Alcohol consumption in male rats increases after sexual interaction

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Abstract

It has been reported that sexual encounters influences not only the subsequent behavior of subjects but also certain physiological states. The purpose of this study was to examine alcohol consumption after different types of sexual interaction in male rats. Male Wistar rats were subjected to a process of induction to alcohol so that they would learn to consume a 10% ethanol solution. Afterwards, they were subjected to four different types of sexual interaction: (1) enforced interval copulation (EIC) to ejaculation (group EIC E); (2) enforced interval copulation up to 3 intromissions (group EIC 3I); (3) *ad libitum* copulation to ejaculation (group ADC E); and (4) *ad libitum* copulation up to 3 intromissions (group ADC 3I). Immediately after the sexual interaction, each rat was exposed to two bottles; one containing water, the other a 10% ethanol solution, for a period of 8 minutes. Only the males that reached ejaculation and those that were allowed to copulate *ad libitum* up to 3 intromissions showed higher alcohol consumption. Considering that sexual behavior activates brain systems that are known to play a role in alcohol intake, such as the dopaminergic and opioidergic systems, it is probable that the activation of these systems brought on by sexual activity could have generated a state of higher motivation to consume alcohol or, alternatively, potentialized its reinforcing properties. These data suggest that alcohol consumption is sensitive to the type of sexual interaction and, hence, to the motivational/arousal state that the male rat experienced prior to exposure to alcohol.

Key words: sexual interaction, alcohol, copulation, rats, enforced interval.

Resumen

Se ha reportado que la conducta sexual no sólo influye en el comportamiento posterior de los sujetos, sino también en ciertos estados fisiológicos. El propósito de este estudio fue examinar el consumo de alcohol después de diferentes tipos de interacción sexual en ratas macho. Ratas Wistar fueron sometidas a un proceso de inducción al alcohol de tal forma que aprendieron a consumir una solución de etanol al 10%. Posteriormente, fueron sometidos a cuatro diferentes tipos de interacción sexual: (1) Cópula de intervalo forzado hasta eyaculación (grupo CIF E), (2) Cópula de intervalo forzado hasta 3 intromisiones (grupo CIF 3I); (3) Cópula *ad libitum* hasta eyaculación (grupo CAD E); y (4) Cópula *ad libitum* hasta 3 intromisiones (grupo CAD 3I). Inmediatamente después de la interacción sexual, cada rata fue expuesta durante un período de 8 minutos, a dos bebederos, uno que contenía agua, y el otro una solución de etanol al 10%. Sólo los machos que llegaron a la eyaculación y a los que se les per-

mitió copular *ad libitum* hasta 3 intromisiones mostraron mayor consumo de alcohol. Ya que el comportamiento sexual activa los sistemas cerebrales que, se sabe, juegan un papel en la ingesta del alcohol, como son los sistemas dopaminérgico y opioidérgico. Es probable que la activación de estos sistemas, provocado por la actividad sexual, pudiera haber generado un estado de mayor motivación para consumir alcohol o, potencializar las propiedades reforzantes de este líquido. Estos datos muestran que el consumo de alcohol es sensible al tipo de interacción sexual y, por lo tanto, al estado de motivación / excitación experimentado por la rata macho antes de la exposición al alcohol.

Palabras clave: interacción sexual, alcohol, copulación, ratas, cópula de intervalo forzado.

Introduction

Sexual behavior includes a hedonic and rewarding component (Whalen 1961; Ågmo & Berenfeld 1990) and its performance influences the subsequent behavior of subjects, as well as certain physiological states. For example, it has been shown that copulatory activity leading to ejaculation in subjects induces a state of relaxation with reduced motor activity and higher aggression levels, compared to subjects that have had no sexual conduct, or that only experienced intromission (Meisel & Sachs 1994; Fernández-Guasti *et al.* 1989). In addition, interrupted copulation and the manipulation of sexual activity produce an aroused state, or alertness, in male rats such that the withdrawal of the female not only reduces the number of intromissions that precede ejaculation but also causes an aroused state that may be manifested in restlessness, motor-hyperactivity, excitement, and intermale aggression (Larsson 1956). There is also evidence indicating that different components of sexual activity can affect both motor activity and learning. In this vein, studies have shown that intromission without ejaculation stimulates motor activation that results in rats taking a shorter time to find their way through a T-maze (Kagan 1955); whereas mounting without intromission was not seen to have this reinforcing effect (Whalen 1961). Changes have also been reported in the quantity, latency and duration of the different phases of sleep in rats immediately after sexual interaction (Boland & Dewsbury 1971; Meerlo & Turek 2001; Vázquez-Palacios *et al.* 2002; Jiménez-Anguiano *et al.* 2002).

Pursuant to their effects on subsequent behavior, the changes in cerebral functionality characteristic of each particular state of copulatory interaction have also been described. For example, it has been demonstrated that the electrical activity in different brain structures shows specific changes in relation to both the appetitive (attention, pursuit of the female, mounting responses), and consummatory (intromission, ejaculation, post-ejaculatory interval) components of sexual interaction (Kurtz *et al.* 1973; Horio *et al.* 1986; Hernández-González *et al.* 1997; Hernández-González *et al.* 1998; Hernández González *et al.* 2007)

Also, many studies have shown that sexual behavior is associated with changes in the activation and levels of several systems of neurotransmitters (Szechman *et al.* 1981; Ågmo & Paredes 1988; Damsma *et al.* 1992; Paredes & Ågmo 1992). Certain microdialysis studies have indicated that extracellular DA in the Accumbens nucleus (Acc) increases when male rats are exposed to inaccessible receptive females (Wenkstern *et al.* 1993), and rises even more during the intromission and ejaculation responses that constitute the consummatory components of male sexual behavior (Pfaus *et al.* 1990; Damsma *et al.* 1992; Hull *et al.* 1993). Increased activation of μ-opioid receptors in the medial preoptic area has also been described (Coolen *et al.* 2004), as have changes in the levels of other neurotransmitters, such as serotonin (Qureshi & Sodersten 1986; Ahlenius *et al.* 1987) and GABA, in several brain structures (Fernandez-Guasti *et al.* 1986; Paredes & Ågmo 1992).

Alcohol consumption is an artificial rewarding behavior that, like copulation and other rewarding behaviors, activates the dopaminergic mesolimbic system through the release of endogenous opioids, DA and other neurotransmitters involved in the functioning of this brain's dopaminergic system. Opioid peptides have been implicated in the reinforcing effects of alcohol and in ethanol-drinking behavior, and it has

been suggested that μ-opioid receptors play an important role in these processes (Koob 1992; Ulm *et al.* 1995; Mendezet *et al.* 2001). This has also been shown with respect to DA. Biochemical and pharmacological evidence suggests that the dopamine mesolimbic system plays a key role in mediating the reinforcing properties of alcohol and other drugs of abuse (Kaczmarek & Kiefer 2000), so that clear increases of this neurotransmitter have been found in the Nucleus Accumbens (Acc), the ventral tegmental area (VTA) and the central nucleus of the amygdala, regardless of the route of alcohol administration (Yoshimoto *et al.* 1991; Yoshimoto *et al.* 1996; Di Chiara *et al.* 1998; Tizabi *et al.* 2002).

Thus, considering that the performance of sexual behavior influences the subsequent conduct of subjects, and that copulatory interaction activates cerebral systems that have been shown to play a role in alcohol intake, the scope of the present work was to investigate the effect of different types of sexual interaction on alcohol consumption in male rats.

Materials and methods

Subjects

Male Wistar rats (n=60) were obtained from a colony bred at the Institute of Neurosciences of the University of Guadalajara. All rats were housed individually in a room at 22–23 °C under a 12:12 h reversed light/dark cycle (lights on from 2000 to 0800 h) with food and water available *ad libitum*. Temperature, feeding and the light/dark cycle conditions were held constant throughout the course of the study. At 80 days of age, all animals were tested for sexual activity in at least three consecutive tests. Only sexually active males (*i.e.*, those with a latency to ejaculation below 15 min) were selected for the experiments. Animal care and all other procedures involving the rats were approved by our Institutional Animal Care and Use Committee, in accordance with NIH specifications.

Period of alcohol induction

For the purpose of familiarizing the rats with the taste of alcohol, all males were subjected to a process of induction to alcohol which consisted in exposing them to water and a solution prepared with tap water and different concentrations of ethanol during a period of 31 days. Phase 1 of the alcohol induction period lasted 12 days. During this phase, the concentration was increased gradually from an initial 2% (99.8% Merck) v/v, by adding an additional 2% every 2 days up to a maximum of 10%. In phase 2, the 10% ethanol concentration was maintained for 10 days (during 24 h) until day 22, when it was clear that alcohol consumption had stabilized. In phase 3 (days 23 to 31 of the alcohol induction period), the male rats were subjected to a repeated process of liquid restriction that lasted for 15 h, from 20:00 h to 11:00 h on the following day, based on previous data that such withdrawal periods may help increase total liquid consumption by rats (Wolffgramm & Heyne 1995). At the end of each day's liquid restriction period, each rat was exposed to two bottles, one with water, the other with a 10% ethanol solution, for a period of 8 minutes. Immediately afterwards, alcohol and water consumption were measured, and a bottle with water was placed for each male rat from 11:30 to 20 h, when the process of liquid restriction began again. This process was maintained during the final 9 days of the period of alcohol induction (to day 31). After that, subjects were assigned to 4 groups (n=15): (1) enforced interval copulation (EIC) to ejaculation (group EIC E); (2) enforced interval copulation up to 3 intromissions (group EIC 3I); (3) *ad libitum* copulation to ejaculation (group ADC E); and, (4) *ad libitum* copulation up to 3 intromissions (group ADC 3I). The rats in each group were subjected to their corresponding sexual interaction tests every third day between 9:00 and 11:00 h (days 32, 35 and 38). At the end of the sexual interaction, the bottles with 10% ethanol and tap water, respectively, were placed such that each male was allowed access for 8 min. On the intervening days (33–34 (D1), 36–37 (D2), when the males had no sexual interaction, they were exposed only to the 8 min of 10% ethanol and tap water consumption at 10:00 h. after that, a bottle with water was placed for each male rat until the next day.

Sexual behavior tests

General: The *ad libitum* and enforced interval sexual behavior tests were conducted in test

cages. The male was allowed to adapt to the test cage for 5 min before the female was introduced. Female rats were given estradiol benzoate (50 µg/rat, SC) and progesterone (500 µg/rat, SC) 48 h and 4-6 h, respectively, prior to being used as stimuli in the tests of the male rats' sexual responses in all experiments.

***Ad libitum* condition:** The *ad libitum* sexual test (free, constant access to the female). The parameters recorded were mount latency (ML) (time in seconds from the introduction of the female into the arena to the first mount); intromission latency (IL) (time in seconds from the introduction of the female into the arena to the first intromission); ejaculation latency (EL) (time in seconds from the first intromission to ejaculation); number of mounts and intromissions preceding ejaculation; and Hit Rate (HR) (number of intromissions divided by the total number of mounts and intromissions). Mounts (M), intromissions (I), and ejaculations (E) were identified on the basis of their particular behavioral characteristics.

EIC condition: Enforced interval copulation tests were performed as described previously by Larsson, 1956. The female was withdrawn for 1 min after the male achieved each intromission up to a total of 3 intromissions (EIC 3I), or until ejaculation (EIC E). Mount and intromission latency, as well as the number of mounts and intromissions preceding ejaculation were recorded.

Statistical analyses

Alcohol consumption after sexual interaction (at 32, 35 and 38 days) was compared with the mean alcohol consumption measured during the intervening days; *i.e.*, 33–34 (D1) and 36–37 (D2). ANOVA (sexual interaction × days) was used to compare water (ml) and alcohol consumption (g/kg). For the copulatory parameters, an ANOVA was applied to compare each type of sexual interaction on all recording days. The copulatory parameters for each sexual interaction at 32, 35 and 38 days were compared with those of the last sexual interaction task to which the male rats were exposed in order to make them sexually active (basal condition).

Results

Water consumption

A significant increase in water consumption was shown during the intervening days —33-34 (D1) and 36-37 (D2)— compared to the days on which the male rats were exposed to different types of sexual interaction [$F(4,224) = 163.51$, $p \leq 0.0001$] (Figures 1 A, B, C, D).

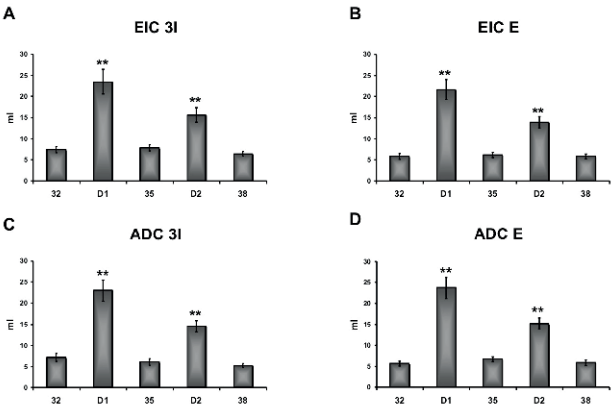

Figure 1. Water consumption (mean ± SE) shown by subjects in the different groups during the 8 min period without previous sexual interaction: 33-34 (D1), 36-37 (D2) and post-sexual interaction (days 32, 35 and 38). ** p<0.01 compared to days 32, 35 and 38.

Ethanol consumption

No significant differences were found in alcohol consumption after EIC 3I (Figure 2A). Immediately after EIC E, subjects showed a significant increase in alcohol consumption on days 32 and 35 [$F(4,224) = 18.10$, $p \leq 0.0001$], compared to the mean for days 33–34 (D1) and 36–37 (D2), when no sexual interaction was allowed, and to day 38's post-sexual interaction (Figure 2B). A similar increase was observed after ADC 3I, when subjects showed elevated alcohol consumption levels during the 3 days when they were allowed sexual interaction (32, 35, 38), as compared to the mean for days 36–37 (D2) (Figure 2C). Subjects in ADC E also showed increased alcohol consumption post-sexual interaction on days 32, 35 and 38, compared to D1 and D2 [$F(4,224) = 18.10$, $p \leq 0.0001$] (Figure 2D).

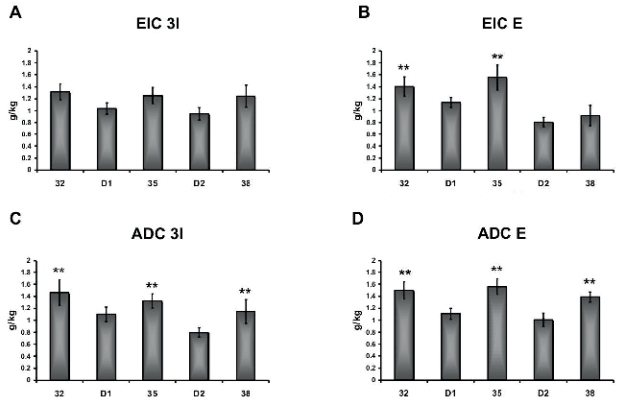

Figure 2. Alcohol consumption (mean ± SE) shown by subjects in the different groups during the 8 min period without previous sexual interaction: 33-34 (D1), 36-37 (D2) and post-sexual interaction (days 32, 35 and 38). ** p<0.01 compared to days D1 and D2.

Copulatory parameters

No significant differences were found in ML, IL, EL and HR with respect to the sexual interaction recorded for the basal condition and days 32, 35 and 38. As expected, the number of mounts shown by subjects during the basal sexual recording test was significantly higher than those shown on days 32, 35 and 38 by EIC 3I [$F(3,56) = 8.27$, $p \leq 0.0001$], EIC E [$F(3,56) = 4.64$, $p \leq 0.0057$] and ADC 3I [$F(3,56) = 8.67$, $p \leq 0.0001$] (Figures 3 A,B,C).

Subjects in the EIC E group showed a higher number of intromissions during the basal sexual interaction recording compared to days 32, 35 and 38 [$F(3,56) = 11.77$, $p \leq 0.0000$]; whereas subjects in ADC E showed no significant changes in this copulatory parameter compared to the later recording days (Figures 4 A, B).

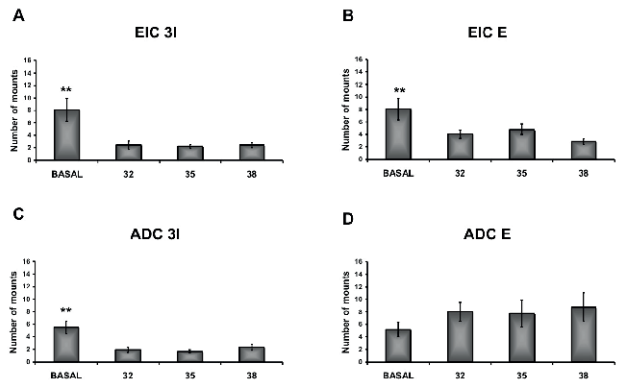

Figure 3. Number of mounts (mean ± SE) shown by subjects in the different groups on the day of the basal ad libitum sexual activity test and on days 32, 35 and 38. **p<0.01 as compared to days 32, 35 and 38.

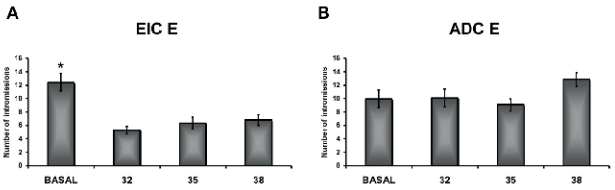

Figure 4. Number of intromissions (mean ± SE) shown by subjects in groups EIC E and ADC E on the days of basal sexual interaction recording, and days 32, 35 and 38. *p<0.01 as compared to days 32, 35 and 38.

Discussion

To the best of our knowledge, this is the first study to evaluate the effect of different types of sexual interaction on alcohol consumption in male rats. The conditions of *ad libitum* copulation up to 3 intromissions and until ejaculation, and the enforced interval copulation with ejaculation, all produced clear increases in ethanol consumption compared to the condition of enforced interval copulation up to 3 intromissions.

Enforced interval copulation (EIC), as described and evaluated by Larsson in 1956, consists in repeated interruptions of copulation by establishing fixed intervals of time between each intromission that the male rat performs during its sexual interaction. This manipulation of male rats' sexual interaction results in a reduction in the number of intromissions required to reach ejaculation, and has been associated with restlessness, motor-hyperactivity, excitement, and inter-male aggression. The behavioral results of the present study agree with Larson's reports, as the males that were subjected to EIC needed a lower number of intromissions to reach ejaculation and, although motor-hyperactivity and excitement were not specifically measured in this work, all males that were subjected to EIC up to 3 intromissions or ejaculation manifested this aroused state during the periods in which the female was removed.

The male rats that were exposed to copula *ad libitum* up to 3 intromissions or to ejaculation were those that showed the largest increases in

alcohol consumption during the three recording days; whereas the subjects in the EIC-to-ejaculation group showed increased consumption only on recording days 32 and 35. Increases in alcohol intake were evident with respect to the intermediate days without sexual interaction, and it was possible to replicate those results over several days. On the intervening days, when the males were not subjected to sexual interaction, water intake increased; whereas on the days when the different types of sexual interaction were allowed, the males showed an increase in alcohol consumption.

No easy explanations are available for these results, though it may be that the neurochemical changes that occur in relation to copulatory behavior will help to elucidate them. One of the main hormonal changes associated with sexual behavior is activation of the hypothalamic-pituitary-adrenal axis (Mason 1972). In fact, it has been shown that the adrenal axis is activated in different copulatory conditions, such as when males are exposed to the mere presence of a receptive female even without physical contact, and when they are allowed to mate *ad libitum* (Bonilla-Jaime *et al.* 2006). An increase in corticosterone levels has been associated with sniffing (Morely & Levine 1982), exploratory behavior (Takahashi *et al.* 1989), attention, motivation (DeWied 1980), alerting (Vazquez-Palacios *et al.* 2001), and an intensification of the reinforcing properties of substances of abuse (Goeders 2002, for a review). There is also evidence that glucocorticoid secretion may exert positive hedonic effects. The reinforcing effects of corticosterone may be mediated by the dopaminergic mesocorticolimbic system, since these neurons contain corticosteroid receptors (Harfstrand *et al.* 1986) and are considered a substrate for the reinforcing effects of various substances of abuse (Goeders 2002; Fernandez-Espejo 2002). In turn, many positively-reinforced activities, including feeding and mating, are associated with elevated secretion of glucocorticoids (Dallman *et al.* 2004; Laugero 2001; Frye *et al.* 1996).

Coolen *et al.* 2004, showed that sexual behavior consisting of only one copulatory series leading to ejaculation induced activation of μ-opioid receptors in the medial preoptic area, which tested the hypothesis that sexual behavior is a biological stimulus for the release of endogenous opioid peptides. Their data are supported by pharmacological manipulations in which the injection of μ-opioid agonists into the VTA increases male sexual behavior (Mitchell & Stewart 1990), while naloxone extends the post-ejaculatory interval (Szechtman *et al.* 1981; Van Furth *et al.* 1994; Van Furth & Van Ree 1996) and inhibits the resumption of mating in sexually-sated males after re-introduction of a female (Miller & Baum 1987). In addition, naloxone blocks the expression of ejaculation-induced place preference (Ågmo & Berenfeld 1990; Mehrara & Baum 1990), indicating that opioids also play a role in the reward-related aspects of sexual behavior. In addition, it has been found that opioid agonists can increase other rewarding behaviors, such as feeding. For example, injections of μ-opioid agonists into the VTA increase eating (Hamilton & Bozarth 1988), whereas naloxone has the opposite effect (Sanger *et al.* 1983; Yeomans & Gray 1997). Similar results have been obtained with water (Goodwin *et al.* 2001; Holter & Spanagel 1999; Carey *et al.* 1981) and alcohol intake behaviors (Juárez & Barrios de Tomasi 2007).

As mentioned previously, it is generally accepted that sexual behavior is rewarding (Whalen 1961), a circumstance that may be due to the liberation of opioid peptides during copulatory behavior. Thus, it is possible that in the present experiment, the rewarding properties of the opioids released during sexual interaction are responsible for the subsequent increases in alcohol intake that were seen immediately after the ejaculation (with or without EIC) and intromission responses in the *ad libitum* conditions.

Many lines of evidence indicate that the dopaminergic mesoaccumbens system is activated by both natural and artificial rewards, and causes an increase in dopamine (DA) levels in the Acc. It is also thought that this DA activity mediates appetitive or approach behaviors triggered by incentive stimuli associated with rewards (Ikemoto & Panksepp 1999; Berridge & Robinson 1998; Blackburn *et al.* 1992). Damsma *et al.* 1992, and various other authors (Pfaus *et al.* 1990; Pleim *et al.* 1990; Wenkstern *et al.* 1993; Hull *et al.* 1993; Fiorino *et al.* 1997, have shown that DA

levels increase in such structures as the Accumbens nucleus (Acc) and ventral tegmental area (VTA) in relation to pre-copulatory and copulatory behaviors. Moreover, certain microdialysis studies have indicated that extracellular DA in the Acc increases when male rats are exposed to inaccessible receptive females (Pfaus *et al.* 1990; Wenkstern *et al.* 1993), and rises even more during copulation (Pleim *et al.* 1990; Damsma *et al.* 1992; Wenkstern *et al.* 1993).

There is a close relationship between the opioid and DA systems. It is well known that the activation of μ-opioid receptors in the VTA leads to an increased release of DA in the accumbens (Spanagel *et al.* 1990; Devine *et al.* 1993). Furthermore, the repeated stimulation of μ-opioid receptors in the VTA leads to a progressive increase in DA-mediated behaviors (such as feeding and sexual activity) and in extracellular DA activity in the Accumbens (Kalivas & Stewart 1991). Intromission and ejaculation responses constitute the consummatory components of male sexual behavior, which induce a reward state that, it has been suggested, results from increased levels of dopamine (Pfaus *et al.* 1990; Spanagel *et al.* 1990; Wenkstern *et al.* 1993; Hull *et al.* 1993; Devine *et al.* 1993, and endogenous opioids in several brain structures (Szechtman *et al.* 1981; Ågmo & Berenfeld 1990). Thus, it is probable that the increased activation of the opioids and DA systems associated with the consummatory acts of sexual behavior could generate a physiological state that increases the motivation for alcohol consumption in male rats.

Another possible explanation is that as a result of the increases in opioid and DA transmission induced by sexual activity, the incentive salience of alcohol is greater and may potentialize the reinforcing properties of ethanol. Certain studies have demonstrated that events that increase extracellular levels of DA in the nucleus accumbens septi (NAS), such as shocking or pinching the tails of rats (Louilot *et al.* 1986; D'Angio *et al.* 1987; Abercrombie *et al.* 1989; Bertolucci-D'Angio *et al.* 1990), induce the performance of motivated behaviors such as feeding (Antelman & Szechtman, 1975; Antelman *et al.* 1975 b and sexual activity (Sachs & Barfield 1974; Antelman *et al.* 1975a; Wang & Hull 1980; Meisel *et al.* 1980; Leyton & Stewart 1990. One interpretation of these observations is that shocking or pinching the tails of rats increases males' state of readiness to respond to incentive stimuli, such that in the presence of an estrous female, or food, this enhanced readiness results in heightened motivation, thus facilitating sexual or feeding behavior. Moreover, it has been shown that certain rewarding behaviors affect the subsequent performance of other natural or "artificial" rewarding behaviors (Antelman & Szechtman 1975; Antelman *et al.* 1975. In the present study, all animals were subjected to an induction process for voluntary alcohol consumption that allowed them to become familiarized with the taste and effects of ethanol, such that it became a reinforcing stimulus. In this sense, it is probable that consummatory sexual acts (mainly when performed without interruption), increase the state of readiness in males to respond to the incentive value of alcohol, thus increasing intake.

Other neurotransmitters have also been implicated in modulating the male rat's sexual behavior; for example, it is known that the concentration of GABA increases more than 1000% in the cerebrospinal fluid after ejaculation (Fernandez-Guasti *et al.* 1986; Paredes & Ågmo 1992). Similarly, an increase in serotonin synthesis in the neostriatum and nucleus accumbens has been found in relation to sexual behavior (Ahlenius *et al.* 1987). Thus, it is likely that the complex interaction among the different neurotransmitters that are released in relation to consummatory sexual acts could generate a major motivation for alcohol consumption by increasing its incentive value and/or the reward value from its consumption. The conditions of this experiment do not allow us to determine whether greater alcohol consumption was associated with increases in different brain neurotransmitters; however, this suggestion is plausible if we take into account the suggestion that various neurotransmitters seem to orchestrate the recompensing profile in relation to ethanol and, therefore, influence the search conduct for that drink (Porrino *et al.* 1998; Kiianmaa *et al.* 2003).

In conclusion, alcohol consumption was only affected by those types of sexual interaction characterized by reaching ejaculation or *ad libi-*

tum copulation up to 3 intromissions; *i.e.*, in the conditions in which the male rats reached the major rewarding state. Thus, these data suggest that alcohol consumption is sensitive to the type of sexual interaction and, hence, to the motivational/arousal state that the male rat experienced prior to exposure to alcohol.

Additional research is required, particularly concerning the pharmacological manipulation and simultaneous measures of the different brain neurotransmitters in order to discern whether the different types of sexual interaction are related to increased or decreased levels and if these, in turn, are related to changes in alcohol consumption; data that could help explain the neurochemical basis of these results.❖

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