PHARMACOLOGY AND CELL METABOLISM

GABA and Glutamate Overflow in the VTA and Ventral Pallidum of Alcohol-Preferring AA and Alcohol-Avoiding ANA Rats after Ethanol

Heidi Kemppainen, Noora Raivio, Harri Nurmi and Kalervo Kiianmaa*

Department of Drugs, Alcohol and Addiction, National Institute for Health and Welfare, Helsinki, Finland
*Corresponding author: Department of Drugs, Alcohol and Addiction, National Institute for Health and Welfare, POB 30, 00271 Helsinki, Finland. Tel: +358-20-610-6000; Fax: +358-20-610-8133; E-mail: kalervo.kiianmaa@thl.fi

(Received 26 June 2009; first review notified 21 August 2009; in revised form 12 October 2009; accepted 16 November 2009)

Abstract — Aims: Earlier findings suggest that dopaminergic neurons are probably not critically involved in ethanol self-administration behavior and in the differential intake of ethanol by the alcohol-preferring AA (Alko Alcohol) and non-preferring ANA (Alko Non-Alcohol) rat lines. The purpose of the present study was, therefore, to clarify the role of GABAergic and glutamatergic afferents and efferents with the mesolimbic dopamine system in the control of ethanol intake as well as in differential intake of ethanol by AA and ANA rats. Methods: The effects of an acute dose of ethanol (1 or 2 g/kg i.p.) on the levels of GABA and glutamate in the ventral pallidum and the ventral tegmental area of AA and ANA rats were monitored with in vivo microdialysis. The concentrations of GABA and glutamate in the dialysates were determined with a high performance liquid chromatography system using fluorescent detection. Results: Ethanol significantly decreased the extracellular levels of GABA in the ventral pallidum but not in the ventral tegmental area. The ANA rats were more sensitive than the AA rats to the suppressive effect of ethanol on pallidal GABA levels. Ethanol did not have any effect on the concentrations of glutamate in either rat line. Conclusions: The suppressive effect of ethanol on the extracellular levels of GABA in the ventral pallidum suggests a role for pallidal GABAergic transmission in the control of ethanol consumption.

INTRODUCTION


Drug-induced increase in dopamine release in the nucleus accumbens is proposed to be a sufficient condition to produce reward, although it may not be a required condition (Koob, 1992; Chick and Erickson, 1996). Studies using post mortem neurochemical techniques as well as in vivo microdialysis or voltammetry have provided evidence that ethanol increases the extracellular concentrations of dopamine in the nucleus accumbens (Kiianmaa et al., 1995; Koob et al., 1998). Numerous studies, however, suggest that the reinforcing effects of ethanol are probably not mediated exclusively through the dopaminergic system and that dopaminergic neurones are not critically involved in the reinforcement from ethanol and in the difference in ethanol intake between the AA and ANA rat lines. For instance, destruction of the mesolimbic dopamine pathways or dopaminergic terminals in the nucleus accumbens does not attenuate acquisition or maintenance of ethanol self-administration behavior (Kiianmaa et al., 1979; Koistinen et al., 2001).

Besides the mesolimbic dopamine neurons, the afferents and efferents of these neurons have also been seen as important elements of drug reward circuitry and, consequently, as substrates of the reinforcing actions of drugs of abuse (Wise, 2002). Although ethanol directly stimulates mesolimbic dopamine neurons (Brodie et al., 1999), it probably can also modulate their inputs in the VTA (Xiao and Ye, 2008; Xiao et al., 2009). SOURCES OF INPUT ARE, E.G., GLUTAMATERGIC AFFERENTS FROM THE MEDIAL PREFRONTAL CORTEX AS WELL AS FROM THE AMYGDALA, PEDUNCULOPONTINE SEGMENTAL NUCLEUS AND LATERODORSAL PONTINE SEGMENTAL NUCLEUS, STRIATUM AND SEGMENTAL GABAERGIC AFFERENTS AS WELL AS CHOLINERGIC FIBERS FROM PEDUNCULOPONTINE AND LATERODORSAL PONTINE SEGMENTAL NUCLEI (Sesack and Pickel, 1992; Wallace et al., 1992; Lavoie and Parent, 1994; Charara et al., 1996).

Reinforcement from ethanol may also be mediated by a mechanism downstream of the nucleus accumbens. The mesolimbic dopamine neurons synapse on GABAergic medium spiny neurons of the nucleus accumbens. One population of the medium spiny neurons also expressing enkephalin projects to the ventral pallidum (VP) and has been viewed as a final common path for drug and other rewards (Wise, 2002; Smith et al., 2009). Therefore, ethanol-induced release of β-endorphin in the nucleus accumbens could probably inhibit medium spiny neurons through dopamine-independent mechanisms (Marinelli et al., 2003, 2005, 2006). Another important input to reward circuitry is the glutamatergic afferents to dopaminergic neurons from the prefrontal cortex (Sesack et al., 1989, Sesack and Pickel, 1992).
The purpose of the present study was to clarify the role of the GABAergic and glutamatergic afferents and efferents of the mesolimbic dopamine system, especially in the VTA and VP in the regulation of ethanol consumption as well as the differential intake of ethanol by alcohol-preferring AA and alcohol-avoiding ANA rats. More specifically, the effects of an acute dose of ethanol on the extracellular levels of GABA and glutamate in the VP and the VTA of AA and ANA rats were monitored with in vivo microdialysis.

MATERIALS AND METHODS

Animals
Male alcohol-preferring AA, 160 in total, and alcohol-avoiding ANA rats, 132 in total, (National Institute for Health and Welfare, Helsinki, Finland) from generations F_{94–95} were used in the present study. The rats were from 2 to 4 months of age and weighted from 250 to 450 g at the time of surgery. The rats were housed in groups of four or five in plastic cages (Makrolon IV 56 cm × 34 cm × 19 cm) until the implantation of the microdialysis guide cannula. After the surgery, each rat was caged individually in a Plexiglas cage (35 cm × 23 cm × 30 cm) until the end of the experiment with food (SDS RM1, 2.7 mM KCl, 1.2 mM CaCl₂, 0.85 mM MgCl₂·6H₂O, pH ~7.00) was perfused through the probe with a flow rate of 1.5 μl/min using a CMA 100 microinjection pump. Samples were collected with a refrigerated sample collector (Univentor 820, Zejtun, Malta) every 20 min from the VP and every 15 min from the VTA. Baseline samples were collected for 2 h; thereafter, the rats were given an injection of ethanol, 1 or 2 g/kg (12% w/v), or saline, and samples were collected for the next 4 h. The samples were then divided into two vials for separate analysis of GABA and glutamate, and stored at −70°C until analysis.

The neuronal origin of GABA and glutamate was tested with high potassium chloride solution (Rea et al., 2005). After finishing an experiment, 60 mM KCl (in Ringer) solution was perfused through the probe and samples were collected for another 2 h. In total, six control tests were done for glutamate and eight for GABA.

Analyses of GABA and glutamate
The concentrations of GABA and glutamate in the microdialysis samples were determined with high performance liquid chromatography (HPLC). The HPLC system consisted of an isocratic pump with a degasser unit and a refrigerated autoinjector (Hewlett Packard 1100 series, Palo Alto, CA, USA). The concentrations of GABA and glutamate were determined in separate runs using fluorescent detectors (Waters 2475 Multi λ, Milford, MA, USA) for GABA and CMA/280, CMA Microdialysis, Stockholm, Sweden for glutamate) equipped with an 8 μl flow cell and was operated at an excitation wavelength of 330 nm and emission at 440 nm. The columns were Discovery®RP Amide C16 150 × 3 mm i.d., particle size of 5 μm (Supelco, Bellefonte, PA, USA) for GABA and Hichrom Hypersil HSODS-200M 200 × 1 mm i.d., particle size of 5 μm (Hichrom, Berkshire, UK) for glutamate. The microdialysis samples were mixed with 2 μl of o-phthalaldehyde-β-mercaptoethanol for pre-column derivatization, and the injection volumes were 4.5 and 14 μl for glutamate and GABA, respectively. The mobile phase for glutamate was 0.3 M acetic acid buffer containing 16% (v/v) acetonitrile and 0.1 mM Na–EDTA at pH 5.85, and for GABA, 0.1 M acetic acid buffer containing 45% (v/v) methanol and 0.1 mM Na–EDTA at pH 5.12. The flow rate of the mobile phase was set to 0.07 and 0.3 ml/min for glutamate and GABA, respectively. The chromatograms were acquired and processed with Class VP Software (v 6.12, Shimadzu Corporation, Kyoto, Japan). The microdialysis data (in micro molar) were converted into percentages of the baseline consisting of the mean of the four baseline samples, which were not corrected for probe recovery.

Surgery
The rats were anesthetized with halothane (4% during induction for 4 min and 1.5–2% during the surgery) and attached to a stereotactic frame for implantation of a guide cannula (CMA/12, CMA Microdialysis, Stockholm, Sweden) into the brain just above VP or VTA. The coordinates for the microdialysis guide cannula were based on the neurochemical work on VP and VTA were based on the neurochemical work on VP and 5.2 mm posterior to bregma, 0.6 mm lateral to ma, 3.2 mm lateral to midline and 5.1 mm below the dura for the brain just above VP or VTA. The coordinates for the microdialysis guide cannula. After the surgery, each rat was caged individually in a Plexiglas cage (35 cm × 23 cm × 30 cm) until the end of the experiment with food (SDS RM1, 2.7 mM KCl, 1.2 mM CaCl₂, 0.85 mM MgCl₂·6H₂O, pH ~7.00) was perfused through the probe with a flow rate of 1.5 μl/min using a CMA 100 microinjection pump. Samples were collected with a refrigerated sample collector (Univentor 820, Zejtun, Malta) every 20 min from the VP and every 15 min from the VTA. Baseline samples were collected for 2 h; thereafter, the rats were given an injection of ethanol, 1 or 2 g/kg (12% w/v), or saline, and samples were collected for the next 4 h. The samples were then divided into two vials for separate analysis of GABA and glutamate, and stored at −70°C until analysis.

In vivo microdialysis
Microdialysis was performed in the home cages. A probe (CMA/12, membrane length 1 mm for VTA and 2 mm for VP, o.d. 0.5 mm, polycarbonate membrane with a 20-kDa cutoff; CMA Microdialysis, Stockholm, Sweden) was inserted into the guide cannula at 1600 h on the day preceding the experiment and left there without perfusion overnight. In the morning, the rats were tethered to the counterbalancing arm and stereotaxically fastened to the skull with three stainless steel screws and dental cement. Body temperature was kept constant at 37°C during the procedure with a thermostatically controlled thermal mattress. After the surgery, the rats were administered buprenorphine (Temgesic®, 0.05 mg/kg s.c.) once and placed in individual cages. Rats were allowed to recover at least for 5 days during which they were also habituated to the experimental procedures by tethering them to a counterbalancing arm several times.

In vivo microdialysis
Microdialysis was performed in the home cages. A probe (CMA/12, membrane length 1 mm for VTA and 2 mm for VP, o.d. 0.5 mm, polycarbonate membrane with a 20-kDa cutoff; CMA Microdialysis, Stockholm, Sweden) was inserted into the guide cannula at 1600 h on the day preceding the experiment and left there without perfusion overnight. In the morning, the rats were tethered to the counterbalancing arm and stereotaxically fastened to the skull with three stainless steel screws and dental cement. Body temperature was kept constant at 37°C during the procedure with a thermostatically controlled thermal mattress. After the surgery, the rats were administered buprenorphine (Temgesic®, 0.05 mg/kg s.c.) once and placed in individual cages. Rats were allowed to recover at least for 5 days during which they were also habituated to the experimental procedures by tethering them to a counterbalancing arm several times.
Blood ethanol determination

Blood ethanol determination was done for the rats in the VTA groups. For determination, two parallel 10 μl blood samples were taken from all rats and drawn from an incision in the rat’s tail 30 min after the ethanol injection, and blown into 190 μl of distilled water in 22 ml gas chromatograph vials. The samples were stored at −20°C until analysis. They were analyzed with headspace gas chromatography (Perkin Elmer GC 8410 gas chromatograph and HS 40 headspace autosampler, Shelton, CT, USA) as described elsewhere (Nurmi et al., 1994).

Histology

The positions of the probes were verified by fixing the brain in 10% formalin and making frozen 100 μm coronal sections stained with thionine after completion of the experiments. Prior to the experiment, it was decided that data would be analyzed only from rats in which at least 50% of the probe membrane was verified to be in the VP or in the VTA. Histological examination of the microdialysis probe placements showed that all of the samples met these criteria, being collected in the central or caudal portions of the VP or in the central and anterior VTA (Fig. 1).

Chemicals and reagents

Ethanol (Etax A, 96% v/v, Altia, Rajamäki, Finland) was purchased from Berner Ltd (Helsinki, Finland), 2-bromo-2-chloro-1,1,1 trifluoroethane (Halothane BP) from Nicholas Piramal India Ltd (Ennore, Chennai, India) and buprenorphine (Temgesic® 0.3 mg/ml injection fluid) from Schering-Plough (Brussels, Belgium). o-Phthalaldehyde was obtained from Pickering Laboratories (CA, USA) and 2-mercaptoethanol from Merck KGaA (Darmstadt, Germany). The other common reagents were of HPLC quality and were obtained from Sigma-Aldrich (St. Louis, MO, USA) or Merck (Darmstadt, Germany).

Statistical analysis

The microdialysis data were analyzed with a mixed-design, three-way analysis of variance (ANOVA) with treatment (saline, ethanol) and rat line (AA, ANA) as the between-subjects factors and measuring interval (time) as the within-subjects repeated measure. After finding significant main effects, differences within the rat lines were examined with a subsequent repeated measures two-way ANOVA. Post hoc comparisons...
between the group means were conducted using Student’s t-test when appropriate. The criterion for significance was set at 0.05.

RESULTS

Ventral tegmental area

The basal concentrations of GABA in the VTA were 8.13 ± 0.97 nM (mean ± SEM) for the AA and 10.61 ± 1.94 nM for the ANA lines; for glutamate 0.52 ± 0.08 μM for the AA and 0.60 ± 0.09 μM for the ANA lines, respectively. None of differences in the basal extracellular levels of GABA or glutamate between the rat lines were significant.

The effect of acute administration of ethanol on the extracellular levels of GABA and glutamate in the VTA of AA and ANA rats is shown in Figs. 2 and 3. Ethanol did not modify the levels of either GABA or glutamate in the VTA in either rat line.

Ventral pallidum

The basal concentrations of GABA in the VP were 214.3 ± 48.2 and 134.3 ± 25.3 nM for AA and ANA line, respectively. The basal GABA levels did not differ significantly.

The basal concentrations of glutamate were 6.33 ± 0.80 and 3.32 ± 0.63 μM for AA and ANA line, respectively. The level of glutamate was significantly higher in the AA than in the ANA rats [F(1,50) = 7.481; P = 0.009]. Acute injections of ethanol did not modify the extracellular levels of glutamate in the VP of either AA or ANA rats (Fig. 5).

Application of 60 mM KCl doubled the concentration of GABA relative to the baseline verifying that the bulk of the measured concentrations of GABA were of neuronal origin and hence the concentrations reflected true changes in neuro-
Blood ethanol concentrations

The concentrations of ethanol in the tail blood of the rats in the VTA groups taken 30 min after the administration of 1 or 2 g/kg of ethanol i.p. are given in Table 1. The levels did not significantly differ between the two lines.

DISCUSSION

The objective of the present investigation was to clarify the role of the GABAergic and glutamatergic afferents and efferents of the mesolimbic dopamine system in the regulation of ethanol consumption and in the differential intake of ethanol of alcohol-prefering AA and alcohol-avoiding ANA rats by studying the effects of acute administration of ethanol on the extracellular levels of GABA and glutamate in the VP and the VTA of the two rat lines. Ethanol suppressed the levels of GABA in the VP but not in the VTA. Furthermore, the ANA rats seemed to be more sensitive than the AA rats to the effects of ethanol on GABA. Ethanol could not modify the concentrations of glutamate in either VP or VTA.

According to the prevailing hypothesis, dopamine released in the nucleus accumbens inhibits GABAergic medium spiny neurons projecting to the VP, also viewed as a final common path for drug reward (Wise, 2002; Smith et al., 2009). It would appear to be depression of medium spiny neurons’ output, i.e. suppression of GABA release, that is common to various drugs of abuse and could be important for their reinforcing properties (Wise, 2002). In accord with this hypothesis, amphetamine, cocaine and heroin—and now ethanol—have been shown to suppress extracellular levels of GABA in the VP (Bourdelais and Kalivas, 1990; Caille and Parsons, 2004; Tang et al., 2005; Li et al., 2009). Our result is not consistent with an earlier study where pallidal levels of GABA were unchanged after oral administration of 5 ml of 20% ethanol, a dose comparable to the dosage used here (Cowen et al., 1998), but oral administration of ethanol probably results in lower blood ethanol concentrations than intraperitoneal injections, which may be a factor explaining the differential results since the lower dose of ethanol (1 kg/kg i.p.) did not lower the levels of GABA in the present study. Furthermore, in line with the view, excitotoxic lesions of the VP produce changes in intravenous self-administration of cocaine and heroin (Hubner and Koob, 1990; Robledo and Koob, 1993), cocaine injected into the VP increases locomotor activity (Gong et al., 1996) and infusions of a ligand binding at GABA_A1 receptors into the VP reduces ethanol-maintained responding (June et al., 2003). Drug-induced suppression of pallidal release of GABA may result from the modulation of the activity of the medium spiny neurons by the drugs on the level of nucleus accumbens. Ethanol, for instance, can increase the release of dopamine and β-endorphin as well as attenuate glutamatergic transmission in the nucleus accumbens thereby increasing or decreasing inhibitory drive on medium spiny neurons (Kiaunmaa et al., 1995; Selim and Bradberry, 1996; Dalchour et al., 2000; Marinelli et al., 2003, 2005, 2006). Furthermore, dopaminergic input from the mesencephalon as well as glutamatergic terminals from the prefrontal cortex may also exert their effect on GABAergic tone in the VP (Fuller et al., 1987; Sesack et al., 1989; Klitenick et al., 1992a).

The higher sensitivity of the alcohol non-prefering ANA rats than the alcohol-prefering AA rats to the suppressive effect of ethanol on pallidal GABA is, however, opposite to the hypothesis that the reinforcement from ethanol comes from its suppression of GABA release in the ventral pallidum. Assuming that the AA rats get more reinforcement from ethanol than the ANA rats, one might expect more inhibition of medium spiny neurons and overflow of GABA in the VP of ethanol-treated AA than ANA rats. AA rats, however, showed signif-

Table 1. The concentration of ethanol (mM) in the tail blood of alcohol-preferring AA and alcohol-avoiding ANA rats 30 min after intraperitoneal administration of ethanol

<table>
<thead>
<tr>
<th>Ethanol dose (g/kg)</th>
<th>AA</th>
<th>ANA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.2 ± 1.2</td>
<td>15.7 ± 1.7</td>
</tr>
<tr>
<td>2</td>
<td>30.4 ± 3.1</td>
<td>34.5 ± 4.3</td>
</tr>
</tbody>
</table>

Mean ± SEM is given; n = 6–11.
significantly less suppression of GABA levels in the VP than ANA rats. Our results, therefore, suggest that this suppression of GABA release is an effect of ethanol more likely associated with its aversive intoxicating effects than with positive reinforcement. Since ethanol increases the levels of dopamine in the nucleus accumbens of AA and ANA rats in a similar manner, the higher sensitivity of ANA rats is probably not based in differential inhibition of medium spiny neurons by dopamine on the level of nucleus accumbens.

The AA rats obtain much more reinforcement from ethanol than do the ANA rats, but they showed significantly less suppression of GABA levels in the ventral pallidum. Our results suggest that this suppression of GABA release is an effect of ethanol more likely associated with its aversive intoxicating effects than with positive reinforcement.

Glutamatergic input from the prefrontal cortex to VP has been described (Sesack et al., 1989), but the effects of ethanol or other drugs of abuse on the overflow of glutamate in the VP are not well characterized. Ethanol did not modify the extracellular levels of glutamate in the VP in the present study. Somewhat in contrast to this finding, self-administered heroin did not initially have any effect on the levels of glutamate in an earlier study, but an increase was detected subsequent to 1 h of self-administration (Caille and Parsons, 2004). Sizemore et al. (2000) reported small increases in glutamate levels during cocaine self-administration sessions. Furthermore, studies using pallidal microinjections of pharmacological agents selective to metabotropic glutamate receptor 7 have been found to modulate rewarding effects of cocaine (Li et al., 2009), suggesting some involvement of glutamatergic mechanisms in the effects and self-administration of drugs of abuse on the level of VP.

Ethanol, along with several other drugs of abuse, has been shown to stimulate mesolimbic dopamine neurons and increase the release of dopamine in the nucleus accumbens (Brodie et al., 1990, 1999; Kiianmaa et al., 1995). Interestingly, rats also learn to self-administer ethanol into the VTA (Gatto et al., 1994; Rodd-Henricks et al., 2000, 2003; Rodd et al., 2004). It is, however, not clear whether this is based on the effect of ethanol on mesolimbic dopamine neurons or on ethanol modulating their input indirectly via GABAergic, glutamatergic or cholinergic afferents in the VTA (Xiao and Ye, 2008; Xiao et al., 2009).

In the present study, ethanol did not, however, modify the extracellular levels of GABA in the VTA. This result is in agreement with the study of Cowen et al. (1998) where levels of extracellular GABA in the VTA were not significantly affected by oral administration of ethanol to rats. Furthermore, it is also in line with the study of Ojanen et al. (2007) showing that an acute dose of morphine to morphine-naive rats or a challenge dose of ethanol to rats repeatedly treated with morphine did not produce any response in the extracellular levels of GABA in the VTA.

It has been suggested that the excitation of mesolimbic dopaminergic neurons may be attributed to disinhibition produced by a primary inhibitory effect on GABA-containing neurons of the substantia nigra and VTA (Mereu and Gessa, 1985). In line with this view, recent electrophysiological studies have demonstrated that ethanol suppresses GABAergic transmission onto VTA dopamine neurons (Stobbs et al., 2004; Xiao and Ye, 2008). In an analogous manner, it has been suggested that a decrease of GABA release via activation of μ-opioid receptors located on GABAergic interneurons is a principal mechanism mediating actions of morphine and other μ-opioids on dopaminergic transmission in the VTA (Klitnick et al., 1992b; Leite-Morris et al., 2004). Klitnick et al. (1992b) demonstrated a reduction in levels of GABA after administration of morphine through a dialysis probe directly into the VTA. Since no changes in the extracellular levels of GABA were found here, the present results do not support these views. Therefore, the involvement of GABAergic neurons in the VTA in the differential intake of ethanol of AA and ANA rats as well as in the mediation of reinforcement from ethanol remains an open question.

The role of glutamatergic mechanisms in the activation of mesolimbic dopaminergic neurons by drugs of abuse has not been fully clarified either. Earlier studies have reported that an acute dose of cocaine or morphine has no effect while an acute dose of amphetamine can increase the extracellular levels of glutamate in the VTA (Xue et al., 1996; Kalivas and Duffy, 1998; Ojanen et al., 2007). In the present study, an acute dose of ethanol did not modify the extracellular levels of glutamate in the VTA. Acute administration of ethanol has earlier been found to increase the extracellular levels of glutamate in the nucleus accumbens of high-alcohol sensitive rats (HAS) (Dahchour et al., 2000), but the availability of information on the effect of ethanol on glutamatergic transmission in the VTA is very limited. In a previous study, a challenge dose of ethanol did not modify the extracellular levels of glutamate in the VTA of rats repeatedly treated with morphine (Ojanen et al., 2007). In contrast to these findings, a recent electrophysiological study, however, provided evidence of ethanol facilitating glutamatergic transmission to mesolimbic dopaminergic neurons in the VTA (Xiao et al., 2009).

Microdialysis has been widely used to sample GABA and glutamate from the brain. It has, however, been pointed out that there may be problems in detecting subtle changes in amino acid levels with in vivo microdialysis technique, possibly because a portion of amino acids in the extracellular space is derived from sources that are not directly involved in neurotransmission (Frantz et al., 2002). This does not necessarily argue against the functional significance of changes in extracellular amino acid levels in the brain (Nyitray et al., 2006). According to Bourdelais and Kalivas (1992), basal extracellular levels of GABA in the VP may be maintained, at least partially, by ongoing neuronal activity, and that at least 50% of extracellular GABA of VP results from neurotransmission. This is in agreement in the present study in which 60 mM KCl doubled the concentration of GABA, and hence the alterations in the concentrations of GABA reflected true changes in neuronal activity (Rea et al., 2005). Here, KCl did not have any effects on glutamate levels, which might point to a non-neuronal origin of the glutamate and suggest that the present results of measurements of glutamate should be interpreted with caution.

Taken together, in the present study based on the use of the genetic animal model of alcohol-prefering AA and alcohol-avoiding ANA rats, an acute dose of ethanol suppressed the extracellular concentrations of GABA in the VP but not in the VTA. The finding of ethanol-induced suppression of pallidal concentrations of GABA is in agreement with views and earlier findings suggesting a role for striatopallidal mechanisms in the mediation of drug reward and a role for pallidal GA-BAergic transmission in the control of ethanol consumption.
The finding that the ANA seemed to be more sensitive to the suppressive effect of ethanol on the pallidal levels of GABA is, however, not consistent with the view that a decrease of GABA release in the VP causes drug-induced reinforcement. The significance of this finding remains to be characterized. Administration of ethanol to AA and ANA rats produced no changes in the levels of glutamate either in the VP or the VTA.

Acknowledgements — This work was supported by the Academy of Finland. We thank Ms. Leena Tanner-Väisänen and Ms. Pirkko Johansson for their technical assistance.

REFERENCES


Kemppainen et al. 118