Nicotinic Acetylcholine Receptors in the Anterior, but Not Posterior, Ventral Tegmental Area Mediate Ethanol-Induced Elevation of Accumbal Dopamine Levels

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Received February 4, 2008; accepted March 26, 2008

ABSTRACT

Ethanol-induced elevations of accumbal dopamine levels have been linked to the reinforcing properties of the drug. However, it has not yet been demonstrated where the primary point of action of ethanol is in the mesolimbic dopamine system, and there appear to be conflicting findings depending on methodology (electrophysiology, microdialysis, or intracranial self-administration). We have suggested that ethanol acts in the nucleus accumbens (nAc), where it activates a neuronal loop involving ventral tegmental nicotinic acetylcholine receptors (nAChRs) to elevate dopamine levels in the nAc. Application of ethanol in the nAc results in elevated dopamine levels in the same brain region, whereas administration in the anterior ventral tegmental area (VTA) fails to influence dopamine output. In the present study, we were able to repeat these findings. In addition, application of ethanol in the posterior VTA also failed to influence nAc dopamine levels. Perfusion of the nAChR antagonist mecamylamine in the anterior VTA completely blocked the elevation of accumbal dopamine levels observed after ethanol perfusion in nAc, whereas mecamylamine in the posterior VTA had no effect. To detect a possible influence on phasic dopamine release, the dopamine transporter inhibitor nomifensine was included in the accumbal perfusate. In addition, under these conditions, ethanol in the anterior or posterior VTA failed to influence dopamine release in the nAc. These results support previous suggestions of distinct functions of the anterior and posterior VTA and give further evidence for our hypothesis of a nAc-anterior VTA-nAc neuronal circuitry involved in the dopamine-activating effects of ethanol.

The mesolimbic dopamine system is suggested to mediate reward-related behaviors and addictive processes, such as alcoholism and drug addiction (Wise and Rompre, 1989; Koob, 1992). Ethanol elevates dopamine levels in the nucleus accumbens (nAc) in several species, including humans (Boileau et al., 2003), and this elevation is believed to be involved in the stimulatory and reinforcing properties of the drug (for review, see Koob and Le Moal, 2001; Wise, 1998). The mechanisms underlying ethanol activation of this dopamine system are not clearly understood, but increased knowledge of these should enable the development of new, more efficient pharmacotherapies against alcohol abuse and alcoholism.

Our previous microdialysis studies demonstrated no effects on nAc dopamine output by local perfusion of ethanol into the ventral tegmental area (VTA) (Ericson et al., 2003; Löf et al., 2007). Rather, we have suggested that ethanol elevates extracellular dopamine levels in the nAc by acting at glycine receptors in or around the nAc (Molander and Söderpalm, 2005a,b). However, this effect does not appear to be an isolated local phenomenon since antagonism of VTA nicotinic acetylcholine receptors (nAChRs) prevents this dopamine elevation (Söderpalm et al., 2000; Ericson et al., 2003), indicating the VTA as a secondary site involved in nAc dopamine-activating effect of ethanol and pointing to a neuronal nAc-VTA-nAc loop in this regard (Ericson et al., 2006; Höfödt et al., 2006; Chau et al., 2007; for a simplified schematic drawing over the hypothesized neuronal circuitry, see Fig. 1). However, the above-mentioned studies investigating the involvement of the VTA with respect to ethanol-induced dopamine response explored only the anterior VTA.

ABBREVIATIONS: nAc, nucleus accumbens; VTA, ventral tegmental area; nAChR, nicotinic acetylcholine receptor; ANOVA, analysis of variance; PLSD, protected least significant difference test; aVTA, anterior VTA; pVTA, posterior VTA.

http://jpet.aspetjournals.org.

doi:10.1124/jpet.108.137489.
Literature investigating the dopamine enhancing and reinforcing properties of ethanol is contradictory. Although in vivo microdialysis experiments point toward the nAc as a primary target (Wozniak et al., 1991; Yoshimoto et al., 1992; Yim et al., 1997; Ericson et al., 2003; Lof et al., 2007), this does not agree with data from electrophysiological and local self-administration studies. Several findings originating with the study from Gatto et al. (1994) have demonstrated rats to self-administer ethanol into the VTA (Rodd-Henricks et al., 2000; Rodd et al., 2004). More specifically, the animals appear to self-administer the drug into the posterior, but not the anterior, VTA (Rodd-Henricks et al., 2000), indicating functional heterogeneity in this brain region. These studies were based on electrophysiological findings that ethanol increases the firing rate of VTA dopamine neurons in the rat, both in vivo (Gessa et al., 1985) and in vitro (Brodie et al., 1990), and microdialysis findings demonstrating that systemic ethanol elevates dopamine levels in the nAc (Di Chiara and Imperato, 1988; McBride et al., 1999). In addition, it was recently indicated that microinjections of ethanol into the posterior VTA stimulate dopamine release in the nAc (Rodd et al., 2007), which is contrary to our previous data investigating the anterior VTA.

The anterior (-4.8 to -5.2 mm related to bregma) and posterior (-5.3 to -6.3 mm related to bregma) VTAs appear to differ not only with respect to drug self-administration but also in GABA<sub>A</sub> receptor-regulated inhibition (Ikemoto et al., 1997, 1998). Ethanol is suggested to elevate dopamine levels also by either disinhibiting GABAergic interneurons due to direct activation of GABA<sub>A</sub> receptors, thus removing a tonic inhibitory influence, or by influencing burst firing (Grace, 2000). Floresco et al. (2003) demonstrated that separate afferent pathways to the VTA control the firing properties of the dopamine neurons, which in turn separately can influence tonic and phasic levels of dopamine in the nAc. It is thus possible that the lack of a dopamine response in the nAc following ethanol administration into the anterior part of the VTA in our previous experiments is due to technical limitations of the in vivo microdialysis technique, a method that rarely detects fast alterations of neurotransmitter release, such as during burst firing.

In the present study, we wanted to investigate whether ethanol perfused in the posterior VTA elevates dopamine in the nAc, contrary to our previous findings after perfusion in the anterior VTA. We also wanted to explore whether the ethanol-induced increase in accumbal dopamine levels after local ethanol perfusion in the nAc is antagonized by mecamylamine administered in the posterior VTA (in agreement with our previous findings in the anterior VTA). In addition, we investigated the possibility that ethanol perfusion in the posterior or anterior VTAs influences phasic dopamine output, something that is not generally detected by in vivo microdialysis unless the system is pharmacologically manipulated with a dopamine transporter inhibitor.

**Materials and Methods**

**Animals.** Male Wistar rats (Beekay, Stockholm, Sweden) weighing 270 to 350 g were housed four per cage (55 x 35 x 20 cm) at constant room temperature (22°C) and humidity (65%). The animals were kept under regular light-dark conditions (lights on at 7:00 AM and off at 7:00 PM) and had free access to “rat standard feed” (Harlan Teklad, Madison, WI) and tap water. In all experiments, drug-naïve animals were used. Separate groups of rats were used for each drug/concentration. Animals were allowed to adapt for 1 week to the novel environment before any experiment was initiated. This study was approved by the Ethics Committee for Animal Experiments, Göteborg, Sweden (5/04, 337/06).

**Drugs.** Ethanol (Kemetyl, Haninge, Sweden; 300 mM), the non-selective nAChR antagonist mecamylamine (mecamylamine hydrochloride, Sigma-Aldrich, St. Louis, MO; 100 μM), the dopamine transporter inhibitor nomifensine (nomifensine maleate; Sigma-Aldrich; 10 μM), and nicotine (nicotine hydrogen tartrate; Sigma-Aldrich; 1 mM, based on the tartrate salt) were all dissolved in Ringer’s solution and administered via reversed microdialysis.

**Microdialysis Technique.** Rats were anesthetized by isoflurane, mounted into a stereotaxic instrument (David Kopf Instruments, Tujunga, CA), and put on a heating pad to prevent hypothermia during the surgery. Holes were drilled for the placement of two anchoring screws, and two I-shaped dialysis probes were custom made in the laboratory. The dialysis probes were lowered unilaterally into the nAc (A/P, +1.85; M/L, -1.4 mm relative to bregma; and D/V, -7.8 mm relative to dura) and the anterior VTA (A/P, -5.2; M/L, -0.7 mm relative to bregma; and D/V, -8.4 mm relative to dura) or the posterior VTA (A/P, -5.7; M/L, -0.7 mm relative to bregma; and D/V, -8.6 mm relative to dura; Paxinos and Watson, 2007). The nAc dialysis probes were placed in the core-shell border region (suggesting that sampling was done in both the core and the shell of the nAc), and the probes and the anchoring screws were fixed to the skull with Harvard cement (DAB Dental AB, Stockholm, Sweden). After surgery, the rats were allowed to recover for 2 days before the dialysis experiments were initiated. Brain microdialysis experiments were performed in awake and freely moving animals. On the experimental day, the sealed inlet and outlet of the probes were cut open and connected to a microperfusion pump (U-864 Syringe Pump; AgnTho’s AB, Lidingö, Sweden) via a swivel, allowing the animal to move around freely. The probes were perfused with Ringer’s solution at a rate of 2 μl/min, and dialysate samples (40 μl) were collected every 20 min. The rats were perfused with Ringer’s solution for 1 h to obtain a balanced fluid exchange before baseline sampling began. Animals were sacrificed directly after the experiment, brains were removed, and probe placements were verified using a vibroslicer (Campden Instruments Ltd., Lafayette, IN; Fig. 2).

**Biochemical Assay.** To analyze the dopamine content of the dialysate samples, a high-pressure liquid chromatography system was used for the separation and detection of dopamine as described previously (Ericson et al., 2003). To identify the dopamine peak, an external standard was used containing 2.64 fmol/μl dopamine.
Experimental Design. In the first set of experiments, ethanol (300 mM) was perfused in the nAc (n = 8), the anterior VTA (n = 7), or the posterior VTA (n = 9) for 180 min, during which dopamine levels in the nAc were monitored. In the second set of experiments, mecamylamine (100 μM) was perfused in either the anterior part of the VTA (n = 8) or in the posterior part of the VTA (n = 10) 40 min before the initiation of ethanol perfusion (300 mM in the nAc) and concurrent monitoring of extracellular dopamine levels in the nAc. In the third set of experiments, nomifensine (10 μM) was administered in the nAc after the stable baseline had been obtained. After five samples (100 min), ethanol (300 mM) was applied in the anterior VTA (n = 7) or in the posterior VTA (n = 8), and accumbal dopamine levels were monitored for an additional 180 min. A subset of six animals received nicotine (1 mM) either in the anterior (n = 2) or in the posterior (n = 4) part of the VTA to verify that the neurons were capable of further releasing dopamine in the nAc.

Statistics. Data were statistically evaluated using a two-way ANOVA with repeated measures (treatment group × time) followed by Fisher’s protected least significant difference test (PLSD) or paired Student’s t tests. A probability value (p) less than 0.05 was considered statistically significant. All values are expressed as means ± S.E.M.

Results

In the first set of experiments, ethanol (300 mM) or Ringer’s solution was perfused in the nAc, in the anterior VTA, or in the posterior VTA by reversed microdialysis. As previously observed by others and us, ethanol perfused in the nAc elevated the dopamine levels in the same brain region by approximately 40%. However, when perfused in either of the two ventral tegmental regions, no ethanol-induced elevation of dopamine in the nAc was observed compared with Ringer’s perfusion (ANOVA with repeated measures at time 0–80 followed by Fisher’s PLSD; ethanol (nAc) versus Ringer’s solution, p < 0.001; ethanol (nAc) versus ethanol [anterior VTA (aVTA)], p = 0.004; ethanol (nAc) versus ethanol [posterior VTA (pVTA)], p = 0.010; Fig. 3).

In the second set of experiments, we wanted to explore whether nAChRs in the posterior part of the VTA are involved in the ethanol-induced response of nAc dopamine. Thus, the animals were pretreated with the nonselective nAChR antagonist mecamylamine (100 μM) either in the anterior VTA or in the posterior VTA 40 min before initiation of ethanol perfusion (300 mM in the nAc). Mecamylamine per se did not influence the nAc dopamine output either compared with predrug baseline levels or compared with Ringer’s solution-treated animals (Fig. 4, A and B). Pre- and cotreatment with mecamylamine (100 μM) in the anterior VTA completely abolished the ethanol-induced elevation of dopamine in the nAc [Fig. 4A, ANOVA with repeated measures at time 40–120 min followed by Fisher’s PLSD; Ringer’s solution versus mecamylamine (aVTA) + ethanol, p = 0.937; ethanol versus mecamylamine (aVTA) + ethanol, p = 0.005], whereas pre- and cotreatment with mecamylamine in the posterior VTA did not antagonize the ethanol-induced elevation of dopamine levels in the nAc [Fig. 4B, ANOVA with repeated measures at time 40–120 min followed by Fisher’s
Dopamine Ringer solution versus mecamylamine (pVTA) regions. Nicotine increased the dopamine response significantly when applied in any of the two ventral tegmental areas of the brain (Fig. 6A), indicating that ethanol, applied by reversed microdialysis in the VTA, does not influence tonic or phasic firing of dopamine neurons (ANOVA with repeated measures over time points 40 to 120, followed by Fisher’s PLSD, Ringer’s solution versus mecamylamine (pVTA) + ethanol, p = 0.038; ethanol versus mecamylamine (pVTA) + ethanol, p = 0.03; ethanol versus mecamylamine (aVTA) + ethanol, p = 0.937; Ringer’s solution versus mecamylamine (pVTA) + ethanol, p = 0.029; ethanol versus mecamylamine (aVTA) + ethanol, p = 0.577).

In the final set of experiments, the dopamine transporter inhibitor nomifensine (10 μM perfused in the nAc) was administered to the rats after the initial baseline sampling was satisfactory. This resulted in an increase of extracellular dopamine levels in the nAc by approximately 800% (Fig. 5). After 100 min of nomifensine perfusion, ethanol (300 mM) was perfused in either the anterior or the posterior VTA, and dopamine levels were monitored for an additional 3 h. Ethanol did not influence the nAc dopamine output significantly when applied in any of the two ventral tegmental areas of the brain (Fig. 6A), indicating that ethanol, applied by reversed microdialysis in the VTA, does not influence tonic or phasic firing of dopamine neurons (ANOVA with repeated measures at time 100–260 min, p = 0.364). In addition, to verify that the dopamine neurons still were able to respond with dopamine release during nomifensine perfusion, some animals received nicotine (1 mM) in the two different ventral tegmental regions. Nicotine increased the dopamine response significantly when applied in any of the two ventral tegmental areas of the brain (Fig. 6A), indicating that ethanol, applied by reversed microdialysis in the VTA, does not influence tonic or phasic firing of dopamine neurons (ANOVA with repeated measures over time points 40 to 120, followed by Fisher’s PLSD, Ringer’s solution versus mecamylamine (aVTA) + ethanol, p = 0.005; Ringer’s solution versus mecamylamine (aVTA) + ethanol, p = 0.937; Ringer’s solution versus mecamylamine (pVTA) + ethanol, p = 0.577).

Fig. 4. Effect of mecamylamine (100 μM) perfused in the anterior (A) or posterior (B) ventral tegmental area alone or concomitant with ethanol (300 mM in the nAc) on extracellular dopamine levels in the nAc as measured by in vivo microdialysis in awake, freely moving rats. Drug administration was initiated as indicated by the arrows. Data are presented as means ± S.E.M., n = 6 to 10. ANOVA with repeated measures over time points 40 to 120, followed by Fisher’s PLSD; Ringer’s solution versus mecamylamine (aVTA) + ethanol, p = 0.03; ethanol versus mecamylamine (pVTA) + ethanol, p = 0.005; Ringer’s solution versus mecamylamine (pVTA) + ethanol, p = 0.937; Ringer’s solution versus mecamylamine (aVTA) + ethanol, p = 0.577.

Fig. 5. Effect of the dopamine transporter inhibitor nomifensine (10 μM) after local application in the nAc on extracellular dopamine levels in the nAc as measured by in vivo microdialysis in awake, freely moving rats. Drug administration was initiated as indicated by the arrow. Data are presented as means ± S.E.M., n = 29.
nicotine demonstrated an increased dopamine response. Dialysis probe, thus reaching also the posterior VTA (5.2 mm relative to bregma), the drug would have spread some distance from the anterior VTA completely. However, the previous placements of our dialysis probes were restricted to the anterior VTA. In the present study, ethanol perfusion in the posterior VTA also failed to influence nAc dopamine output. This result was not unexpected since it has to be assumed that following 180 min of ethanol perfusion in the anterior VTA (−5.2 mm relative to bregma), the drug would have spread some distance from the dialysis probe, thus reaching also the posterior VTA (−5.3 to −6.3 mm relative to bregma). The current findings are in line with a study performed on genetically selected rat lines AA/ANA, demonstrating no influence on nAc dopamine levels after ethanol perfusion in the posterior VTA (200, 400, and 800 mM perfused at −5.6 relative to bregma; Tuomainen et al., 2003).

It has been claimed that reversed microdialysis of ethanol is pharmacologically irrelevant since presumably much higher ethanol concentrations reach the tissue immediately surrounding the probe during perfusion than following systemic administration (Gonzales et al., 1998; Tuomainen et al., 2003). There are several factors involved when estimating the concentration of a drug outside of the dialysis probe. For ethanol, perfused at a concentration of 300 mM, we estimate a concentration of approximately 50 mM directly outside the probe based on a preliminary study in our laboratory (M. Ericson, E. Löf, R. Stomberg, P. Chau, and B. Söderpalm, unpublished data). However, because ethanol is a small molecule with both hydrophilic and lipophilic properties, there will be a gradient of ethanol in the surrounding area. Nevertheless, it is estimated that the ethanol concentration that reaches the tissue surrounding the dialysis probe is of a similar magnitude as that self-administered by rats into the VTA (150–300 mg% ethanol; Rödd et al., 2004). However, it may be more important to consider how results obtained by reversed microdialysis compare with findings obtained after systemic ethanol administration. Based on the high degree of pharmacological similarity observed after local, systemic, or voluntary oral ethanol administration, we believe that ethanol concentrations up to 300 mM applied by reversed microdialysis in our set-up are relevant. Thus, mecamylamine administration in the VTA blocks the dopamine elevation observed following local accumbal perfusion of ethanol (300 mM) in the nAc, after systemic injection of ethanol and during voluntary ethanol intake (Blomqvist et al., 1997; Ericson et al., 1998, 2003). Likewise, accumbal strychnine blocks the dopamine elevation observed after nAc ethanol perfusion, systemic ethanol, and voluntary ethanol intake (Molander and Söderpalm, 2005b; Molander et al., 2005).

In the second part of the study, we applied mecamylamine in the two anatomically distinct regions of the VTA and observed whether the nAChR antagonist was able to influence the nAc dopamine elevation after accumbal ethanol perfusion. We were able to repeat our finding that mecamylamine applied in the anterior VTA completely antagonizes the ethanol-induced elevation in accumbal dopamine (Ericson et al., 2003), whereas mecamylamine perfused in the posterior VTA did not influence the ethanol-induced dopamine output. These results provide further support for heterogeneity of the VTA, in line with findings from Ikemoto et al. (1997, 1998) demonstrating that rats self-administer picrotoxin into the anterior, but not the posterior, VTA and muscimol into the posterior, but not the anterior, VTA. There appears not only to be distinct areas within the VTA, but the dopamine neurons in these areas also seem to be differentially regulated.

Microdialysis lacks the ability to monitor fast changes in neurotransmitter release; thus, we investigated in a separate set of microdialysis experiments the possibility that ethanol, applied locally in the VTA, influences not tonic, but burst firing of dopamine neurons. In theory, due to a rapid and efficient presynaptic reuptake mechanism, the method of in vivo microdialysis will not detect fast alterations in synaptic neurotransmitter release, as during burst firing. By treating the rats with nomifensine in the nAc, we eliminated the efficient dopamine reuptake mechanism in the last experiment. This manipulation will allow phasically released synaptic dopamine to escape from the synapse and to be detected as elevated extracellular dopamine levels in the dialysate. During treatment with nomifensine, we were still not able to detect any significant alterations in nAc dopamine levels during ethanol perfusion in either of the two ventral tegmental regions, indicating that ethanol in the VTA does not produce phasic dopamine release in the nAc. Furthermore, the lack of any ethanol-induced effect on dopamine levels in the nAc did not appear to be due to for example dopamine depletion, resulting from the massive dopamine output that had been monitored for 5 h, or to compromised neuronal firing, because nicotine perfusion elevated the nAc dopamine response further under the same conditions. It is well established that nicotine increases both tonic and burst dopamine neuronal firing by activating nAChRs in the VTA (Grenhoff et al., 1986; Schilström et al., 2003).

As pointed out in the Introduction and now further underlined by the present results, the available studies on the dopamine activating and reinforcing properties of ethanol appear contradictory. Thus, rats apparently self-administer ethanol into the posterior VTA, but not into the anterior VTA (Rödd-Henricks et al., 2000). These intracerebral self-administration studies further indicate that ethanol applied in the VTA is reinforcing to the rat, and this effect is suggested to be mediated via activation of mesolimbic dopamine neurons. This possibility is supported by electrophysiological studies in vivo and in vitro showing an excitatory effect of ethanol on dopamine neurons (Gessa et al., 1985; Brodie et al., 1990). However, it should be noted that the in vivo electrophysiological studies merely demonstrated dopamine neuronal activation after systemic ethanol administration, which could be either indirectly or directly mediated. Furthermore, the in vitro studies were performed in preparations lacking a multiple...
titude of afferents, which in vivo could be influenced by ethanol in a manner as to cancel out tentative direct excitatory effects, as indicated by the present and previous microdialysis studies failing to detect a dopamine-activating effect of ventral tegmental ethanol (Ericson et al., 2003; Lof et al., 2007). The microdialysis studies instead point toward a primary action of ethanol in the nAc as regards the dopamine-activating and, in extension, reinforcing effects of ethanol. Whether rats self-administer ethanol into the nAc has not been investigated to our knowledge, but we have previously demonstrated that glycine receptors in this area are involved in the dopamine-activating effect of ethanol and that local interference with these receptors in the nAc modulates ethanol consumption (Molander et al., 2005).

There is no doubt that ethanol is present both in the nAc and in the VTA after oral consumption, and several mechanisms could underlie the reinforcing properties of the drug. The reinforcing effects of intra-VTA administrations could for example be mediated via other mechanisms than dopamine activation, and during oral self-administration, both these mechanisms and the dopamine-elevating mechanisms could be involved. Another possible explanation to the discrepancy between the present vivo microdialysis experiments and the intra-VTA self-administration studies is that the conditions differ in a way as to allow dopamine activation in the latter but not the former setup. A third possibility is that dopamine that have to be measured exclusively in the core or the shell of the nAc to detect dopamine activations after ethanol application in the anterior and posterior VTA, respectively, and/or that the measurements would have had to be made in the posterior nAc after the posterior VTA injections. However, the majority of studies relating oral ethanol consumption to accumbal dopamine activation have used the same nAc coordinates as used in the present study (Weiss et al., 1993; Ericson et al., 1998), which in fact was the reason for choosing these. There is no information available indicating whether dopamine in more posterior parts of the nAc relate to oral ethanol intake. A fourth possibility is that the intra-VTA ethanol self-administration findings are irrelevant. It will thus be important to investigate whether the same pharmacology applies to this behavior as to voluntary oral ethanol consumption.

In summary, ethanol elevates nAc dopamine levels after local application in the nAc only but not after perfusion in the anterior or posterior VTA. This is in line with previous microdialysis findings but not in line with in vitro and intracerebral self-administration studies. To explore whether the lack of effect of ethanol in the VTA was due to ethanol-induced influence on phasic rather than tonic dopamine neuronal activity, we treated the animals with the dopamine transporter inhibitor nomifensine. Ethanol applied in either part of the VTA failed to influence nAc dopamine levels under these conditions. Finally, local administration of the nAcChR antagonist mecamylamine in the anterior but not the posterior VTA completely antagonized the accumbal dopamine elevation observed during ethanol perfusion in the nAc. These results support previous suggestions of distinct functions of the anterior and posterior VTA and give further evidence for our hypothesis of an nAc-anterior VTA-nAc neuronal circuitry involved in the dopamine-activating effect of ethanol. These findings would thus encourage further studies on the mechanism(s) of action of ethanol in the nAc and of the nAc-anterior VTA-nAc neuronal circuitry to find new treatment strategies for alcohol use disorders.

References


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