ELSEVIER

Pharmacology, Biochemistry and Behavior 68 (2001) 685–690

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Behavioral sensitization to ethanol in rats: evidence from the Sprague–Dawley strain

Brian A. Hoshaw, Michael J. Lewis*

Psychology Department, Temple University, Philadelphia, PA 19122, USA

Received 11 September 2000; received in revised form 3 December 2000; accepted 3 January 2001

Abstract

Although it has been shown with other drugs of abuse, behavioral sensitization has not been shown with ethanol in rats. One possible reason for the negative previous findings may be due to the doses of ethanol employed in the different phases of sensitization. In the current experiment, outbred Sprague–Dawley rats were divided into either high or low responders to novelty. They were pretreated for 15 days with intraperitoneal injections of either saline or 1.0 g/kg ethanol, and then given a challenge dose of 0.25 g/kg ethanol after a 3-week period. During the first 10 min after the challenge dose, rats high in response to novelty pretreated with ethanol displayed higher locomotor activity scores relative to the other three groups. These data demonstrated evidence for behavioral sensitization with ethanol in outbred rats.

Keywords: Ethanol; Behavioral sensitization; Rat; Response to novelty; Dose

1. Introduction

Behavioral sensitization is defined as an increase in the locomotor-stimulating effect of a drug after repeated administration (Robinson and Becker, 1986). When amphetamine is repeatedly injected into rats, the locomotor-stimulating effect is enhanced (for review, see Kalivas and Stewart, 1991). Sensitization also has been shown with cocaine, morphine, and nicotine, and is proposed to be a key component in drug addiction (Hunt and Lands, 1992; Robinson and Berridge, 1993).

Repeated activation of the mesolimbic dopamine system is believed to be key to the development of behavioral sensitization. Multiple infusions of amphetamine into the ventral tegmental area (VTA) leads to sensitization when followed by a systemic challenge dose of amphetamine (Vezina, 1993) or morphine (Vezina and Stewart, 1990). Furthermore, the induction of sensitization can be blocked by infusions of the dopamine antagonist Sch-23390 into the VTA (Stewart and Vezina, 1989). Other evidence for the role of dopamine in sensitization comes from the finding that repeated injections of bromocriptine, a D_2 agonist, leads to sensitization of subsequent injections (Hoffman and Wise, 1992). There is also evidence that cross-sensitization occurs between morphine and amphetamine (Vezina and Stewart, 1990), cocaine and amphetamine (Bonata et al., 1997; Pierce and Kalivas, 1995), and ethanol and morphine (Netsby et al., 1997). Behavioral sensitization is not limited to drugs of abuse. Repeated administration of stressors, such as foot shock, can also lead to an augmentation of the locomotor-stimulating effects of amphetamine (Herman et al., 1984).

Ethanol-induced sensitization has been shown in certain strains of mice (Masur et al., 1986; Phillips, 1997). However, to date, there is only one study that has reported ethanol-induced sensitization in the rat (Goldstein et al., 1992). One of the reasons for the failure to observe ethanol-induced sensitization may be the lack of a strong stimulatory effect of ethanol with outbred rat strains as compared to many mouse strains. Though certain mouse strains show a pronounced increase in locomotor activity with a wide range of doses, a dose of 0.75 g/kg and above usually produces only depressant effects in rats. The stimulatory effects of ethanol in rats is only found with low doses (0.10–0.50 g/kg), and only in subgroups of randomly bred rats (Gingras and Cools, 1996; Moore et al., 1993; Pohorecky, 1977; Read et al., 1966).

* Corresponding author. Tel.: +1-215-204-6554; fax: +1-215-204-5539.

E-mail address: mjLewis@temple.edu (M.J. Lewis).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00489-0

The failure to observe ethanol-induced sensitization may also be due to differences in the processes involved with the induction and expression phases of sensitization. During the *induction* phase, the drug is repeatedly administered over a 7–15-day period (Netsby et al., 1997; Stewart and Vezina, 1989). The *expression* phase, which occurs after this initial phase, is when the 'challenge dose' of the drug is administered, resulting in increased locomotor activity (for review, see Kalivas and Stewart, 1991). The two phases may be separate processes in that they may involve different brain areas. It has been shown that activation of the VTA is necessary for the induction of sensitization, since amphetamine infused into the VTA, but not the nucleus accumbens, sensitizes rats to systemic amphetamine (Peruguini and Vezina, 1994) and morphine (Vezina and Stewart, 1990). Also, the dopamine antagonist Sch-23390 infused in the VTA blocks the development of sensitization to amphetamine (Stewart and Vezina, 1989). As a result of this line of research, it has been suggested that the 'neurobiological substrates' for the two phases may be completely independent (Cadoe et al., 1995).

In previous attempts to show ethanol-induced sensitization in rats (Masur et al., 1986; Netsby et al., 1997), the dose of ethanol used for the induction and expression phase were the same. However, it is possible that the low doses that are needed to show the increase in locomotor activity during the expression phase (0.10–0.50 g/kg, Gingras and Cools, 1996; Moore et al., 1993; Pohorecky, 1977; Read et al., 1966) are not enough to cause the neuroadaptive changes necessary to produce sensitization during the induction phase. Likewise, the higher doses, which may be needed for the induction phase, are too high to show the increase in locomotor activity during the expression phase. If the same dose is used for both phases, then either the expression or induction phase would not take place.

Evidence that the difference in required dose between induction and expression may be a factor in the observance of sensitization with ethanol comes from the finding that rats given 1.0 g/kg of ethanol for 15 days show cross-sensitization to 5.0 mg/kg of morphine (Netsby et al., 1997). However, the investigators did not show sensitization to ethanol. Here, the dose of ethanol used to induce sensitization (1.0 g/kg) was apparently sufficient to produce cross-sensitization with morphine, but was too high to observe sensitization to ethanol. In the rat, 1.0 g/kg of ethanol has only depressant effects on locomotor activity (Lewis and June, 1990; Pohorecky, 1977).

The concept of response to novelty is an important factor in ethanol and drug abuse, and may play a role in sensitization to ethanol. It has been shown that when rats are divided into either high or low responders to novelty based on their locomotor activity during their first 2-h presentation to a circular corridor, the high responders will acquire amphetamine self-administration, while the low responders will not (Piazza et al., 1989). In this same study, there was also a significant positive correlation between response to novelty and increase in locomotor activity from an injection of amphetamine. Research from this laboratory has shown that rats classified as high responders to novelty consume more ethanol in the first 2 weeks of home cage limited access as compared to low responders to novelty (Hoshaw et al., 1999, 2000). Moreover, we also found a significant positive correlation between response to novelty and ethanol consumption during this 2-week period (Hoshaw et al., 1999). These findings are similar to those of other labs, which reported that rats classified as high responders to novelty initially self-administered more amphetamine as compared to low responders (Pierre and Vezina, 1997). These authors found that this difference disappeared after 7–10 days of exposure (when the rats were not pretreated with amphetamine).

The present experiment examined the differences in ethanol-induced sensitization between high and low responders to novelty by using a higher induction dose than that used to express sensitization. The data presented here shows evidence of ethanol-induced sensitization in outbred rats.

2. Methods

2.1. Subjects

The subjects for the experiment were 40 male Sprague–Dawley rats (Charles River, Wilmington, MA) approximately 225–250 g at the beginning of the experiment. They were maintained on a reverse light/dark cycle, with lights off at 0700 h and on at 1900 h. The rats were given ad libitum access to food and water throughout the experiment, and were housed in single wire mesh hanging cages. After the rats arrived, they were given a week of quarantine. They were then handled and weighed for 1 week before the experiment began.

2.2. Apparatus and equipment

Locomotor activity was defined as distance traveled (in centimeters) and measured by video path analyzers (Coulbourn Instruments, Allentown, PA). The chambers were 50 cm^2, and black paper was placed on the floor of each chamber prior to each session. Locomotor testing was performed during the rat's dark cycle (between 0900 and 1500 h), and only red lights were on in the room during the testing. Between each session, the cages were wiped down with a nonacidic cleaner and the paper was replaced. Isotonic saline was prepared with 0.9% (w/v) NaCl (Sigma, St. Louis, MO) in tap water, and ethanol solutions were prepared by mixing 100% EtOH (Pharmco, Brookfield, CT) with tap water. Each day, a 15% (v/v) solution of ethanol was prepared for the injections, which were given on a gram/kilogram basis. All injections were given intraperitoneally.

2.3. Procedure

2.3.1. Classification

First, the rats were placed in the locomotor chambers for 1 h, and the locomotor activity scores were recorded. The rats were then divided into either high responders to novelty (HR) or low responders to novelty (LR), depending on whether their locomotor scores fell above or below the median of scores. Next, half of each group was randomly placed into either an EtOH (E) group or a saline group (S). Therefore, the four groups are HR-E, HR-S, LR-E, and LR-S.

2.3.2. Induction phase

For the next 15 days, each group was given an injection of either 1.0 g/kg EtOH or the equivalent volume of saline. The injections were administered at approximately 1330 h each day. After these injections, the animals remained in their home cages for 21 days before the challenge dose of ethanol was administered. Studies investigating sensitization with other drugs such as cocaine have shown that a nondrug period (between 7 and 21 days) is often necessary before testing for the expression of sensitization (Kalivas and Duffy, 1993).

2.3.3. Expression phase (challenge dose)

At the end of the 3 weeks, the rats were given a challenge dose of ethanol to test for any differences in locomotor activity between the groups. First, the rats were placed in the locomotor chambers for an hour in order to become acclimated to the testing environment. Next, the rats were taken from the chambers, given an injection of saline and placed back in the locomotor chambers for a half hour. This was done to acclimate the rats to being lifted out of the chamber and injected. Finally, the rats were taken from the locomotor chambers, given a 0.25 g/kg-injection of EtOH, and placed back in the chambers for another half hour.

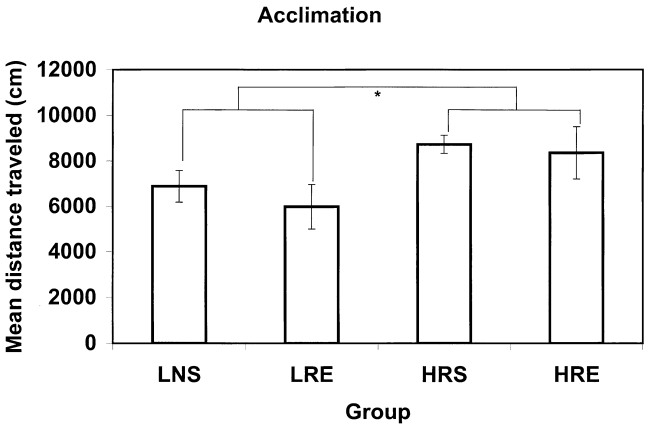

Fig. 1. Shows the mean distance traveled (in centimeters) for the four groups during the 60-min acclimation phase. High (H) and low (L) responders to novelty were pretreated with either ethanol (E) or saline (S) for 15 days prior to the challenge phase. * $P < .05$, represents significant difference between high responders to novelty and low responders to novelty (irregardless of pretreatment condition).

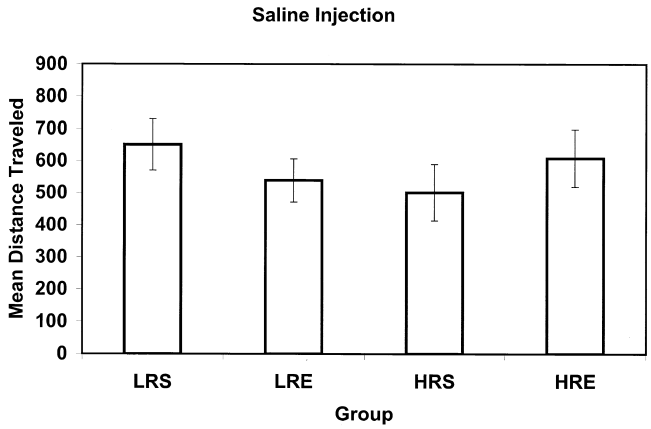

Fig. 2. After 1-h acclimation, the four groups were given an injection of saline, and their locomotor activity scores were monitored. This figure shows the mean distance traveled (in centimeters) for the first 10 min after the saline injection. There were no significant differences between the four groups. (HRE = high responders to novelty pretreated with ethanol, LRE = low responders to novelty pretreated with ethanol, HRS = high responders to novelty pretreated with saline, LRS = low responders to novelty pretreated with saline).

2.4. Data analysis

Locomotor activity scores for each part of the expression phase (acclimation, saline injection and ethanol injection) were compared between the four groups. All tests were performed on data from the challenge day (expression phase). For the acclimation data, the overall activity was compared by two-factor ANOVA, with response to novelty group and drug pretreatment condition as the two factors. For the saline and ethanol injections, the locomotor activity scores during the first 10 min of each phase were compared by two-factor ANOVAs, with response to novelty group and drug pretreatment condition as the two factors. Only the first 10 min was examined because this is when the stimulatory effect of ethanol occurs. Significant differences were further analyzed by tests of simple main effects.

3. Results

The mean locomotor activity scores during the acclimation phase are shown in Fig. 1. Two-factor ANOVA revealed that, although there was not a significant effect for drug pretreatment condition, $F(1,36) = 0.017$, $P > .05$, there was a significant effect for response to novelty group, $F(1,36) = 11.41$, $P < .003$, with the high responders to novelty having higher locomotor activity scores as compared to the low responders to novelty. These data show that, even though this was the second exposure to the

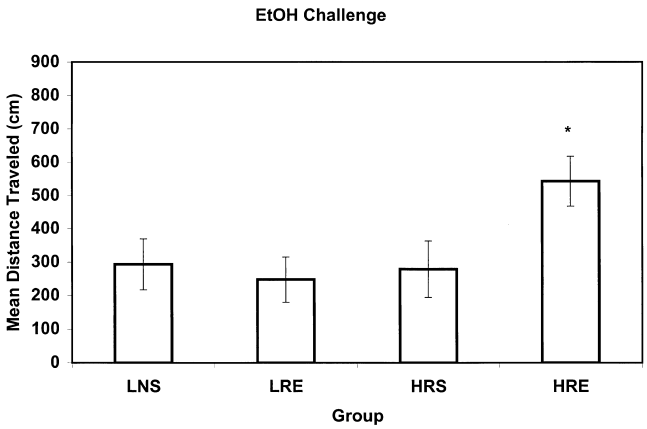

Fig. 3. After the saline injection, the four groups were given a challenge dose of ethanol (0.25 g/kg), and their locomotor activity scores were monitored. This figure shows the mean distance traveled (in centimeters) for the first 10 min after the ethanol injection. Test of simple main effects revealed that the high responders to novelty pretreated with ethanol had significantly higher locomotor activity scores compared to the other three groups. * $P < .02$, represents significant difference between high responders to novelty that were pretreated with ethanol (HRE) and the other three groups. (HRE = high responders to novelty pretreated with ethanol, LRE = low responders to novelty pretreated with ethanol, HRS = high responders to novelty pretreated with saline, LRS = low responders to novelty pretreated with saline).

chamber, there was still a significant difference between the two response to novelty groups in their reaction to the chamber. This difference was not affected by drug pretreatment condition, since there was no interaction between response to novelty group and drug pretreatment condition, $F(1,36) = 1.02$, $P > .05$.

The locomotor activity scores for the first 10 min of the saline phase are shown in Fig. 2. Two-factor ANOVA revealed that there was not a significant effect for response to novelty group, $F(1,36) = 1.10$, $P > .05$, drug pretreatment condition, $F(1,36) = 1.1$, $P > .05$ or interaction, $F(1,36) = 3.01$, $P > .05$. Fig. 3 shows the mean locomotor activity during the first 10 min of the ethanol phase. Two-factor ANOVA revealed that, although there was not a significant effect for response to novelty group, $F(1,36) = 3.34$, $P > .05$, or drug pretreatment condition, $F(1,36) = 2.01$, $P > .05$, there was a significant interaction effect, $F(1,36) = 4.01$, $P < .05$. Tests of simple main effects for drug pretreatment group revealed that, although there was not a significant difference between low responders to novelty pretreated with either saline or ethanol, $F(1,36) = 0.197$, $P > .05$, there was a significant difference between the high responders to novelty. That is, the ethanol pretreated group had higher locomotor activity scores after the challenge dose of ethanol as compared to the saline pretreated group, $F(1,36) = 6.608$, $P < .02$. Although the locomotor activity scores overall were higher during the saline phase than for the ethanol phase, this was due to the animals not being fully acclimated to the locomotor chambers when the saline challenge was administered.

4. Discussion

The results of this experiment show that behavioral sensitization occurs with ethanol in rats. Rats selected as high responders to novelty pretreated with ethanol displayed significantly higher locomotor activity scores during the first 10 min after a challenge dose of ethanol as compared to the other three groups. Since there were no differences between the four groups after the saline challenge injection, it can be concluded that the increase in locomotor activity after the challenge dose is an evidence of sensitization.

Although clearly apparent, the behavioral sensitization found here was not as pronounced as the sensitization observed with other drugs of abuse, such as the psychomotor stimulants, nicotine or morphine. There are two possible explanations for these findings. First, as previously discussed, the stimulatory effects of ethanol are not as easily observed, nor as particularly robust, as they are with other drugs of abuse. Therefore, it is not surprising that the sensitization resulting from repeated doses of ethanol is also not as robust. [Although there is evidence that the stimulatory effect of a drug is not necessary for the initiation phase of sensitization (Vezina, 1993), and that the genetic markers for the stimulatory effect of ethanol and ethanol sensitization are not correlated in mice (Phillips et al., 1995), the stimulatory effect is still necessary for the expression phase of sensitization. That is, the dose of the ethanol used for the expression phase must be within the range of doses where stimulation occurs in order for the expression of sensitization to take place.]

Secondly, it has been shown that environmental cues play a significant role in the stimulatory effects of drugs. For example, when a saline injection is given in the same environment as previous drug injections, there is a conditioned increase in activity. This effect has been shown for amphetamine (Beninger and Hahn, 1983) and morphine (Walter and Kuschinsky, 1989). Rats will also show a conditioned increase in locomotor activity when placed in an environment that has been paired with cocaine infusions into the nucleus accumbens (Hemby et al., 1992).

Environmental cues also play a role in behavioral sensitization. When the challenge dose of a drug, such as amphetamine or cocaine, is given in the same environment as the induction phase, there is a larger increase in activity as compared to when the challenge dose is given in a novel environment (Badiani et al., 1995). Certain drugs, such as the D_2 agonist bromocriptine, will only show behavioral sensitization when the challenge dose is given in the same environment as the injections from the induction phase (Hoffman and Wise, 1992). However, in the current experiment, the induction phase of the experiment took place in the home cages, while the expression phase took place in the locomotor chambers. This aspect of the experiment, combined with the fact that the dose of ethanol used for the induction phase (1.0 g/kg) has only sedative effects (Pohorecky, 1977), may explain why the behavioral sensitization

seen in the current experiment was not as strong as seen with other drugs.

One question that arises whenever chronic administration of any drug is used deals with the role of tolerance. Is the increase in activity seen after the challenge dose a result of sensitization to the stimulatory effect or tolerance to the sedative effect? If the two aspects can be dissociated, then the case for sensitization to the stimulatory effect would have more support. To date, there are only a few experiments that attempted to dissociate the stimulatory and depressant phases of ethanol (Mason et al., 1970; Shippenberg and Altshuler, 1985). Due to the time course of the effect, we feel that the current data presents evidence for sensitization to the stimulatory effect. The motor impairing effects of ethanol in rats generally appear 30–40 min after ethanol administration, during the descending limb of the blood ethanol curve (Lewis and June, 1990; Moore et al., 1993; Pohorecky, 1977). In the current experiment, the difference between the groups appears during the first 10 min after the ethanol injection during the ascending limb of the blood ethanol curve. Furthermore, the dose of ethanol used in the current experiment (0.25 g/kg) is typically too low to see motor impairing effects. However, since the evidence for sensitization presented here is a result of between group differences during the ethanol phase and not within subject differences as compared to the saline phase, it is difficult to rule out tolerance to the motor impairing effects. In addition, there is recent evidence that sensitization and tolerance may be two limbs of a unified process (Reed and Phillips, 2000). In their experiment, there was a high correlation between tolerance to the motor impairing effect and sensitization to the stimulatory effect of ethanol in mice, suggesting that the two cannot be dissociated. Therefore, more research needs to be done comparing sensitization and tolerance to see if the two effects are indeed a part of the same process.

The results found in the present experiment argue for further examination of response to novelty in drug abuse research. This parameter may be of value in predicting vulnerability to the reinforcing effects of drugs. Individual differences in motivational behaviors, such as saccharin intake (Gosnell and Krahn, 1992; Kampov-Polevoy et al., 1990) and impulsivity (Poulos et al., 1995), have been shown to predict ethanol self-administration. It has been proposed that response to novelty may also be a factor predicting drug self-administration, in that rats classified as high responders to novelty self-administer amphetamine, whereas low responders to novelty do not (Piazza et al., 1989). However, this experiment only observed amphetamine self-administration over 4 days. When another study examined high and low responders self-administering over 7 days, it was reported that high responders initially self-administered amphetamine, but only the high responders that were pretreated with amphetamine continued to self-administer (Pierre and Vezina, 1997). Therefore, even though higher levels of response to novelty predicted early self-administration, it also reflected the animals' ability to become sensitized. Since sensitization has been proposed to play a key role in addiction (Hunt and Lands, 1992; Robinson and Berridge, 1993), it should follow that pretreatment with amphetamine, which has been shown to lead to sensitization, would influence subsequent self-administration. It has been proposed that the response to novelty distinction is related to an animal's 'propensity' to become sensitized (Pierre and Vezina, 1997). Though it has been shown to predict self-administration for amphetamine and ethanol, the real value of the response to novelty distinction may be with its role in sensitization. The results of the current experiment are in agreement with the view that response to novelty is related to sensitization, in that rats classified as high responders to novelty became sensitized to a challenge dose of ethanol after repeated exposure.

Although the increase in activity following repeated injections of ethanol was not as substantial as that produced by other drugs of abuse, the evidence for behavioral sensitization with ethanol is an important finding suggesting that, as with other drugs of abuse, ethanol sensitization may play a key role in reinforcement and self-administration.

5. Uncited reference

Vezina and Stewart, 1989

Acknowledgments

The authors would like to thank Kiet Hua for her assistance in the running of the experiment, and Margaret P. Martinetti for her helpful comments on the manuscript. This experiment was supported by the Thomas E. Shipley, Jr. Research Award, and NIDA Grant DA 07237.

References

Badiani A, Browman KE, Robinson TE. Influence of novel versus home environments on sensitization to the psychomotor stimulant effects of cocaine and amphetamine. Brain Res 1995;674:291–8.

Beninger RJ, Hahn BL. Pimozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. Science 1983;220:1304–6.

Bonata P, Swan A, Silverman B. Context-dependent cross-sensitization between cocaine and amphetamine. Life Sci 1997;60:1–7.

Cadoe M, Bjijou Y, Stinus L. Evidence for the complete independence of the neurobiological substrates for the induction and expression of behavioral sensitization to amphetamine. Neuroscience 1995;65:385–95.

Gingras MA, Cools AR. Analysis of the biphasic locomotor response to ethanol in high and low responders to novelty: a study in Nijmen Wistar rats. Psychopharmacology 1996;125:258–64.

Goldstein KR, Knapp DJ, Saiff EI, Pohorecky L, Benjamin D. Sensitization to ethanol demonstrated in place-preference and locomotor activation. Soc Neurosci Abstr 1992;18:107.

Gosnell BA, Krahn DD. The relationship between saccharin and alcohol intake. Alcohol 1992;9:203–6.

Hemby SE, Jones GH, Justice JB, Neill DB. Conditioned locomotor activity but not conditioned place preference following intra-accumbens infusions of cocaine. Psychopharmacology 1992;106:330–6.

Herman JP, Stinsun L, Le Moal M. Repeated stress increases locomotor response to amphetamine. Psychopharmacology 1984;84:431–5.

Hoffman DC, Wise RA. Locomotor-activating effects of the D_2 agonist bromocriptine show environmental-specific sensitization following repeated injections. Psychopharmacology 1992;107:277–84.

Hoshaw BA, Hua K, Lewis MJ. Response to novelty predicts early ethanol administration in Sprague–Dawley rats. Res Soc Alcohol Abstr 1999; 76:18.

Hoshaw BA, Sulkoski J, Lewis MJ. The role of response to novelty in self-administration. Res Soc Alcohol Abstr 2000;53:15.

Hunt WA, Lands WE. A role for behavioral sensitization in uncontrolled ethanol intake. Alcohol 1992;9:327–8.

Kalivas PW, Duffy P. Time course of extracellular dopamine and behavioral sensitization to cocaine: I. Dopamine axon terminals. J Neurosci 1993; 13:266–75.

Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug and stressed-induced sensitization of motor activity. Brain Res Rev 1991;16:223–44.

Kampov-Polevoy AB, Kasheffskaya OP, Sinclair JD. Initial acceptance of ethanol: gustatory factors and patterns of alcohol drinking. Alcohol 1990;7:83–5.

Lewis MJ, June HL. Neurobehavioral studies of ethanol reward and activation. Alcohol 1990;7:213–9.

Mason ST, Corcoran ME, Fibinger HS. Noradrenergic processes involved in the locomotor effects of ethanol. Eur J Pharmacol 1970;54:383–7.

Masur J, De Souza ML, Zwicker AP. The excitatory effect of ethanol: absence in rats, no tolerance and increased sensitivity in mice. Pharmacol, Biochem Behav 1986;24:1225–8.

Moore TO, June HL, Lewis MJ. Ethanol induced stimulation and depression on measures of locomotor activity: effects of basal activity levels in rats. Alcohol 1993;10:537–40.

Netsby P, Vanderschuren LJ, De Vries TJ, Hogenboom F, Wardeh G, Mulder AH, Schoeffelmeer AN. Ethanol, like psychomotor stimulants and morphine, causes long-lasting hyperreactivity of dopamine and acetylcholine neurons of rat nucleus accumbens: possible role in behavioral sensitization. Psychopharmacology 1997;133:69–76.

Peruguini M, Vezina P. Amphetamine administered to the ventral tegmental area sensitizes rats to the locomotor effects of nucleus accumbens amphetamine. J Pharmacol Exp Ther 1994;270:690–6.

Phillips A. Behavioral sensitization to ethanol: genetics and the role of stress. Pharmacol, Biochem Behav 1997;57(3):487–593.

Phillips TJ, Huson M, Gwiazdon C, Burkhart-Kasch S, Shen EH. Effects of acute and repeated ethanol exposures on the locomotor activity of BXD recombinant inbred mice. Alcohol: Clin Exp Res 1995;19(2): 269–78.

Piazza PV, Deminiere JM, Le Moal M, Simon H. Factors that predict individual vulnerability to amphetamine self-administration. Science 1989;245:1511–3.

Pierce RC, Kalivas PW. Amphetamine produces sensitized increases in locomotion and extracellular dopamine preferentially in the nucleus accumbens shell of rats administered repeated cocaine. J Pharmacol Exp Ther 1995;275:1019–29.

Pierre PJ, Vezina P. Predisposition to self-administer amphetamine: the contribution of response to novelty and prior exposure to the drug. Psychopharmacology 1997;129:277–84.

Pohorecky LA. Biphasic action of ethanol. Biobehav Rev 1977;1:231–40.

Poulos CX, Le AD, Parker JL. Impulsivity predicts individual susceptibility to high levels of alcohol self-administration. Behav Pharmacol 1995; 6:810–4.

Read G, Cutting W, Durst A. Comparison of excited phases after sedatives and tranquilizers. Psychopharmacology 1966;1:346–8.

Reed CL, Phillips TJ. Are ethanol sensitization and tolerance limbs of a unified process? Soc Neurosci Abstr 2000;26:1820.

Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine administration. Brain Res Rev 1986; 11:157–98.

Robinson TE, Berridge KC. The neural basis of drug craving: an incentive salience theory of addiction. Brain Res Rev 1993;18:247–91.

Shippenberg TS, Altshuler HL. A drug discrimination analysis of ethanol-induced behavioral excitation and sedation: the role of endogenous opiate pathways. Alcohol 1985;2:197–201.

Stewart J, Vezina P. Microinjections of Sch-23390 into the ventral tegmental area and substantia nigra pars reticulata attenuate the development of sensitization to the locomotor activating effects of systemic amphetamine. Brain Res 1989;495:401–6.

Vezina P. Amphetamine injected into the ventral tegmental area sensitizes the nucleus accumbens dopaminergic response to systemic amphetamine: an in vivo microdialysis study in the rat. Brain Res 1993;605: 332–7.

Vezina P, Stewart J. Amphetamine administered to the ventral tegmental area but not to the nucleus accumbens sensitizes rats to systemic morphine: lack of conditioned effects. Brain Res 1990;516: 99–106.

Walter S, Kuschinsky K. Conditioning of morphine-induced locomotor activity and stereotyped behavior in rats. J Neural Transm 1989; 78:231–47.