PRESENCE OF ESCALATION EFFECT IN SHORT ACCESS AND LONG ACCESS EXPOSURE TO NON-DRUG REINFORCER

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ABSTRACT

Ahmed and Koob (1998) demonstrated an increase in self-administration of cocaine during long-term exposure as opposed to short-term exposure. This increase is described as an increase in the hedonic set point which dictates the amount of drug needed to have an effect. One argument against this increase appearing as a result purely of increase in hedonic set point, is that the increase seen is due to a habituation to negative effects of cocaine. The study presented here attempted support this theory of habituation using an analogous non-drug reinforcer. Water restricted rats were given short-access or long-access to quinine water similar to that of Ahmed and Koob (1998). Total water consumption was used as measurement of habituation. Results show that short-access actually produced an effect similar to escalation rather than long-access. Habituation occurred quickly for long-access rat resulting in a non-significant increase. Short-access allowed for gradual habituation over time.

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CHAPTER 1

EVIDENCE OF ESCALATION EFFECT IN DRUGS OF ABUSE

During prolonged exposure to some drugs of abuse (e.g., methamphetamine, heroin, and cocaine), the amount self-administered over time sometimes increases, an effect called escalation (Ahmed & Koob, 1998; Ahmed, Walker, & Koob, 2000; Kitamura, Wee, Specio, Koob, & Pulvirenti, 2006). For example, in Ahmed and Koob, (1998) rats in one group were permitted to self-administer cocaine for 6 h during each of 12 daily sessions, while rats in a second group were restricted to only 1 h of access to cocaine. They found rats in the long-access group increased their infusions from an average of 71 to 110 across sessions while those in the short-access group maintained a low, but constant self-administration rate of approximately 15.

Ahmed and Koob (1998) explained their escalation result by appeal to the idea that long-duration exposure to a drug elevates cocaine's hedonic set point, while abbreviated cocaine consumption leaves the set point unchanged. Control theory, from which the notion of set point derives, assumes that animals attempt to minimize set-point deviation. Since set-point elevation only occurs for rats chronically exposed to cocaine, increased cocaine consumption only occurs for that group.

Ahmed and Koob (1998) use their escalation account to model changes in reinforcer value that attend use of drugs of abuse. By increasing a drug's set point, their

account suggests that long-duration drug use can become progressively more reinforcing, resulting in compulsive drug use. Such an account is compatible with conventional views of the impact of drugs of abuse on behavior. In addition, it may provide a basis for discriminating the reinforcing efficacy of addictive substances from those that are not. For example, many natural reinforcers, such as food, impact subsequent behavior in a fashion opposed to an escalation effect. In particular, one would imagine that in a long-access food-reinforcement group, consumption rates would drop with time, not rise as in Ahmed and Koob, for the obvious reason that subjects that had eaten earlier are less inclined to do so soon thereafter.

A question the present report addresses is whether Ahmed and Koob's (1998) escalation account may serve as a basis for distinguishing between reinforcers with addictive properties and those without. Perhaps all that need be done to see if a good is addictive is to see if consumption increases with prolonged availability. Such an approach categorizes methamphetamine, heroin and cocaine consumption as addictive, but food consumption as not. By the standard of whether these goods are legally available, this categorization seems valid.

Despite this apparent success, two difficulties remain for escalation to serve as the property distinguishing between substances of abuse and other reinforcers. First, it must be shown that escalation only occurs with abused goods. That it might occur with consumption of non-addictive goods remains a possibility. For example, there are non-addictive goods for which people often say taste must be "acquired" by prolonged exposure (e.g., coffee, beer, olives, etc.). It may be the case that escalation occurs with, say, coffee. That is, coffee grows in reinforcing value as the set point for its reinforcing

feature or features increases with exposure. If so, escalation per se cannot serve as a basis for discriminating between addictive and non-addictive goods.

A second problem is that escalation of consumption, be it with putatively addictive or non-addictive substances, must not reflect some process other than an increase in the homeostatic set point. Consider, for example, cigarette smoking. While there is no doubt that some of the characteristics of this activity have positive valence (Why else would the smoker smoke?), it is also clear that those who initiate smoking make contact with unpleasant effects such as nausea, headaches and the like. Those who smoke typically escalate their consumption over time, however, perhaps because the unpleasant features of this activity habituate with exposure. So, in this case, we may witness escalation, but the escalation may have little to do with an increase in set point. Rather, increased consumption is due to the habituation of unpleasant characteristics that accompany the initiation of smoking.

Consistent with this argument is the fact that there are data showing cocaine escalation is compatible with the notion that this drug has multiple characteristics, some of which are unpleasant. For example, Goudie, Dickens and Thornton (1978) showed that cocaine injections after exposure to saccharin water created a decrease in subsequent saccharin consumption. In this case, it seems that unpleasant aspects of cocaine consumption can be strong enough to deter subjects from consuming liquid associated with the stimulus, at least at first. Eventually, however, rats return to normal consumption levels (Goudie, Dickens & Thornton, 1978). So, in this case, escalation as outcome (increased consumption) may not be due to escalation as process (i.e., elevation

in set point). Instead, the escalation outcome might be due to habituation to unpleasant features of cocaine.

In terms of the arguments offered here, it may be the case that Ahmed and Koob's (1998) escalation effect is: (a) really due to habituation; or (b) that it is due to a true escalation effect, but this effect is not unique to drugs of abuse. Either of these outcomes disqualifies increased consumption attending sessions of long (but not short) duration as a basis for identifying whether a good is addictive or not.

The present work tests only the habituation interpretation of escalation outlined above. In order to make this test, a good with clear positive and negative characteristics must be identified that would not typically be considered addictive. A substance that seems to qualify is quinine-adulterated water.

At moderate dosages quinine adulteration of water suppresses, but does not eliminate, consumption in rats presumably because of its bitter taste. In other words, quinine water qualifies as a good with pleasant (it satisfies physiological needs) and unpleasant (it tastes bitter) characteristics.

In addition, Nicolaidis and Rowland (1975) demonstrated habituation as a process in its consumption. In their report, rats were given access only to quinine-adulterated water for 65 days. Consumption increased over the first few days so that by day seven, daily consumption stabilized between 21 and 25 ml.

Does habituation as process in a non-addictive good like quinine water look like escalation in an addictive good such as cocaine? The objective in this report is to see if rats display an escalation-like effect akin to that seen in Ahmed and Koob's (1998) report

when quinine water rather than cocaine infusions is given in short- vs. long-access sessions.

Three different methods are used in these tests. In the first, quinine water vs. unadulterated water and long-access vs. short-access are factorially combined to create four groups of rats. The purpose of this study is observing the differences in consumption between water and quinine water in relation to session duration. In the second method, rats are allowed to consume quinine water for two weeks prior to their separation into short- and long-access groups. This two-week exposure to the good to be consumed mirrors the method of Ahmed and Koob (1998), although the session durations for each group are shorter than those used in their report. Finally, in the third design, the two-week training period is not used, and the duration of the long- (but not short)-access group is adjusted again. All three variations are described in detail in each experiment's Method section.

CHAPTER 2

EXPERIMENT ONE

Subjects

Twenty male Sprague-Dawley rats, aged 90 days at the start of the experiment, served as subjects. Each was individually housed in a wire-mesh cage (24.3 x 19 x 18 cm) located in a temperature-controlled vivarium (70^{o} F) with a 12-h light/12-h dark cycle (lights on 7:00 AM).

Procedure

For the first ten days, rats were given unrestricted access to food and water. On the next day, their access to water, but not food, was reduced to 4 h. The duration of water access was cut in half over days until, on the fourth day, the criterion duration of 30 min/day was achieved. The rats were then divided into four 5-subject groups for which duration of drinking (30 min or 180 min) and the presence vs. absence of quinine in the drinking water were factorially combined. The quinine concentration in the quinine-adulterated water was 0.35 mM solution (0.114 g dissolved in 1 L of distilled water).

The drinking schedule was designed so that on day one, all four groups had free access to water from 10:00 AM to 2:00 PM. On the following day, water bottles containing either 0.35 mM quinine or unadulterated water were affixed to each cage at 2:00 PM. The two 30-min groups had their bottles removed at 2:30 PM while the two

180-min groups had their bottles removed at 5:00 PM. Free access to water began at 10:00 AM the following day. The alternation between days with free access to water and consumption testing continued for 40 days.

Results

Figure 1 presents mean log mL consumption for each of the four groups in the experiment as a function of test days. Across all test days, rats in the two quinine groups drank less (M = 16.86 ml, SD = 2.85, N = 40) than rats in the water groups (M = 8.46, SD = 3.97, N = 40).

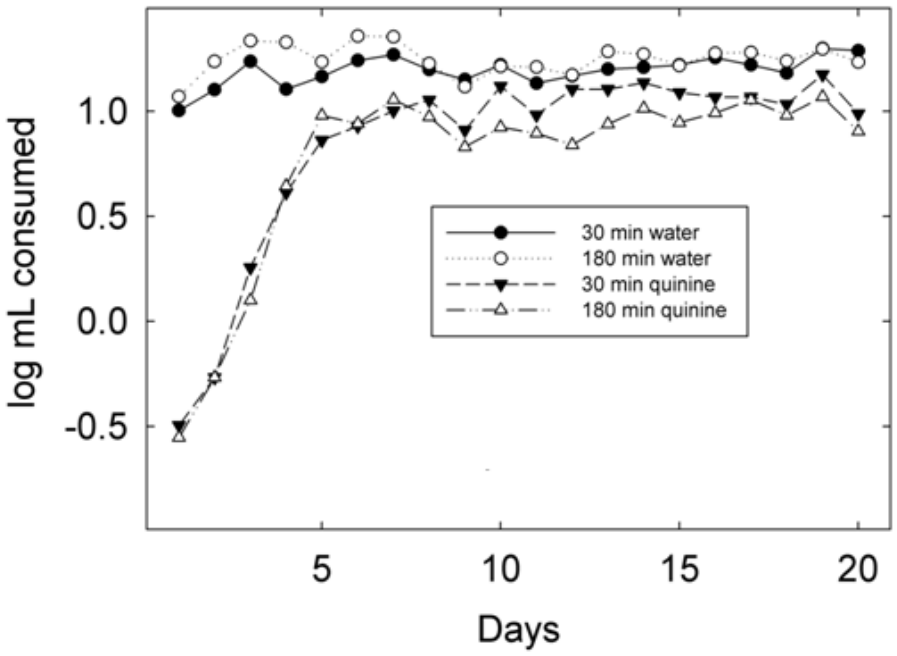

Figure 1. Log consumption of water and quinine-adulterated water for the 30 min and 180-min groups in Experiment 1.

This result was significant (two-sample t-test, $t(71) = 10.87$, $p < .05$). Focusing only on the final ten trials, where the drinking values seem to stabilize, there was no significant difference between the 30-min and 180-min water groups when assessed by a two-sample t-test, $t(20) = 1.39$, $p = .18$ ($M = 16.6$ ml, $SD = 1.89$, $N = 20$ vs. $M = 17.6$ ml, $SD = 1.58$, $N = 20$, respectively). Unlike the water groups, there was a significant difference between the 30-min and 180-min quinine groups ($M = 12.08$ ml, $SD = 1.62$, $N = 20$ vs. $M = 9.21$ ml, $SD = 1.48$, $N= 20$, respectively) when assessed by a two-sample t-test, $t(20) = 4.32$, $p < .01$.

Discussion

This study sought a demonstration of apparent escalation in the long-access quinine rats, similar to that seen by Ahmed and Koob (1998) in cocaine consumption. Had this result obtained, it would suggest that Ahmed and Koob's escalation effect might also be due to habituation. While the rise in quinine consumption over days seen in the present work is consistent with this idea, the finding that the group with the longer access to quinine water consumed less than the group with shorter access is not. After all, the long-access group, by virtue of its longer exposure to quinine, should have habituated more than the short-access group. It should also be noted that Ahmed and Koob's results showed a proportional increase in consumption based on time, meaning the six hour group self-administered cocaine six times more than the one hour group. These same results were not seen in the study presented here. The short-access group actually consumed more quinine water than the long-access group in the final ten trials. One

possibility is that a rat in the short-access group may attempt to have as much quinine water consumption seeing as the wait time until free water the following day is longer for the short-access group than the long-access group (20.5 hours compared to 17 hours). Perhaps the long-access group does not experience the stress of limited time for water consumption.

In order to ensure that the results of Experiment 1 were not due to schedule parameters, a second experiment was conducted that differed in method from that of Experiment 1. In addition, it was designed to resemble more closely the Ahmed and Koob (1998) design. In their study, rats bar pressed for cocaine infusions for two weeks prior to the actual short-access vs. long-access test. In Experiment 2, thirsty rats were also given two weeks' exposure to quinine water for 30 min per day. After this two-week exposure, rats were split into two groups for short-access and long-access to quinine water.

CHAPTER 3

EXPERIMENT TWO

Subjects

Ten male Long-Evans rats, approximately 90 days of age at the beginning of the experiment, served as subjects. The housing and lighting conditions were the same as in Experiment 1.

Procedure

Following one week of unrestricted access to food and water, all rats were introduced to the progressive four-day water-restriction regimen used in Experiment 1. Following this exposure, they received access to water adulterated with quinine at a concentration of 0.35 mM for 30 min beginning at 2 PM every day for 15 successive days. Next, these subjects were assigned to one of two five-subject groups that differed in that one group received five min of access to quinine water, while the other group received 60 min of access. For both groups, they were given 30 min of access to unadulterated water 60 min after each group's exposure to quinine water ended. The experiment ended for each group after six successive days of exposure to these contingencies.

Results

Figure 2 presents mean log consumption of quinine water for all rats during 15 daily 30-min access periods. Following this pretreatment, exposure to quinine continued for six test days, with one group having 5 min of access to quinine water (open circles) and the other group having 60 min of access (inverted closed triangles). During the between-group assay, the 60-min group (M = 11.52, SD = .76, N = 6) consumed more water than the 5-min group (M = 7.87, SD = 1.18, N = 6).

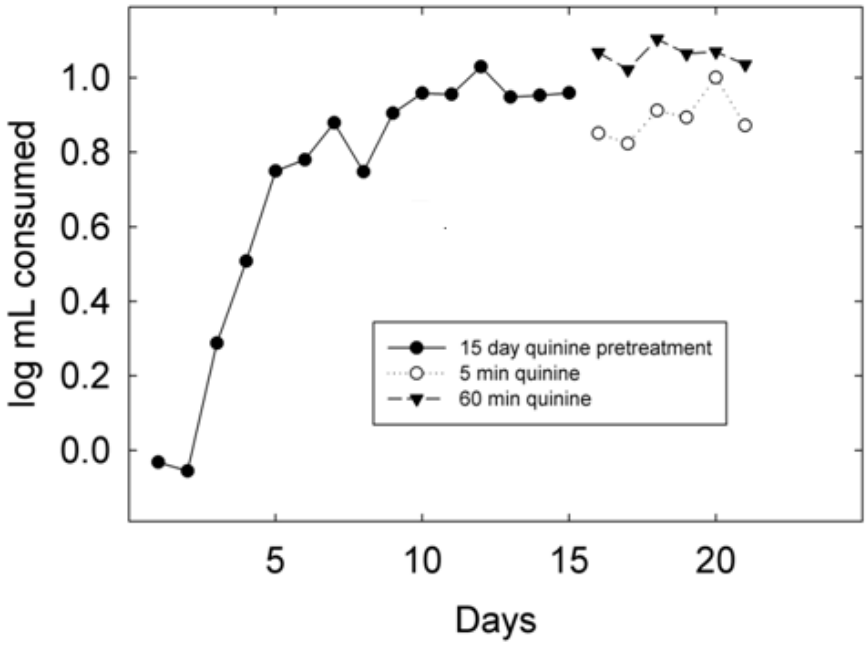

Figure 2. Log consumption in ml of quinine-adulterated water as a function of days. See text for other details.

This result was significant (two-sample t-test, $t(10) = 6.37$, $p < .05$). As had been the case in the prior experiment, the difference between these groups diminished over test days. Based on the last five sessions (days 16 to 21) there was a significant difference between the 5-min and 1-h quinine groups ($M = 7.87$ ml, $SD = 1.18$, $N = 6$ vs. $M = 11.52$ ml, $SD = .76$, $N = 6$, respectively) when assessed by a two-sample t-test, $t(10) = 6.57$, $p < .01$.

Discussion

For two weeks prior to testing, Ahmed and Koob (1998) trained rats to press a lever for cocaine infusions. Once subjects reached the criterion of at least 15 injections per session, they were assigned into short- and long-access groups for testing.

The purpose of this pretaining exercise was ensure that responding and consumption had stabilized before beginning their consumption measures in the short- and long-access groups. Insofar as possible, Experiment 2 mimics this methodology. A dividend of this approach is that the increase in quinine consumption seen in Experiment 1 during initial-training days might be eliminated, permitting a clear comparison between the short- and long-access quinine groups.

As is apparent in Figure 2 and noted in the Results section, the long-access group drank more water than the short-access group during trials 16 to 21. However, there appears to be a trend for this consumption difference to diminish over test trials. Since Ahmed and Koob, as stated in the experiment one discussion, saw proportional increases in the long-access group, one would've expected to see the long-access group drink twelve times the quinine water than the short-access group. This was not seen,

however, this could be due to ceiling effects again. Given the time limits, rats will only drink to satiety.

Experiment 2 ended after 5 post-training trials due to the fact that no escalation was seen in the long-access groups, a result expected if this study serves as an appropriate analogue of Ahmed and Koob (1998). Instead, the long-access group appeared to have stabilized during those five trials, while consumption appears to have increased in the short-access group.

In Experiments 1 and 2, habituation to the quinine occurred within ten days. This result reduces the utility of these experiments to see if habituation plays a critical role in Ahmed and Koob's (1998) escalation effect. In order to increase the likelihood that habituation to the quinine would be occurring during the test period, the pre-exposure time for the short-access group was shortened to 5 min while that of the long-access group remained at 30 min. This would allow for the rats to have access to the adulterated water for hydrating purposes while also prolonging the escalation process.

CHAPTER 4

EXPERIMENT THREE

Subjects

Thirty male Sprague-Dawley rats, approximately 90 days of age when the experiment began, served as subjects. They were housed under the same conditions as in Experiments 1 and 2.

Procedure

For seven days prior to the beginning of the experiment, all rats were given unrestricted access to food and water in their home cages. For days 8 through 11, access to water, but not food, was gradually restricted using the technique described in Experiment 1. Following their exposure to a single session of 30 min of access to water, the rats were split into two groups composed of 15 rats each. The groups differed in that one received 5 min of exposure to water adulterated with 0.35 mM quinine while the other group received 30 min of exposure to this solution. One h after their exposure to quinine water ended, all rats were given 30-min access to unadulterated water. Testing continued in this manner for 30 days.

Results

The top panel of Figure 3 presents log bar presses for cocaine infusions as a function of test days for the 1-h and 6-h groups from Ahmed and Koob (1998), Figure 1A. The bottom panel presents log ml of quinine water consumed by the 5-min and 30-min groups in Experiment 3. The vertical lines that cross between panels identify the daily sessions in Experiment 3 that correspond to the terminal sessions from Ahmed and Koob. The analysis relevant to this report is based on the data between these vertical lines (sessions 15 to 26).

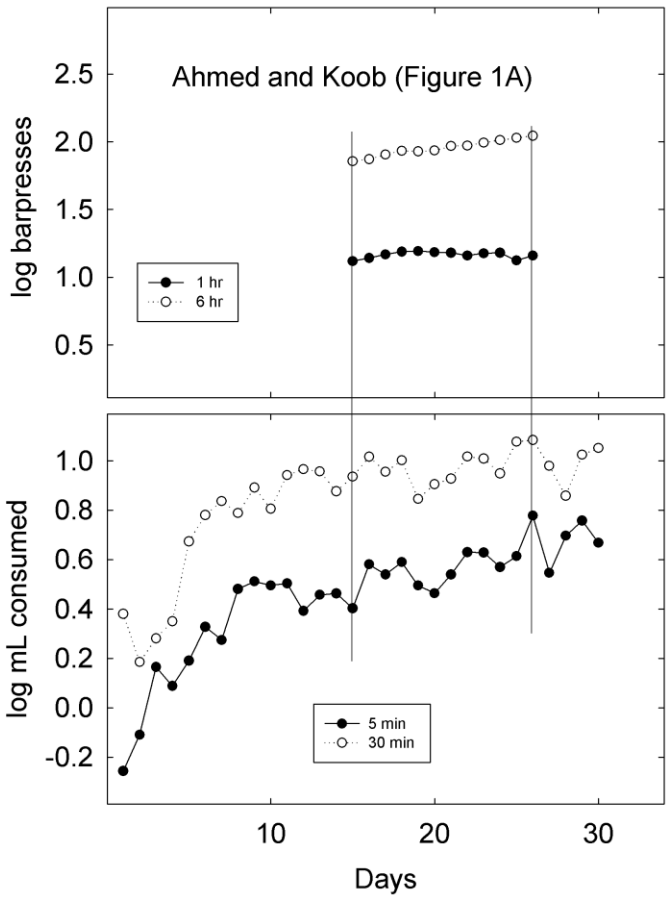

Figure 3. Top panel presents results for Ahmed and Koob (1998). Bottom panel presents the results of the present experiment. See text for other details.

Experiment 3 shows a significant difference of consumption totals between the 5-min and 30-min groups (M = 3.54 ml, SD = 0.57, N = 12 vs. M = 9.22 ml, SD = 1.42, N = 12, respectively), $t(22) = 12.87$, $p < .001$. A one-way repeated measures ANOVA test on the log values from sessions 15 to 26 is also significant, $F(11, 198) = 3.120$, $p<.05$. A one-way, repeated-measures ANOVA test on the 5-min data shows a significant increase from trial 15 to 26, $F(11, 99) = 3.272$, $p <. 05$ that is not evident in the 30-min data, $F(11, 99) = 1.837$, $p > .05$. Here can be seen a between-study difference.

Discussion

Ahmed and Koob's 1998 study showed that when given long access (6 h) to cocaine, rats escalate their intake more than rats with short access (1 h) to cocaine leading to long access rats injecting more cocaine overall. The analog of this experiment displayed similar results in terms of overall consumption, not escalation. Rats that had access to thirty-min of quinine consumed overall more of the solution compared to the five-min short access group. With a mean of 9.22 mL, the long-access group received their daily limit of drinking water. The short-access group consumed less than their daily limit; however, they were provided with the opportunity to drink unadulterated water to prevent any confounds regarding having enough water. In terms of cocaine, Ahmed and Koob argued that this difference between short-access and long-access was a result of an increase in the hedonic set point. As the rats continue to use the drug, the amount needed to produce even just baseline increases, the set point being the minimum amount needed for baseline. Applying this theory to quinine consumption, however, seems less likely

unless the set point refers to the acceptable level of tolerance to the quinine. Since quinine has aversive effects such as a bitter taste, the only true reinforcing quality to the quinine solution is that it is hydrating to the rat. As previously stated, natural reinforcers often show the opposite of escalation. Seeing as hydration is a natural reinforcer, the set point of a natural reward should not fluctuate greatly. Therefore the escalation in this case may be attributed more to habituation to the negative qualities of the quinine. The short-access group provides evidence for this theory. Given the evidence of the original study, it may seem as though more access should equal more habituation. As stated before, it's possible that the long-access rats had habituated to their daily intake amounts faster than the short-access group. Once they reached this amount, they consumed no more quinine solution.

One area of interest, also seen in Experiment 2, is that there is not a significant increase in the long-access quinine group like there is in the long-access cocaine group. Instead, the short-access quinine group shows significant increases from trial 15 to 26. The long-access group displays a more stable trend, albeit at a higher level of consumption than that of the short-access group. Ahmed and Koob's short-access cocaine group showed little to no increase in drug intake, a trend more similar to the quinine long-access. This may be more evidence for the idea of habituation rather than an increase in a set point. Perhaps if given the same cumulative time for short-access as there was for long-access (for example, 12 x 30 min sessions = 360 min total; 12 x 5 min sessions = 60 min) the short-access quinine rats would have the same overall consumption rates as the long-access. This would make the difference between the two groups a case of time needed to habituate. The stabilization of the long-access group of

quinine could be construed as the rats drinking their average daily intake in one thirty min period, also seen in Experiment 1. These results, however, are only applicable to trials 15 to 26. Ahmed and Koob focused only on the trials after the two week training period. Experiment 3 did not recreate the two-week training process, as seen in Experiment 2, but rather used trials 15 to 26 for statistical analysis.

CHAPTER 5

GENERAL DISCUSSION

Ahmed and Koob (1998) came to the conclusion that when exposed to a drug of abuse for an extended period of time, the amount of drug consumed will gradually increase. The observed escalation is determined by the newly created hedonic set point. The longer the access to the specific drug, the higher the set point becomes; therefore, the required amount of drug to reach even the baseline will be increased. Ahmed and Koob argue that this escalation in set point is the basis behind drug addiction and abuse.

The original thesis of this study was that escalation could be attributed to habituation, or more specifically, habituation to the negative qualities of the drug itself. Quinine was used as the analog to cocaine because of its bitter flavor. Rats would require the adulterated water for hydration, but would also need to habituate to the bitter flavor of the quinine. This was originally perceived to be analogous to a person becoming habituated to the negative initial effects (paranoia, increased heart rate, etc.) of cocaine use. Three separate studies were conducted in order to test habituation vs. escalation in regards to Ahmed and Koob's theory. Each study was modified from the previous study in order to manipulate length of exposure and access to unadulterated water after testing; however, after running three different techniques based on the original Ahmed and Koob study, the results failed to show that habituation was the major factor behind escalation.

This finding does not suggest that escalation is the only possible explanation for the observed effect in Ahmed and Koob's original study. Despite being unable to show that habituation alone accounts for the increase, it is a possibility that habituation plays a role in the escalation process and that this role was not able to be expressed in the conducted experiment. For example, habituation to some degree is seen in the short-access groups in Experiments one and two. In the provided time, the rats gradually became habituated to the bitter taste of the solution. It might be possible to slow down the habituation by decreasing the time limits for both groups even further. Perhaps this would show escalation to a greater degree. The escalation in the short-access group was a trend that was expected in the long-access group, but still provides some evidence that it is possible that it plays a role in the overall escalation and enough to support the idea that escalation is not the only possible explanation.

The argument could also be made that perhaps there is not a design yet that properly tests the Ahmed and Koob study. Three attempts were made in this current study, but it is possible that a design exists. Length of exposure, valence of the stimuli to the subject and type of analogous property are variables that may be adjusted in future testing. Since the rats seemed to adjust to the negative qualities of the quinine water within a certain number of trials, perhaps another design could employ other stimuli with stronger, less habitable negative qualities. Another possibility is the idea that maybe water is less "desirable" a reward when compared to a drug like cocaine. For example, animals seek water when they are thirsty – a strictly physiological response. Drug-seeking behavior, however, can be seen fairly consistently in drug-addicted individuals. The more drug per use results in higher hedonic set points and therefore, stronger

anhedonic states. Anhedonia leads an individual to seek out the drug to get even to baseline levels. This is not a behavior typically seen of a rat unless they are dehydrated. Ceiling effects may also be at play in terms of using water as reward. When sated, the rat will stop drinking. It will not consume more water than it needs in a given time window. The same barriers may not be at play for drug use. Another analogue may achieve the desired escalation of the long-access rats more so than the presented study. For example, rerunning this experiment in a purely operant setting could possibly provide the proper paradigm for testing. Enforcing particular fixed ratio schedules could potentially slow down the short-access group in their habituation allowing for the long-access group to show the escalation they were unable to in this study. Much of the studies presented looked at decreasing the time of the short-access group, however, another study could actually increase time. If given time periods similar to that of Ahmed and Koob's original study, perhaps a greater effect would be seen in the long-access.

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