeit not all, of the criteria for operant behavior (e.g., greater responding than yoked controls and persistence of this difference after withholding the reinforcer). Operant self-administration of ethanol in infant rats seems to be, at least partially, mediated by endogenous opioid transmission and can be enhanced by prior exposure to ethanol. Furthermore, acquisition of ethanol-mediated operant learning seems to facilitate drug self-administration during adolescence. Relative to older subjects, infants exhibit lower sensitivity to ethanol's sedative, hypnotic and motor impairing effects. On the other hand, they exhibit increased sensitivity to the motor stimulant and rewarding effects of ethanol. We suggest that this pattern of response to ethanol may favor the rapid acquisition of operant self-administration in infant rats.

Contents

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1. Introduction

The study of alcohol effects can be done at several levels. Cell cultures and brain slices provide a controlled environment in which the interaction of ethanol and specific neurons or their receptors can be carefully scrutinized. Behavioral studies, on the other hand, provide a benchmark to analyze mechanisms and treatment effects in vivo, as well as ethanol-related learning that can shape alcohol seeking and intake. Passive exposure to ethanol, via intraperitoneal, gavage administration or inhalation offers a method by which the researcher can carefully manipulate dose, concentration and interval of administration. These are key variables in the expression of phenomena such as ethanol-induced inflammation, or behavioral sensitization. Behavioral sensitization, the gradual increase in the stimulant effect of ethanol following chronic ethanol administration in mice [27], is more clearly observed after intermittent administration of low doses of ethanol, whereas continuous exposure to high ethanol doses is more likely to induce tolerance. This is just an example, but illustrates the usefulness of using a controlled, dose–response approach to analyze ethanol's effects.

As relevant as experimenter-administered studies are, ethanol oral self-administration is preferred in a wide-variety of situations, notably because the oral route is better to model the typical pattern of consumption found in humans. Moreover, oral self-administration procedures allow examining how ethanol's pharmacological, post-ingestive effects are modulated by the orosensory properties of ethanol (e.g., taste, smell). Several researchers have postulated that the bitterness of alcohol serves as a natural protection to prevent initial escalation into alcohol consumption. Kiefer [42] found significantly lower ingestive and higher aversive orofacial responses in rats given familiarization with alcohol than in naïve counterparts. Pautassi et al. [78] found avoidance of a texture that lined a chamber in which pups received intraoral infusion of 5% ethanol. Yet pups developed conditioned preference for the texture when it was paired with the delayed, post-ingestive effects of ethanol. This result suggests motivational dissociation between the aversive effects of ethanol odor and taste and the apparent reinforcing effects that take place following its ingestion. Two-bottle choice studies, in which animals are given access to water and ethanol [97] and taste reactivity studies (in which animals are subtly stimulated on the tongue with drops of liquid) also provide support for this "taste barrier" hypothesis [42]. Moreover, neurotransmitter release and utilization of glucose after administration of morphine or cocaine are different when using forced or self-administration procedures [91]. Other important phenomena, such as the usual peak in alcohol consumption after a period of abstinence (i.e., alcohol-deprivation effect) and its modulation by opioid antagonism [37] can only be analyzed through the use of self-administration models [10].

There are several examples of ethanol self-administration models, two of which are consummatory in which alcohol is readily available from tubes in forced or, more commonly, in two- or three bottle choice tests [111]; or operant self-administration models, in which animals have to execute an arbitrary behavioral response, such as pressing a lever or nose-poking, to obtain a small quantity of ethanol [48].

In the present review we will focus on operant self-administration studies of ethanol intake, and particularly in those conducted in immature, so called "developing" animals: infant rats [80]. It may seem illogical to study ethanol intake in infants, given that children usually rely on parental control to access food and liquids and, therefore, the possibilities for self-administration of alcohol would be scarce. Exposure to alcohol in infants, however, seems more common than usually thought, both due to accidental exposure, cultural practices such as use of cloths embedded with alcohol for analgesic purposes, and also due to maternal alcohol drinking during lactation in spite of scientific warning against it [109]. Perhaps more important, recent studies indicate that the onset of alcohol initiation is quickly descending worldwide. A birth cohort study, for instance, indicated that almost 20% of a sample of Brazilian children aged 11–12 years had already experimented with alcohol [76]. A more recent study conducted in Argentina [89] indicated alcohol sipping and tasting in 58% of its sample (n = 367) of 8–12 year old children. These early alcohol experiences could facilitate subsequent engagement with alcohol during adolescence, which in turn significantly enhances the possibilities of alcohol abuse and dependence later in life. Several works, notably a large state-wide Canadian study [20], have found greater ratio of alcohol-related problems in those who begin to drink before age 15, compared to those that delayed alcohol initiation till after age 15. These works may appear as a group of isolated studies, yet when taken together indicate the need for further analysis of drinking initiation during infancy and their impact on subsequent alcohol preference.

An added advantage of using an immature rat model is that the developing brain provides an opportunity to correlate normal, programmed changes in brain function with corresponding changes in learning and behaviors, or in sensitivity to or predisposition to ingest drugs. For instance, assessment of ethanol intake in infants through an independent feeding procedure revealed a sudden upward shift in ethanol acceptance by postnatal day 6, which coincides with the shift in function of the GABA system (from excitatory to inhibitory) around this age [98].

The review will provide a historical overview and in-depth discussion of studies analyzing operant self-administration of ethanol. The challenges and pitfalls of studies in adult, mature subjects will be discussed, yet the focus will then shift to studies conducted during early ontogeny. The main aim is to provide an updated and systematic review of studies on operant self-administration of ethanol during infancy. Particular emphasis will be put on how these studies shed light on the effects of early active exposure to alcohol on later alcohol preference at late adolescence and adulthood. Based on results obtained from more traditional, classical conditioning approaches [80] or from non-operant self-administration methods [98], the working hypotheses will be that operant self-administration of ethanol can be readily established in infants and that such ethanol-mediated learning is (a) enhanced by prior experience with alcohol odor, taste or post-ingestive effects, (b) comparable to that induced by non-drug reinforcers (e.g., sucrose), (c) dependent on the integrity of the endogenous opioid system, and (d) is associated with greater predisposition for later alcohol intake.

As we will find out, it is not always distinctively clear when a behavior falls under the umbrella of operant conditioning. When should we consider that operant behavior occurs in the context of ethanol self-administration in infancy? We propose that, to fully claim such a finding, any given study should exhibit several (and if possible all) of the following criteria: a) a seemingly arbitrary behavior is made contingent with alcohol access, b) after this arrangement the target behavior significantly grows in magnitude when compared to baseline, as well as vs vehicle and vs yoked, unpaired control groups; c) after withholding the reinforcer an extinction curve is observed and subsequently the behavior emerges from time to time without exposure to any explicit stimuli (i.e., spontaneous recovery). Last but not least, there should be evidence indicating that response is maintained by the post-ingestive, pharmacological effects of alcohol [97]. The use of yoked, unpaired controls should not be underestimated in studies assessing drug-mediated operant learning. Yoked animals are given the reinforcer each time the paired animal receives it, yet the delivery of this reinforcer is completely independent of the behavior. That is, yoked controls are exposed to equivalent amounts of the reinforcing stimulus as experimental animals but have no control over the relationship between operant behavior and reinforcement. The use of a yoked control provides similar advantages to those yielded by an unpaired control in classical conditioning studies. An unpaired control is exposed to both conditional and unconditional stimuli (CS and US, respectively) but in an unrelated manner. This reduces the possibility of pseudoconditioning and, in pharmacological studies, controls for unspecific (e.g., toxic) effects of drug exposure.