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Alcohol-Deprivation Effect in Rats Genetically Selected for Their Ethanol Preference

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SINCLAIR, J D *Alcohol-deprivation effect in rats genetically selected for their ethanol preference* PHARMAC BIOCHEM BEHAV **10**(4) 597–602, 1979 —Alcohol deprivation and alternate-day access increase voluntary alcohol drinking by normal rat strains in a consistent manner In contrast, the ANA strain developed by selective outbreeding for low alcohol intake during continuous access showed no increase in their alcohol drinking during alternate-day access and only a small increase after a week of deprivation The AA strain developed for high alcohol intake showed an increase after a week of deprivation similar in magnitude to that of normal rats but persisting much longer In order to have been selected, these deviant reactions to deprivation must have been related to deviant baseline levels of alcohol drinking during continuous access, but presently even the AAs with the lowest baselines show the persistent increase and the ANAs with the highest baselines show only small increases Strain differences were also found in spontaneous alternation in a T-maze A modification of Pinel and Huang's inhibitory factor model accounting for these results is presented

Ethanol Alcohol-deprivation effect Rat strain differences Spontaneous alternation Voluntary alcohol drinking

ONE of the most reliable characteristics of voluntary alcohol drinking by rats is the increase caused by deprivation This can be seen as the "alcohol-deprivation effect" (ADE) after a single period of several days without alcohol [4, 8, 9, 14, 17, 18] or as the increase which develops during alternate-day access to alcohol [1, 5, 6, 19, 20, 21]

Nearly all of the previous evidence has suggested that these increases are not related to the prior level of alcohol drinking during continuous access In the case of the ADE, despite widely varying differences in the prior baselines, the magnitudes of the increases and the time courses for returning to baseline have been all nearly the same. Among my studies [8, 9, 10, 14, 15, 17, 18] the overall correlation between the mean baselines of the various groups and their increases on the first post-deprivation day was only –0.17 (15 df, NS) The relatively heavy-drinking Long-Evans strain showed an ADE similar to that of the light-drinking Sprague-Dawley strain [8]. When a group of 25 Long-Evans rats were divided into 5 subgroups ranging from the animals with the highest baselines to those with the lowest, the ADEs were nearly identical, and a diet containing calcium cyanamide which suppressed the baseline did not alter the ADE [10]

The only evidence suggesting that some relationship might exist between the ADE and the baseline came from a few extreme individual rats Although nearly all rats studied have shown an ADE, there have been a few exceptions, and these have usually been rats which had drunk almost no alcohol before deprivation Occasionally rats were also found which drank very large amounts before deprivation and then showed somewhat more persistent increases than normal after deprivation These exceptions were so rare that they seldom had much effect on the group means Consequently, although a relationship was not apparent in most normal laboratory rats, there was some possibility that one might be seen in the animals at the extremes of the normal range of alcohol drinking. One way to examine this possibility was with two strains of rats which have been developed by selective outbreeding for extreme baseline levels of alcohol intake· the AA strain which drinks much more alcohol than normal strains, and the ANA strain which consumes very little alcohol [2,3].

The present studies examined whether these strains react differently from each other and from normal laboratory rat strains to alternate-day access to alcohol and to a week of alcohol deprivation In addition their rates of spontaneous alternation in a T-maze were determined, since previous work had suggested this might be related to the ADE and other compensatory activities [13].

EXPERIMENT 1 ALTERNATE-DAY ACCESS

Method

Eleven male AA and 10 male ANA rats of the 30th generation were raised in group cages until the age of 3 months and then individually housed in 19×17×23 cm galvanized wire cages After a week of acclimation they were given a free choice between tap water and 7% (v/v) alcohol solution (prepared from 96% ethanol) in 100 ml graduated bottles with glass spouts After 18 days of continual access, when the mean weights were 293 and 317 g for the AA and ANA rats, respectively, they were switched to "alternate-day access," during which the alcohol was available only every second day, for the next 20 days. Water and powdered food were always present A 12 hr light-12 hr dark illumination schedule was used, and the temperature was maintained between 21–24°C and the humidity at 55%

These represent the standard procedures which have been used in several previous experiments from this laboratory for preparing rats for subsequent study while their alcohol intake was elevated by alternate-day access [11]. Consequently, although no control group was run concurrently, the data from the preliminary portions of these other studies are available for comparison These studies have used male rats of the following strains: 19 Long-Evans, 18 Sprague-Dawley and 14 rats of a special mixed strain created by crossing of these and Wistar strains The duration of continual access before alternate-day access has varied from 18 to 35 days, but this has not altered the effects of alternate-day access Although the baseline levels of consumption differed, with the Long-Evans rats drinking somewhat more alcohol, the increases from baseline caused by alternate-day access have been almost identical

Results

As expected the AA rats drank considerably more alcohol during continual access than the ANAs: during the last 5 days, used as the baseline, the AAs drank a mean of 6 61 g/kg body wt of ethanol per day, while the ANAs drank only 1 14 g/kg The respective ratios of ethanol solution to total fluid intake (E/T) were 0.86 and 0 20

Figure 1 shows the changes caused by alternate-day access in the AAs and ANAs and the mean changes previously seen in the 51 normal laboratory strain rats. The arc sin values of the E/Ts are shown and were used for all analyses, rather than the E/Ts themselves in order to compensate for the inherent limitations of this measurement The normal strain rats showed a progressive increase in alcohol consumption and were significantly ($p<0$ 01) higher than their baseline on every pair of access days The ANAs showed almost no increase, were never significantly above their baseline and had significantly ($p<0$ 05) smaller changes from baseline with both measurements than the normal strain on each of the last 3 pairs of access days The AA strain showed increases intermediately between the ANA and normal strains Their consumption during alternate-day access was significantly above baseline on 3 of the 5 pairs of access days when measured with g/kg, but their changes in arc sin E/T did not reach significance The changes in the AAs were not significantly different from those of the normal strains and, with the exception of the g/kg measurement on the last pair of access days, were not significantly different from those of the ANAs

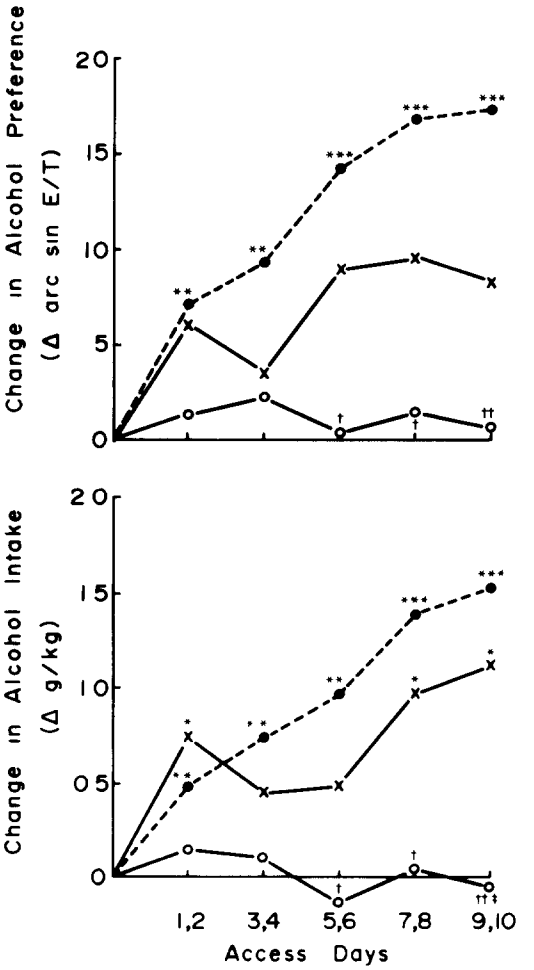

FIG 1 The effect of alternate-day access to 10% (v/v) ethanol solution on alcohol consumption in AA (X——X) and ANA (○——○) rats, compared to previous results with 51 rats of different normal laboratory strains (● - - - ●) The mean changes in alcohol preference from the baselines shown during the last 5 days of continuous access to alcohol are presented in the upper frame, and the mean changes in g of ethanol consumed per kg body wt are presented in the lower frame *significantly different from the baseline, $p<0$ 05, **$p<0$ 01, ***$p<0$ 001 †significantly different change from baseline than that shown by the normal laboratory strains, $p<0$ 05, ††$p<0$ 01 ‡significantly different change from baseline than that shown by the AA strain, $p<0$ 05

EXPERIMENT 2 ADE AND SPONTANEOUS ALTERNATION

Method

Sixty-four AA and 53 ANA males of the 32nd generation and 25 male rats of the Long-Evans×Sprague-Dawley× Wistar mixed strain were raised in group cages on new Astra-Ewos powder rat diet, under conditions similar to those in Experiment 1 At the age of 4 months for the AAs and ANAs and 5 months for the mixed strain, the animals were tested for spontaneous alternation in a T-maze, as previously described [13] Each animal, having had continual access to food and water, is placed in the start alley of the maze After entering either arm, it is gently removed and placed in the start position for a second trial Alternation, which most rats show, consists of going in the opposite arm on the second trial than on the first Three AAs and 2 ANAs on the first trial ran back into the other arm before they could be removed and, therefore, are not included in the tabulation

From these animals, 44 AAs, 29 ANAs and 23 mixed strain rats were selected on the basis of better health for testing with alcohol deprivation The animals were individually housed as in Experiment 1 During the first week, 10% (v/v) ethanol solution was the sole fluid available There was then a choice between the alcohol solution and water, with the positions of the bottles reversed weekly After 3 weeks of choice, the rats were deprived of alcohol for 1 week, and then given 2 more weeks of choice

Results

Table 1 shows the alcohol consumption during the last week before deprivation These values were used as the baselines Both the ANAs and the mixed strain rats were

TABLE 1

BASELINE VALUES FOR ALCOHOL DRINKING DURING THE LAST WEEK BEFORE ALCOHOL DEPRIVATION (MEANS ± SD)

	AA	Mixed Strain	ANA
g ethanol/kg b wt	4 81 ± 1 73	1.30 ± 1 47 *	1 06 ± 0 62 *
E/T†	0 609 ± 0 241	0.204 ± 0 248	0 172 ± 0 115*

*Significantly different than AAs, $p<10^{-8}$
†Ratio of ethanol solution to total fluid consumption

TABLE 2

MEAN CONSUMPTION DURING THE FIRST HOUR AFTER ALCOHOL RETURNED

	AA	Mixed	ANA
ml 10% (v/v) ethanol	2 07*†	2 52*†	0 21
ml water	0 14	0 22	0 14
(body weight (g))	313	418	302
g ethanol/kg body wt	0 52*†	0 42*†	0 06
increase from predeprivation rate (g ethanol/kg/h)	0 32*	0 37*	0 01
% rats drinking (1 ml) ethanol solution	82*	87*	17

*Significantly different from ANA rats, $p<0$ 01
†Significantly different from own predeprivation rate, $p<0$ 01

significantly lower than the AAs, but they were not significantly different from each other

After deprivation, the alcohol bottles were returned between 3 and 4 p m Fresh water was provided at the same time, and the consumption was measured after 1 hr As has been previously observed [8] with normal laboratory strains, the mixed strain rats immediately began drinking alcohol, but ignored the water almost completely. A somewhat similar behavior was observed with the AA rats their volume of alcohol solution drunk was less than that of the mixed strain, but because of their lighter weight, the g/kg intake was slightly higher (see Table 2) The ANAs, however, did not generally start drinking alcohol, and differed significantly from both the AAs and the mixed strain animals

Figure 2 shows the daily changes in alcohol consumption after deprivation relative to the baseline levels The mixed strain showed the same pattern observed previously in normal laboratory rats a large increase followed by a gradual return to baseline

Deprivation also caused a significant increase in the alcohol drinking by the AA rats, but it followed a different temporal pattern On the first post-deprivation day they showed less increase than the mixed strain (significantly less with arc sin E/T) Subsequently, as the mixed strain returned to baseline, the AAs remained at an elevated level of alcohol intake, significantly above their baseline and usually significantly different from the increases in the mixed strain rats and the ANAs until the 9th post-deprivation day

The ANAs showed only a small effect from alcohol deprivation. Their alcohol consumption was significantly above baseline for the first 4 days, but they showed neither the large initial increase of the mixed strain nor the sustained increase of the AAs

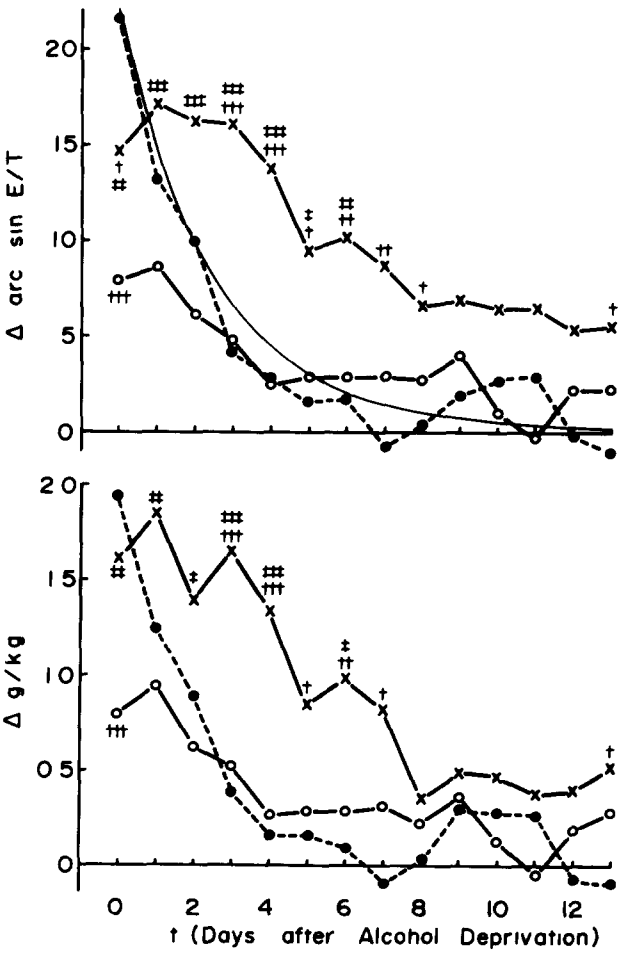

FIG 2 The mean increases in alcohol consumption caused by a week of alcohol deprivation in 44 AA (X——X), 29 ANA (○——), and 23 mixed strain (● – – – ●) rats The smooth curve represents the best-fitting curve for the previous results from 271 rats of different normal laboratory strains (see Table 4) †significantly different change from predeprivation baseline than that shown by the mixed strain rats, $p<0$ 05, ††$p<0$ 01, †††$p<0$ 001 ‡significantly different change from predeprivation baseline than that shown by ANA rats, $p<0$ 05, ‡‡$p<0$ 01, ‡‡‡$p<0$ 001

In order to separate the effects of the different baseline levels of alcohol intake from the inherent differences between the strains, a comparison was made between the 10 AAs with the lowest baseline E/Ts, the 10 highest mixed strain and the 10 highest ANAs The mean baseline E/Ts for these subgroups were, respectively, 0 30, 0 37 and 0 30 Figure 3 shows the changes in arc sin E/T after deprivation. The

results are quite similar to those from the entire groups shown in Fig 2 The 10 lowest AAs showed a sustained increase; the 10 highest ANAs showed only a small increase, and the 10 highest mixed strain rats had the largest mean increase on the first day and rapidly returned to baseline One exception should be mentioned the mixed strain rat with the highest baseline, in fact higher than any of the AA rats, showed a persistent ADE like the AAs

Table 3 shows the spontaneous alternation results from the present study along with those from a previous report [13] using the same procedure The present mixed-strain rats showed approximately the same rate of alternation (80%) as the previously-studied ones (82%), so these were combined The AAs showed significantly less alternation than either the mixed strain or the ANAs

DISCUSSION

The pattern of increase in alcohol drinking after a week or more of deprivation has previously been found to be surprisingly constant in normal laboratory rat strains In my studies [8, 9, 10, 14, 15, 17, 18], involving 17 groups (without additional treatments other than alcohol deprivation) composed of 184 Long-Evans, 39 Sprague-Dawley and 48 Wistar male rats under a wide variety of laboratory conditions, every group has shown an increase in alcohol consumption after deprivation The mean increase in arc sin E/T has been 22 1, with a standard deviation between groups of only 4 3 The return to baseline has also been similar in all groups, following very closely a negative exponential function of the form $\triangle = Me^{-at}$, where $\triangle$ is the increase over baseline, M is the increase on the first post-deprivation day, t is the number of prior post-deprivation days (0, 1, 2) and a is a time constant The best-fitting curve of this sort (see Table 4) accounts for over 99% of the variance from day to day for the mean of all groups combined

The mixed strain in the present experiment showed an ADE in which both the magnitude (M) and the time course (a) were quite similar to that previously observed with normal laboratory strains (see Table 4)

In contrast, both the heavy-drinking AA strain and low-drinking ANA strain showed ADEs which differed markedly from those of normal rats and of the present mixed strain The AAs differed primarily in returning to baseline at a slower rate Their data, with the exception of that from the first post-deprivation day, fit very closely to an exponential curve (see Table 4) The magnitude term is almost the same as that with the mixed strain and with normal strains The time constant for the AAs is, however, much smaller and out of the range found in previous studies

The ANAs differed from both normal strains and AAs in showing only a very small increase in alcohol drinking after a week of deprivation and none during alternate-day access Due to the small magnitude of their ADE after a week of deprivation, the time constant for their return to baseline cannot be estimated very accurately and less of their day-to-day variation is explained by an exponential formula

It is not possible to explain these results as being consequences of the differences in the predeprivation baselines of alcohol consumption As was shown in Fig 3, the strain-specific differences in their ADEs were maintained in the subgroups with similar baselines

This may seem to present a paradox The AA and ANA strains were developed on the basis of the voluntary alcohol drinking on continual access under identical conditions to those employed here The outbreeding program is such that it is unlikely that factors unrelated to this baseline alcohol intake would have been selected As mentioned in the introduction, ADE patterns like those seen in the AAs and ANAs have been observed in very few individual rats of the normal strains In order for these extremely deviant characteristics to have been selected so that nearly all of the present AAs and ANAs show them, these ADE characteristics must have been strongly related to the level of consumption during continual access Nevertheless, within these strains today, the specific ADE characteristics were displayed regardless of the baseline intake

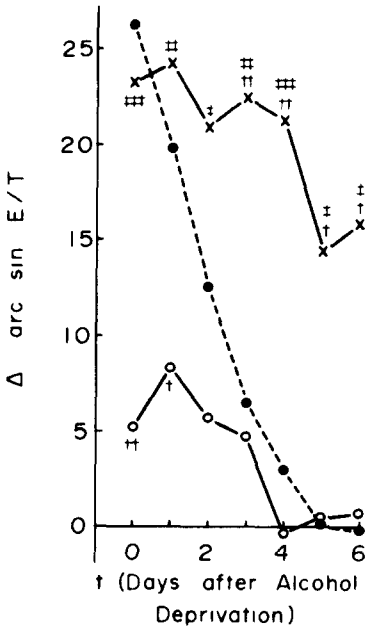

FIG 3 The mean increases in alcohol preference caused by a week of alcohol deprivation in the 10 AA rats with the lowest predeprivation E/T (mean=0 30) (X——X), the 10 ANA rats with the highest predeprivation E/T (also 0 30) (——), and the 10 mixed strain rats with the highest predeprivation E/T (0 37) (● – – – ●) Similar results are found with the g/kg measurement †significantly different change from predeprivation baseline than that shown by the 10 mixed strain rats, $p<0$ 05, ††$p<0$ 01 ‡significantly different change from predeprivation baseline than that shown by the 10 ANA rats, $p<0$ 05, ‡$p<0$ 01, ‡‡‡$p<0$ 001

It is possible to explain this paradox that the two deviant ADE characteristics were related to baseline during the initial development of the strains, but are no longer related to it in the present AA and ANA rats, by assuming that the characteristics are both determined by a relatively small number of genes having a very strong influence on alcohol drinking during continuous access Over the many generations in which the strains have been developed, the individuals possessing these characteristics have almost invariably been selected for breeding Consequently, the AAs are now nearly homogeneous for having the genes responsible for persistent ADEs, and the ANAs for showing very small ADEs These are not, of course, the only factors influencing baseline intake Environmental factors plus any genetic factors which are still largely hetereogeneous in the strains produce the present variation within the strains in baseline alcohol consumption. Therefore, it is possible to find, for instance, AA rats which because of these other factors drink less alcohol

TABLE 3

SPONTANEOUS ALTERNATION IN T-MAZE

	Hamsters	AA	Mixed	ANA
number alternating	34	41	70	45
number perseverating	27	20	16	6
% alternating	55 7	67 2	81 4	88 2
probability from χ^2 test				
hamsters	—	0 1928	0 0008	0 0002
AA		—	0 0488	0 0087
mixed			—	0 2918

TABLE 4

BEST-FITTING CURVES FOR THE TIME COURSE OF THE RETURN OF ALCOHOL DRINKING TO BASELINE AFTER ALCOHOL DEPRIVATION (AS THE INCREASES IN ARC SIN E/T)*

	Formula	r^2†	$t_{1/2}$ (in days)‡
all previous results combined	$22e^{-0.40t}$	0 99	1 7
present results			
mixed strain rats	$22e^{-0.48t}$	0 95	1 4
AA rats	$18e^{-0.10t}$	0 89	6 9
	$21e^{-0.12t} - 6.3e^{-1.7t}$	0 96	5 8
ANA rats	$9e^{-0.19t}$	0 76	3 6

* The normal procedures using logs for determining the best-fitting exponential curves are not applicable here because of the existence of some negative data points Consequently, the curves were determined with a successive-approximation computer program which selected the formula producing the smallest sum of squared deviations The best-fitting curve for the development of the increase on the first postdeprivation day as a function of number of deprivation days [18] is $22-22e^{-0.47t}$

†r^2 represents the amount of the variation in the daily means accounted for by the formula

‡t=The number of preceding post-deprivation days, $t_{1/2}$ is the time to return halfway to baseline

than some normal rats, but which nevertheless show the AA pattern of ADE

Why then do rats which return to baseline very slowly after deprivation drink very large amounts of alcohol during continuous access, while rats which show only a little increase after deprivation drink only a small amount? One explanation can be formulated from the hypothesis suggested by Pinel and Huang [5] They proposed that an inhibitory factor accumulates when there is continuous access to a particular flavor, which lowers intake of that flavor In vernacular terms, the animals get "tired" of it, just as one would get tired of having the same food for every meal The inhibition than dissipates during deprivation and, consequently, when the flavor is returned, consumption begins at a higher, uninhibited rate

Their hypothesis does not specify what input associated with continuous access is responsible for producing the inhibition It seems very unlikely, however, that the input is always coming in, even when, for instance, all the alcohol has been metabolized out of the system and the animal is asleep Consequently, probably both accumulation and dissipation of the inhibition are occurring within a day of continuous access, and that the relative rates of accumulation and dissipation have a strong influence on the baseline level of alcohol consumption An animal which accumulated inhibition slowly when drinking (or when alcohol is in the body) but lost it rapidly when the input was not present would tend to drink a larger amount of alcohol than an animal which accumulated inhibition rapidly but lost it slowly

In more formal terms, in a day's time a rat will have some time (t_a) when the input responsible for the inhibition is present, and the remainder of the time ($1-t_a$) when the input is missing and the inhibition is dissipating If the rate of accumulation is r_a and the rate of dissipation is r_d, the net change in inhibition in a day will be $r_a t_a - r_d(1-t_a)$ During normal conditions, the total amount of inhibition is balanced against various other factors (e g , positive reinforcement from ethanol) to determine the amount of alcohol drunk If the other factors remain constant, the total amount of inhibition must also remain constant for the daily alcohol intake to remain the same, as is known to occur in rats after the first few weeks of access Therefore, the net change in the level of inhibition on days of continuous access must be zero and $r_a t_a = r_d(1-t_a)$ Consequently, t_a and thus the amount of alcohol drunk must be a function of the two rates

$$t_a = \frac{r_d}{r_a + r_d}$$

Therefore, an animal with a low r_a would be a heavy drinker and in the development of a AA and ANA strains would have been chosen for breeding in the AA line The present AA rats would thus be expected to have a low r_a Although r_a was not measured directly in the present study, it should be proportional to the rate at which the rats return

to baseline after deprivation, which was found to be very low for the AA rats

If r_d could be increased, it would also increase alcohol drinking, the AAs might, therefore, be expected to have a high r_d This cannot be determined from the present studies, but the fact that their *M* value (Table 4) is similar to that of normal rats suggest that at least their r_d is not much smaller than that of normal rats and could be larger.

Previous research has suggested thah the ADE is related, not only to the saccharin elation effect [5], but also to compensation for food and water deprivation and, more surprisingly, to spontaneous alternation, since one species, the golden hamster, and only one had been found to fail to show all of these compensatory behaviors [7, 13, 16] This can be seen as suggesting that inhibition develops not only to consumption of flavored solutions, but also to eating and water drinking and to going in one direction in the T-maze. Again in the vernacular, a rat gets tired of going into the right arm of the maze after having just gone into it and, therefore, if all else is equal, will go to the left on the next trial A certain amount of random factors are, of course, present and sometimes override the biasing from the inhibition, so that not all normal rats alternate. only about 82% do If the amount of inhibition accumulating during the first trial is reduced, the percentage alternating should regress towards chance (50%) The AA rats with a low rate of accumulating inhibition, therefore, would be expected to show less alternation, as was indeed found

The results with the ANA rats can also be fitted into this hypothesis Their smaller ADE could be the result of a slower loss of inhibition, i.e , lower r_d, so that after one week of deprivation a large fraction of the original inhibition still remained Lower r_d is a factor which would cause lower t_a and, therefore, a lower baseline level of alcohol drinking, this factor thus would have been selected in the development of the ANA strain This could also have a small effect in increasing the amount of inhibition still present on the second trial in the T-maze, thus elevating the rate of alternation Conceivably, a lower r_d could also be responsible for the nearly complete lack of increase in alcohol consumption shown by the ANA rats during alternate-day access, in which each drinking occasion is preceded by only one day of deprivation as opposed to the seven days in the ADE study Alternatively, the small magnitude of the ADE in the ANAs and their low baseline level of alcohol consumption might be caused by some other limiting factor which generally prevents them from drinking more alcohol

One could argue that the increased consumption of alcohol after deprivation was caused by an increased "hunger" for alcohol or by an increase in its reinforcing properties due to its relative novelty, rather than by a loss of inhibition At present these are, however, merely semantic arguments, as can be seen by a close examination of the mathematical model presented here The model remains exactly the same if one postulates a positive factor (hunger, novelty) which increased during deprivation at a rate of r_d and disappears when input associated with drinking is present at a rate r_a It seems most likely that even physiologically this distinction is meaningless and that there is no such thing as a true unmodified level of alcohol drinking, but merely various points of equilibrium between interacting factors

Nevertheless, the semantic distinction between inhibitory factors and positive factors may be important for our conceptualization of the regulation of drinking, since our concepts are at one level phrased in semantic terms Consequently, one could conceptualize at one level that heavy alcohol drinking, such as shown by AA rats, is partially caused by (a) a low r_a, and, at another level, by either (b) a nearly insatiable hunger for alcohol or (c) merely not getting tired of alcohol quickly

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