Relationship between risky decision making and ethanol self-administration in a rodent model

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Abstract

Elevated levels of risk-taking behavior are associated with substance use, but causal relationships between risk taking and substance use are not clear. In a previous study, we used a rat model to show that elevated risk taking predicts subsequent high levels of cocaine self-administration. The goal of this study was to determine whether a similar relationship is present with ethanol self-administration.

Male Long-Evans rats were first characterized in the Risky Decision-making Task (RDT), in which they make discrete-trial choices between two response levers: one which delivers a small, "safe" food reward and the other which delivers a large, "risky" food reward associated with varying probabilities of mild footshock punishment. Rats tested in this task display considerable and reliable individual differences in choice performance, ranging from strong aversion to strong preference for the large, risky reward. Following RDT testing, rats underwent ethanol self-administration procedures. During 13 overnight (14 h) sessions, rats had the opportunity to make an operant response (nosepoke) to gain access to a 20% ethanol solution.

Comparison of RDT performance (% choice of the large, risky reward) with ethanol consumption (g/kg intake) revealed a negative correlation between these two variables, such that higher levels of risk taking were associated with less ethanol intake. This relationship is opposite of that observed with risk taking and cocaine self-administration, and suggests that high levels of risk aversion may be a risk factor for ethanol consumption. However, further research is needed to determine whether this relationship generalizes to other models of ethanol intake.

Introduction

Previously it was discovered that a rat model could demonstrate a direct relationship between risk-taking behavior and cocaine self-administration. More specifically, higher levels of adolescent risk-taking behavior have shown to lead to more frequent self-administration of cocaine (Mitchell et al., Submitted). Furthermore, prior exposure to cocaine causes an increase in risk taking behavior as well as greater impulsive choice in a delay-discounting task (Mendez et al., 2010). Much effort has gone toward exploring the effects of cocaine as well as other stimulant drugs of abuse on risky behavior and vice-versa (Setlow et al., 2009). However, ethanol has been explored to a lesser extent and the previous cocaine studies have led some to believe that there may be a potential relationship between risky-decision making and the propensity to consume ethanol.

A previous study in our lab showed that acute administration of ethanol showed not to affect choice behavior in a risky decision-making task (Mitchell et al., 2011). However, the relationship between chronic ethanol administration and risk taking are unclear. Therefore, this project sought to uncover the possible link between risk-taking in rats and their likelihood to self-administer a 20% ethanol in water solution as a model of human behavior in drug abuse (Simms et al., 2010). This was done by exposing the rats to a series of self-administrations of ethanol followed by sessions in our lab's Risky Decision-making Task (RDT-a rat model of risk taking behavior). This was to detect whether chronic ethanol consumption altered risk taking behavior. A second experiment was conducted in which the rats first underwent sessions of RDT followed by sessions of ethanol self-administration to determine if the rats with a predetermined high level of risky behavior had a higher amount of ethanol consumption in comparison to those of a lower level of risky behavior.

Methods

Subjects

Male Long-Evans rats (obtained from Charles River Laboratories) were housed individually and maintained on a 12-hour light/dark cycle with full access to food and water unless otherwise specified. The first experiment involved 6 adult male Long-Evans rats and the second experiment used 12 adult male Long-Evans rats. The subjects were weighed three times a week and during the ethanol self-administration sessions the rats had unlimited access to food in their cages. Their weights during free feeding ranged from 450 to 550 grams. However, during the Risky Decision-making Task (RDT) their weights were maintained at 85% of free feeding; their weights ranged from 350 to 450 grams.

Apparatus

Ethanol self-administration was conducted in 12 standard behavioral testing chambers (30.5 × 25.4 × 30.5 cm, Coulbourn Instruments, Whitehall, PA) kept in sound-attenuating boxes. Two nosepoke holes located on either side of a front wall in the test chamber could be illuminated by a light within the hole. Between the holes was a trough where a liquid dipper could enter with a specified amount of ethanol upon contact with a particular nosepoke hole. Graphic State 3.0 software (Coulbourn Instruments) recorded data and controlled the delivery of ethanol.

In a separate room, similar rat testing chambers (Coulbourn Instruments, Whitehall, PA) kept in identical boxes to those in the ethanol self-administration were used to conduct the Risky Decision-making Task (RDT). A recessed food pellet trough that could be illuminated with a 1.12 W light was equipped with a photobeam to record the rats' head entries into the trough. The food trough was in the center of the front wall and 2 cm above the floor. It was surrounded by two retractable levers on either side that were 11 cm above the floor. The floor consisted of steel

rods capable of delivering footshocks. On the ceiling of the chamber was an infrared activity monitor to assess locomotor activity (including x, y, and z planes) by relative infrared energy differences upon each detector. Graphic State 3.0 software was also used to record data and control footshock as well as food pellet delivery.

Experiment 1

Ethanol Drinking

Experiment 1 was designed to determine chronic ethanol consumption's effect on the rats' risk-taking behavior. Six male Long-Evans rats (labeled ETH101-ETH106) underwent 17 sessions of ethanol self-administration. These sessions occurred three times a week and went on for 14 hours at a time. The trials began at approximately 8:00 p.m. and continued overnight until approximately 10:00 a.m. the following morning (Sunday-Monday, Tuesday-Wednesday and Thursday-Friday). The rats had two holes on either side of a liquid trough to nosepoke. One hole was illuminated with red light whereas the other hole remained unlit; the holes were counterbalanced between rats to control for any sort of side preference confounding variables. The non-illuminated hole measured nonspecific behavior and the red lit hole activated the liquid trough. When the hole with red light was nosepoked the red light turned off and the liquid trough was simultaneously illuminated with white light. At the same time, the dipper with a 20% ethanol in water solution lifted into the trough for the rat to drink for a duration of 10 s. After the allocated time the light in the trough turned off and the dipper returned to the ethanol cup below the liquid trough where it remained inaccessible to the rat. The red light in the hole for ethanol self-administration turned back on at the same time in preparation for another trial. Motion sensors measured the number of nosepokes in both holes and in the liquid trough. The primary variable of interest was the number of times in each session that rats nosepoked to get ethanol.

Behavioral Procedures

Shaping

Rats first underwent magazine training where they learned to associate the sound of the food hopper spinning and the sound of the food pellets hitting the food trough with the appearance of food pellets in the trough. Rats were then trained to press a lever (that was counterbalanced between rats) for a food pellet while the other lever remained retracted. The rats were required to achieve 50 lever presses within 30 minutes followed by achieving the same requirement under the same conditions with the other lever. Subsequent training included further shaping with both levers retracted and rats having to nosepoke into the food trough while the trough and houselights were illuminated. After a nosepoke either the left or right lever extended and a lever press resulted in delivery of a single food pellet. Rats were required to make 30 lever presses on each lever in 60 min. Shaping required a period of four sessions for the majority of the rats. Some required an extra session if they did not reach the criterion for a particular training stage.

Assessment of Risk Taking

After training the rats completed eighteen 1 h sessions in the risky decision making task (RDT). This offered insight to the degree of preference for risk taking of each rat. Two levers were on either side of a food trough that delivered food pellets on a schedule of continuous reinforcement (fixed ratio: one (FR1)). This meant that after one press of either lever food was delivered into the food trough. These levers were counterbalanced like the nosepoke holes to avoid any sort of side preference confounding variables. One lever delivered a small reward of one food pellet for a response while the other delivered a large reward of three food pellets for a response. However, the large reward came with the possibility of a foot shock punishment. The probability of a foot shock from a large reward response increased every 10 responses. Each

group of 10 responses was considered a block and in each block there was a particular probability of foot shock delivery (0, 25, 50, 75, 100%). The foot shock current was usually maintained at 350 microamps, which is widely considered a less than mildly painful stimulus for the rat. The footshock current was adjusted at the start of the series of sessions to achieve a gradual decrease in responses as the footshock probability increased. If the subjects maintained characteristically similar large reward response frequencies between each footshock probability, then the footshock current was increased and if they showed a characteristically similar low level large reward response, then the current was decreased. After appropriate response modulation, the current was maintained for the remainder of the sessions.

Experiment 2

12 adult male Long-Evans rats (labeled ETO101-112) underwent the same tasks as the ETH group; however they first participated in 25 sessions of RDT followed by 13 sessions of ethanol self-administration rather than the reverse order as the ETH group. The ETO group was further tested on five sessions of 45-minute ethanol self-administration to gain insight to the rate of ethanol consumption reflected during the 14-hour ethanol self-administration sessions. The following week the subjects took on three extinction sessions in which their lever presses no longer caused the liquid dipper trough to provide ethanol. The goal of the extinction sessions was twofold: first, to see if the rats' risk-taking profile (risk taking vs. risk averse) was related to how much they responded during extinction; this can be used as a measure of how motivated the rats were to obtain ethanol. Secondly, extinction reduced the level of responding to low levels, which would make it easier to see an enhancement in responding that might be caused by yohimbine. After the three regular extinction trials was another extinction trial following a yohimbine injection. The yohimbine injection was done to see if making the rats anxious would

increase their motivation to obtain ethanol. Yohimbine has been shown in both rats and humans to induce anxiety; anxiety can cause increased drinking and relapse to drinking. Thus, we wanted to see whether rats risk taking profile was related to the degree to which yohimbine increased their attempts to obtain ethanol.

Statistical Analysis

SPSS 20 was utilized to conduct the data analysis. The rats' stable RDT performance was evaluated with a two-factor repeated measures ANOVA conducted on data from five consistent sessions. Stable performance was defined by a significant main effect on trial blocks and the lack of main effect or interaction involving session (Mitchell et al., Submitted). To explore the relationship between risk taking behavior and ethanol SA, the rats were split into two groups (risk taking and risk averse) based on their RDT performance. Ethanol SA (averaged across all 13 SA sessions) was then compared between the two groups using a t-test. Pearson's correlations were also conducted to directly compare RDT performance (average large rewards choice percent and risky reward average across the 5 blocks) with average ethanol consumption. For each analysis, p values less than 0.05 were significant.

Results

Experiment 1

Rats first achieved a stable ethanol SA before undergoing RDT. Secondly, they attained a consistent performance on the RDT during adulthood and varied largely in individual choice preference (Figure 1).

Ethanol Consumption and the Relationship to Risk Taking Behavior

To understand the relationship between ethanol self-administration and risk taking, the rats were

split into subgroups: risk averse and risk taking. In comparing the subgroups, no significant difference in ethanol self-administration between the risk averse and risk taking rats was discovered ($t(4)=1.15$, $p=0.32$).

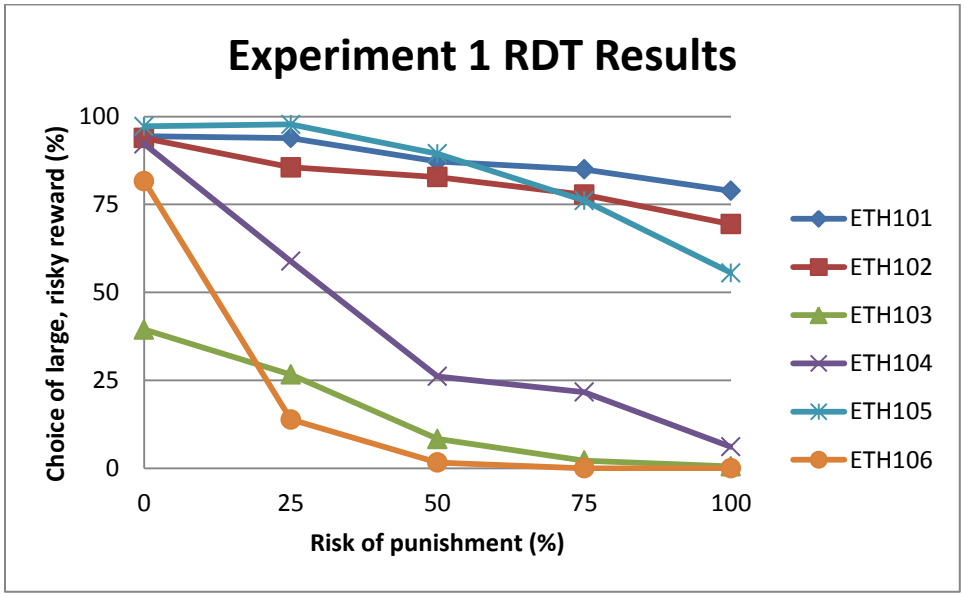

Figure 1

Experiment 2

After experiment 1, 12 new rats were assessed for risk taking and risk averse behavior in the RDT before ethanol self-administration. Like the rats in experiment 1, these were segregated into risk taking and risk averse groups (median split like experiment 1). When compared with experiment 1, the data indicate that the risk averse rats consumed higher rates of ethanol than their risk taking counterparts (Figure 2), although this difference did not reach statistical significance ($t(10)=1.53$, $p=0.16$).

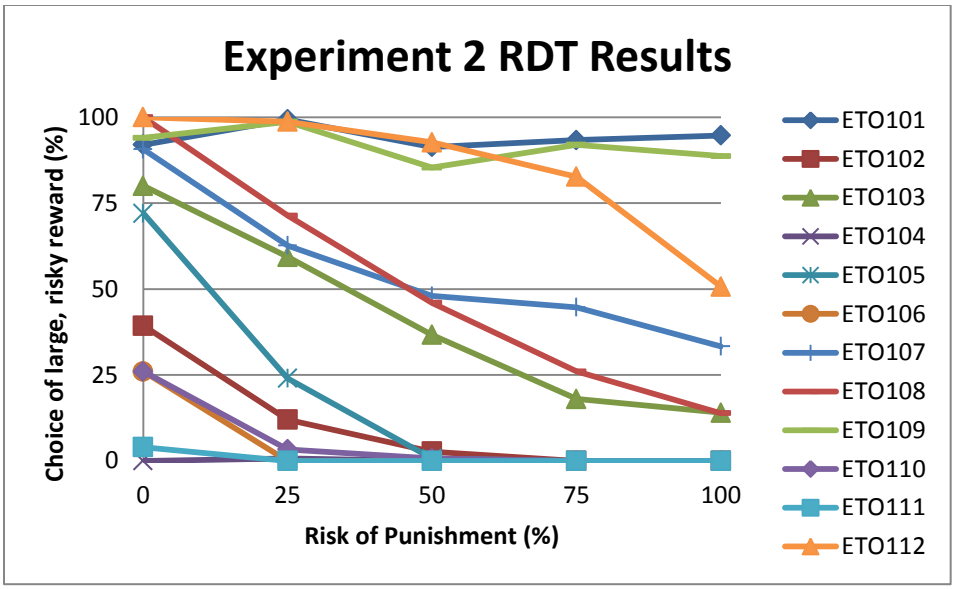

Figure 2

After three regular 45-minute SA extinction trials, the rats experienced a 45-minute extinction trial after an injection of yohimbine. Risk taking and risk averse rats did not differ in their ethanol consumption under either extinction or yohimbine conditions.

Because the sample sizes for Experiments 1 and 2 were small, data from the two were combined in order to determine whether any relationships between risk taking and ethanol consumption were evident with a larger sample size. With this analysis, risk averse rats showed near-significantly greater ethanol consumption compared to risk taking rats ($t(16)=2.04$, $p=0.06$). This relationship was also evident using a Pearson's correlation, which showed that less risk taking (fewer choices of the large, risky reward) was associated with greater ethanol consumption ($r=-0.49$, $p<0.05$). These findings suggest that a risk averse profile of behavior is associated with greater ethanol consumption.

Discussion

Drug use in humans corresponds with elevated levels of risk taking; however causal relationships between the two are difficult to elucidate. The results suggest that lower levels of risk taking in adults may increase susceptibility to higher rates of ethanol consumption. Therefore, the data may indicate a possible association of risk averse behavior as a contributing factor to higher rates of ethanol consumption.

Studies on adult rats showed that measures of impulsive choice and action predicted cocaine SA and similar studies conducted by our lab led us to believe that similar relationships might exist in regard to ethanol SA (Dalley et al., 2007). However, the experiments described above indicated the opposite of the predicted relationship. Future research could be conducted to explore other possible reasons behind ethanol abuse and addiction. Notably, the differences in choice and SA behavior between the risk taking and risk averse subgroups was not because of differential learning abilities, as demonstrated by one of our previous experiments in which rats did not differ on the visual discrimination task or delayed response working memory task, which were conducted in similar rat chambers in this experiment (Shimp et al., Submitted).

Steady escalating rates of ethanol consumption is consistent with literature that showed acquisition phases of 20% ethanol groups drinking significantly more ethanol than others consuming 10% with a sucrose fade as well as having a greater blood ethanol concentration (Simms et al., 2010). It should also be noted that increases in choice of large reward after SA of drugs of abuse (i.e. cocaine) was not likely because of perseverative choice behavior nor increased preference for large rewards (Mendez et al., 2010; Mitchell et al., Submitted).

In experiment 2, a negative correlation was found when comparing RDT performance (% choice of large, risky rewards) with ethanol consumption (g/kg intake) in which higher rates of risk

taking was more characteristic of lower ethanol consumption. These results oppose what has been previously discovered with risk taking behavior and cocaine SA, which could reflect that higher rates of risk aversion could be a contributing factor for higher rates of ethanol consumption (Mitchell et al., 2011). However, because risk aversion can be associated with anxiety, and anxiety can predict ethanol consumption, further research is needed to determine whether anxiety mediates the relationship between risk aversion and ethanol consumption.

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