

Polydipsia-Induced Alcohol Dependency in Rats

We are concerned that Heintzelman *et al.* (1) claim a failure to replicate our technique for the production of physical dependence on ethanol in rats (2). Clearly, a technique which is difficult to replicate is of little use to biomedical research; however, we question whether their report is, in any important sense, a failure to replicate. The main "negative" finding was that key-shaking failed to precipitate convulsions in ethanol-withdrawn rats in their experiment whereas this treatment did produce convulsions in our experiment. What they did observe was that 3 hours after removal of ethanol, three of seven animals exposed to key-shaking leaped out of the observation cages and ran about the room. The same three rats duplicated this behavior in response to the same stimulus 7 hours after withdrawal. In a more detailed report of our experiment (3), we described similar behavior in the two animals we tested with brief key-shaking (less than 5 seconds) at approximately the same two postwithdrawal times (3 and 9.5 hours) used by Heintzelman *et al.* Animals leaped from their cages and circled to the left with strong, clonic, running movements for 2 minutes or more. Clonic movements, tremors, and other symptoms were observed in other rats in that experiment, but the other animals were not exposed to key-shaking. The leaping and running responses described by Heintzelman *et al.* and our own descriptions (3) appear quite similar and do not occur in normal rats. They are less dramatic signs of withdrawal than seizures, but are indicative of dependence nonetheless.

Heintzelman *et al.* suggest that the convulsions we observed "may have been a result of the rats' inherent proneness to seizures." However, we tested normal Holtzman rats with prolonged key-shaking, but no convulsions or preconvulsive, hyperactive behaviors could be evoked (2-4). Further, we found that the same stimulus failed to evoke any such behaviors "in animals under the ethanol polydipsia condition prior to ethanol withdrawal, in animals reduced to 80 percent of normal body weight, and in similarly weight-reduced animals under a water polydipsia condition" (4). Animals

held to 80 percent of normal body weight with 5 percent ethanol available as the sole drinking fluid likewise failed to go into convulsions (5). These last three groups were more reduced in weight (to 80 percent of normal) when tested than were the animals described in our original report (2). It is the withdrawal from excessive ethanol drinking, and not an inherent proneness coupled with reduced feeding, which is the crucial event predisposing these animals to preconvulsive behaviors and frank convulsions in response to brief key-shaking.

A question might remain as to why Heintzelman *et al.* did not obtain seizures while we did. This too is not difficult to reconcile. While they consider the mean intake reported in their experiment (11.7 g of ethanol per kilogram of body weight per day) to be equivalent to the 13.1 g/kg we obtained, this may not be the case. The point of our technique is to maintain overdrinking stably throughout 24-hour cycles so that intake outpaces the rat's considerable capacity to metabolize ethanol, and blood ethanol levels remain elevated for the major portion of each cycle. This was achieved for most animals in our report, as shown by the tracking of 24-hour blood ethanol concentration values for every animal [figure 2 in (2)]. The somewhat smaller intake Heintzelman *et al.* report may not exceed the ethanol elimination rate sufficiently to allow the maintenance of a high blood ethanol concentration necessary for development of severe physical dependence. This is consistent with their observation of a less severe physical dependence, as indicated by running episodes without convulsions. But without a presentation of their 24-hour blood ethanol values the issue cannot be resolved completely.

Using an identical procedure, we have replicated our original mean intake value (13.1 g per kilogram per day) with another group of animals (6). We have also produced mean intakes between this value and that reported by Heintzelman *et al.* (5). Animals maintained on our schedule for 9 to 10 months can decrease their intakes eventually to values of about 10 g/kg. Nonetheless, they all showed dyski-

nesia upon ethanol withdrawal (7). On the other hand, an augmented mean intake of 15.1 g/kg was obtained by adding saccharin to the standard 5 percent ethanol solution (6). The brief key-shaking stimulus produced tonic-clonic seizures in all animals in this last group 8 hours after ethanol withdrawal (6). We recommend this latter method for those who wish to work with physical dependence at the severe level constituted by withdrawal convulsions.

To summarize the empirical issues involved, we perceive no inconsistency between the general findings of Heintzelman *et al.* and results we have reported both in our original report and in subsequent publications. At most, their initial values for ethanol polydipsia and their mean terminal 3-month value are somewhat lower than we typically obtain; the less severe signs of physical dependence they observed are in accordance with this suboptimal ethanol polydipsia.

Finally, Heintzelman *et al.* introduce the theoretical notion that ethanol dependence should imply maintenance of the ethanol overdrinking to avoid the abstinence syndrome. This issue has been discussed elsewhere (8); an adequate discussion is beyond the scope of this comment.

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