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Ethanol but not acetaldehyde induced changes in brain taurine: a microdialysis study

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Summary. Research has suggested that catalase plays a role in mediating ethanol's psychopharmacological effects. Catalase is an enzyme that oxidizes ethanol to acetaldehyde. It has been reported that when catalase activity is reduced by 3-amino-1,2,4-triazole (AT), rats reduce their intake and preference for ethanol. The present study assessed the effects of AT on the brain amino acids levels following ethanol administration in Wistar rats. The study consisted of three parts. In the first part, we found no effects of acute and chronic intraperitoneally administered acetaldehyde on amino acids dialysate levels in nucleus accumbens. In the second part, AT was administered five hours prior to ethanol or its vehicle. Ethanol significantly affected the levels of taurine in rat pre-treated with AT. In the final part, ethanol was administered following the pre-treatment with AT but the dependent variable was the concentration of ethanol in the brain.

Keywords: 3-Amino-1,2,4- triazole – Ethanol – Acetaldehyde – Microdialysis – Catalase

1 Introduction

Acetaldehyde is the first and important product of ethanol oxidation. Ethanol may be metabolized via alcohol dehydrogenase (ADH) (Raskin and Sokoloff, 1970), oxidized by ascorbic acid (Cohen, 1977), cytocrome P-450 (P450IIEI) (Paul et al., 1977), or catalase (Cohen et al., 1980).

The enzyme catalase is capable of converting ethanol to acetaldehyde in the brain (Cohen et al., 1980; Gill et al., 1992). Catalase activity was shown to correlate significantly and positively with voluntary ethanol consumption in humans (Amit et al., 1999; Koechling and Amit, 1992; Koechling et al., 1995), rats (Amit and Aragon, 1988; Aragon et al., 1985a; Gill et al., 1992) and mice (Koechling and Amit, 1994) suggesting that catalase activity mays be important for ethanol consumption. In addition, inhibition of catalase by 3-amino-1,2,4-triazole (AT) was reported to attenuate the acquisition (Rotzinger et al., 1994) and maintenance (Aragon and Amit, 1992; Koechling and Amit, 1994) of voluntary ethanol consumption. These findings support the notion that the enzyme catalase may play a role in mediating ethanol consumption by decreasing the production of acetaldehyde. Finally, AT administration was shown to attenuate several ethanol-induced behaviours such as conditioned taste aversion (CTA) (Aragon et al., 1991a), locomotor depression (Aragon et al., 1991a), narcosis and lethality (Aragon et al., 1991b) suggesting that catalase and acetaldehyde play an important role in behaviours induced by ethanol.

Brain catalase activity showed a decrease of 40% in animals pretreated with AT independent of the contiguous drug treatment (Aragon et al., 1985b). Furthermore, Sinet et al. (1980) observed in a time course study catalase inhibition of 82–90% in the rat brain for 5 hours following administration of AT (1 g/kg).

Earlier studies produced controversial evidence on the ability of acetaldehyde to traverse the blood-brain barrier (Baranova et al., 1987; Eriksson and Sippel, 1977) and on the residual brain acetaldehyde that could be the result of local ethanol metabolism either by inducible P450IIEI system (Hansson et al., 1990) or by brain catalase (Oshino et al., 1973). The presence of acetaldehyde in the brain is also dependent on the speed at which it is removed from the brain tissues by aldehyde dehydrogenase (ALDH). Pettersson and Kiessling (1976) showed that a low K_m ALDH was important for the oxidation of brain acetaldehyde.

The present experiments have investigated the action of acetaldehyde alone and in combination with ethanol on several excitatory and inhibitory amino acids, which are known to be influenced by ethanol. The mesolimbic dopamine system, with projections from the ventral tegmental area (VTA) of the midbrain to Nucleus Accumbens (NAC), appears to be of particular importance in the mediation of drug reinforcement (Di Chiara and Imperato, 1988; Koob, 1992; Wise et al., 1987) and was, therefore, chosen for these microdialysis studies.

2 Materials and methods

2.1 Animals, conditioning and surgery

Male Wistar rats, 300–350 g, were maintained in a temperature and light controlled environment (12 h light/12 h darkness cycle) with food and water ad libitum. After anesthesia with chloralhydrate (400 mg/kg) a guide cannula was inserted into the NAC using standard stereotaxic techniques (A/P 1.2 mm; M/L 1.4 mm; D/V −5.7 mm) according to the atlas of Paxinos and Watson (1982). The guide cannula was secured to the skull with two steel screws and cranioplastic cement and kept patent with a 26-gauge stainless steel obturator. The dialysis experiments commenced after 4 days of post operation recovery period.

Experiments consisted of three parts. In the first part, we studied the effects of acute and chronic intraperitoneal (i.p.) administration of acetaldehyde on exchanges of amino acids in the NAC. For these assays, a Ringer solution (189 mM NaCl, 3.9 mM KC1, 3.4 mM $CaCl_2$, pH 7.2) was continuously perfused at 1.1 μl/min through the NAC. Perfusates were collected every 20 min in micro centrifuge tubes connected to the outer cannula. After a period of 2 h, during which the perfusate amino acid content stabilised, the rats were administered with either acetaldehyde (20 or 100 mg/kg) or saline and the microperfusate was collected for 20-min time periods for a total of 180 min. Then, acetaldehyde (20 or 100 mg/kg) was administered for 8 days to two groups of rats, while a control group of rats received saline. On Day 8, microdialysis procedure was repeated as described above.

In the second part of the experiments, groups of freely moving rats with microdialysis probes were pre-treated with AT (0.5 g/kg) or saline and five hours later received i.p. injections of either ethanol (1 or 2 g/kg) or saline. Injections were given 2 hours after the microdialysis probe insertion. Microdialysate samples were collected every 20 min over a 3-h period and analysed for the amino acids content by HPLC with electrochemical detection using pre column derivatization.

In the third part, the same study design was applied to measure the brain concentration of ethanol. After injection of ethanol, dialysis samples were collected every 30 minutes for a total of 300 min.

2.2 Brain microdialysis procedure

The dialysis probes were constructed as described by Robinson and Whishaw (Robinson and Whishaw, 1988). Dialysis tubing extended 3 mm beyond the tip of the probe. The probe was connected to a micro-infusion pump (Infusion syringe pump 22, Harvard apparatus) and continuously perfused at 1.1 μl/min with Ringers solution containing 145 mM NaCl, 4 mM KCl, 1.3 mM $CaCl_2$, buffered to pH 7.2 with phosphate buffer.

The derivatizing agent, O-phthaldialdehyde (OPA, 27 mg) was dissolved in 1 ml methanol (HPLC grade) to which 10 μl mercaptoethanol was added. This solution was diluted with 9 ml 0.1 M sodium tetraborate, pH 9.3, and stored at 4°C in the dark. The working solution was freshly prepared by diluting 1 ml of this solution with 3 ml 0.1 M sodium tetraborate. The dialysate sample (15 μl) was mixed with the derivatization solution (10 μl) within the automatic sampler after the internal standard homoserine 5×10^{-6} M had been added. The sample was then injected onto the HPLC system, which consisted of a LDC ConstaMetric 3200 pump delivering 0.93 ml/min of the mobile phase (0.1 M Na_2HPO_4, 0.13 mM EDTA, 27% methanol HPLC grade, 73% water, Millipore grade, pH 6.4) at a pressure of 5300 psi. Separation of the amino acids was achieved by the reversed phase column chromatography, (125 × 3 mm, ODS Hypersil 3 μm) (VDS Optilab, Chromatographie Technik, GmbH) and detected coulometrically (ESA Coulochem II; Bedford, Mass. USA) using three electrodes, a guard (+0.5 V), preoxidation (+0.3 V) and working (+0.52 V) electrodes (analytical cell ESA5011). The position and height of the glutamate and taurine within the dialysates were compared to a solution of amino acids containing glutamate and taurine, 5×10^{-6}, and the areas of each compound quantified by a PC Integration pack (Kontron Instruments) by using the internal standard homoserine which was added to the each sample.

2.3 Histology and statistics

Upon completion of the experiments, rats were killed and the brains fixed with 10% formalin. Coronal sections through the extent of the cannula tracks were cut (100 μm) with a vibratome (Polaron H 1200, Biorad, Cambridge, MA, USA). Dialysis probe placement was localized according to the atlas of Paxinos and Watson (1982).

The results are presented as mean ± standard error. The mean baseline taurine and glutamate levels were calculated by averaging the concentrations of the three perfusate sample values immediately before the injection of ethanol or saline. Then, the glutamate and taurine concentrations in each perfusate were expressed as percentage of the baseline value and analysed by three-way analysis of variance (ANOVA) (factors: saline vs. ethanol, AT vs. saline, time) with repeated measures on one factor (time) followed by the Dunnett's and Bonferroni's tests (SAS-STAT software, ver. 6.11, Cary, NC).

These experiments were approved by the Belgian governmental agency (authorization number LA 1220028) as well as the European Communities Council Directive concerning the Use of Laboratory Animals.

3 Results

3.1 Effects of ethanol

Figure 1 shows the effects of acute ethanol (1 and 2 g/kg) and saline on the extracellular concentrations of taurine and glutamate. Ethanol failed to modify the glutamate concentrations in the microdialysates from the NAC (Fig. 1B). In contrast, ethanol induced rapid and significant increases in taurine concentrations at all doses tested (Fig. 1A). Parametric three-way ANOVA with repeated measures revealed the significant influence of both doses of ethanol on taurine concentrations at 20-min ($F(2,40) = 12.70$, $p < 0.0001$), at 40-min ($F(2,40) = 20.15$, $p < 0.0001$) and at 60-min time points post-ethanol ($F(2,40) = 3.37$, $p = 0.046$). However, the following analysis (Dunnett's Multiple Comparisons test) did not reveal significant differences between saline + ethanol 1 g/kg and saline + saline groups (Fig. 1A). Meanwhile, these differences were significant for 2 g/kg ethanol at 20- and 40-min time points (Fig. 1A).

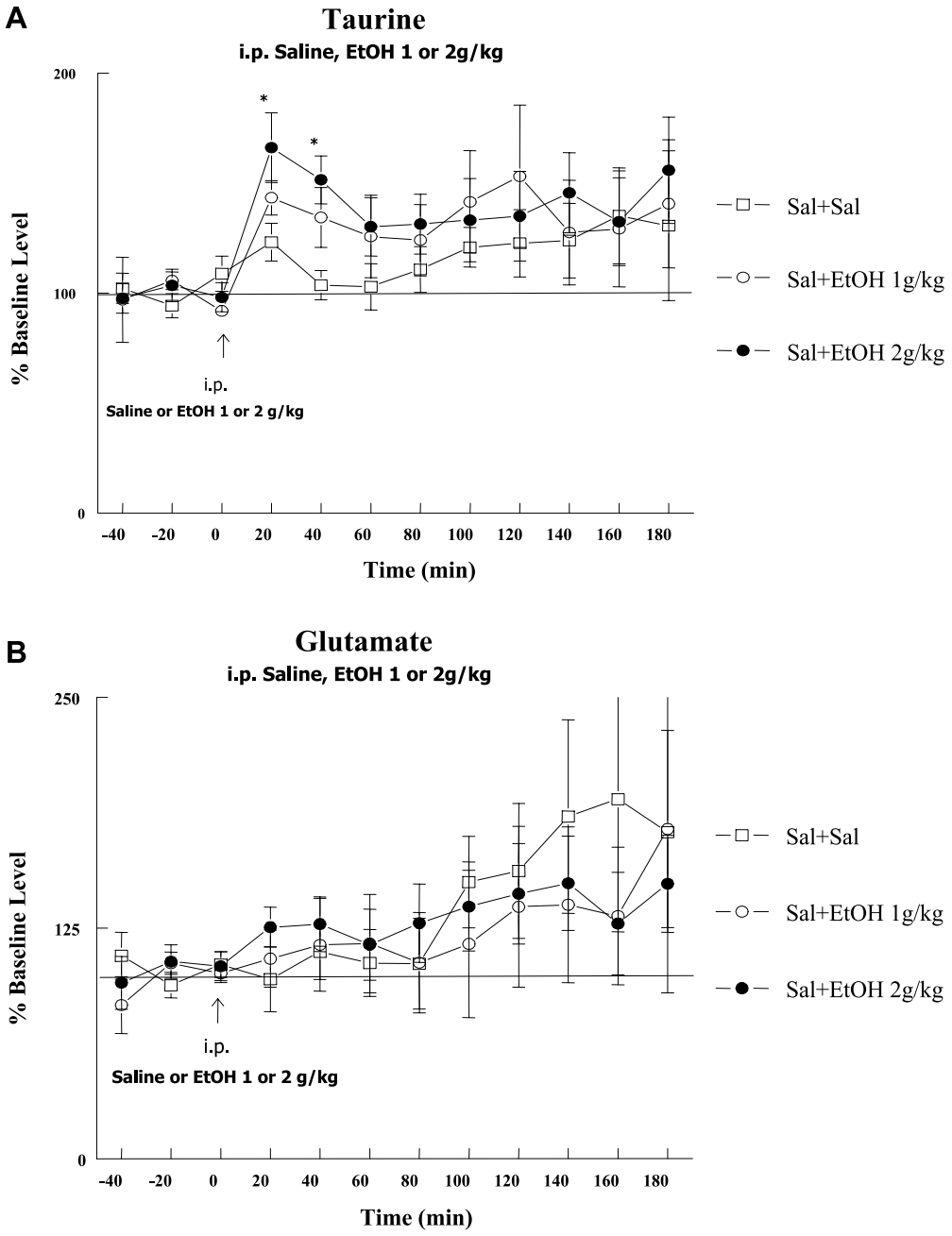

Fig. 1. Effects of an acute injection of ethanol (1, 2 g/kg body weight, IP) or saline on extracellular taurine (**A**), glutamate (**B**) contents of the microdialysate from the nucleus accumbens of naive rats. $^{*}P < 0.05$ relative to respective baseline level

3.2 Effects of ethanol in rats pretreated with 3-amino-1,2,4-triazole

Figure 2 shows the effects of ethanol (1 and 2 g/kg) and saline on the extracellular concentrations of taurine and glutamate after the pretreatment with AT. Ethanol failed to modify the extracellular glutamate concentrations in the microdialysate from the NAC (Fig. 2B) but did cause rapid and significant increases in taurine concentrations at all doses tested (Fig. 2A). Parametric three-way ANOVA with repeated measures revealed the significant influence of both doses of ethanol on the taurine concentrations only at the first 20-min time point post-ethanol ($F(1,40) = 4.19$, $p = 0.0483$). Post hoc comparisons confirmed statistically significant effects of both doses of ethanol on taurine concentration at 20, 40 and 60 min time points.

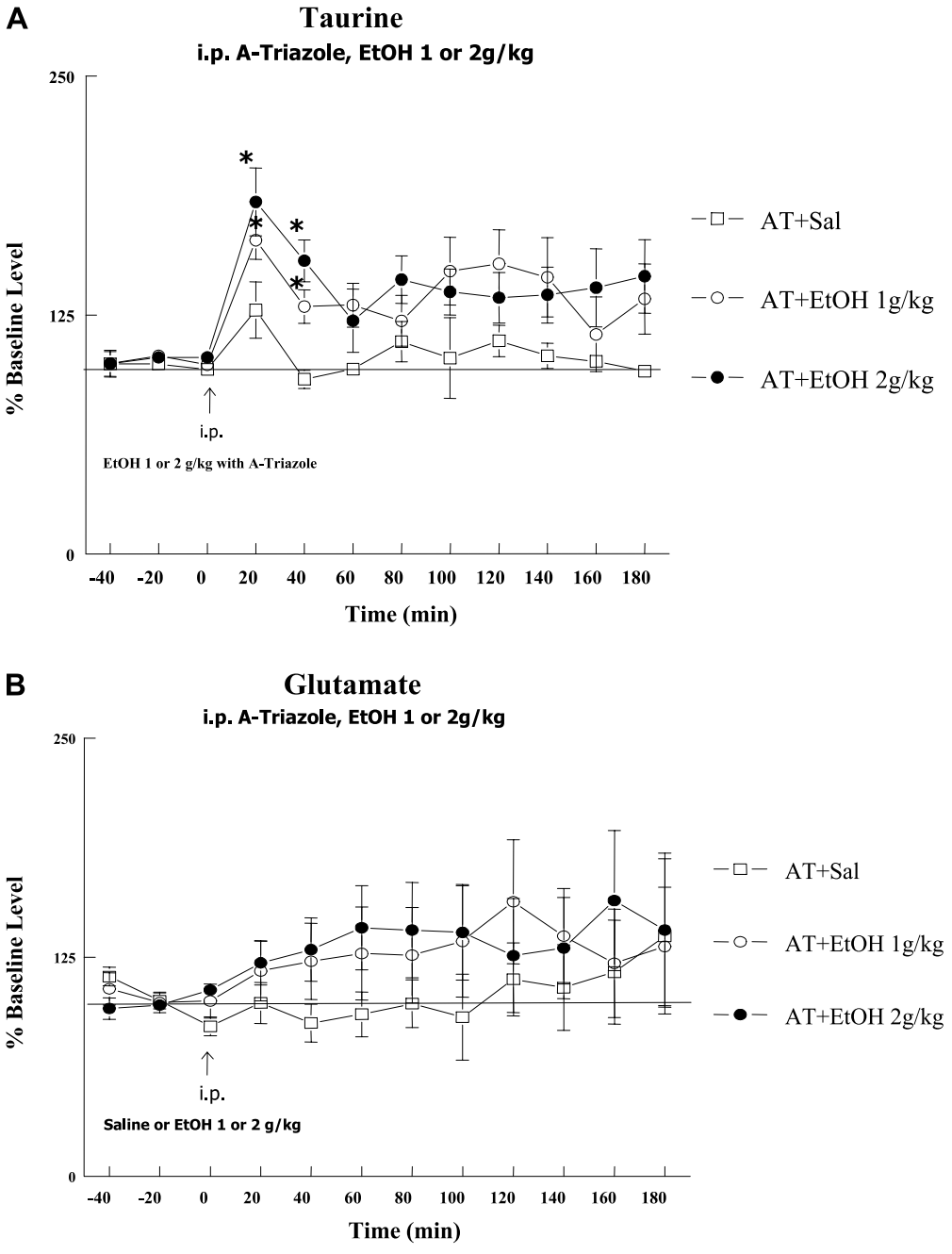

Fig. 2. Effects of an acute injection of ethanol (1, 2 g/kg body weight, IP) or saline on extracellular taurine (**A**), glutamate (**B**) content of the microdialysate from the nucleus accumbens after a pre-treatment of 3-amino-1,2,4-triazole ethanol-treated rats AT. $^{*}P < 0.05$ relative to respective baseline level

3.3 Effects of acetaldehyde

It was found that neither acute nor chronic acetaldehyde affected microdialysis contents of taurine or glutamate (Fig. 3A–B and Fig. 4A–B) as well as the other amino acids in the NAC. The excitatory amino acids, glutamate and aspartate, together with the inhibitory amino acids, taurine and GABA, showed no significant change in their extracellular concentration after acute and chronic administration of either doses (20 and 100 mg/kg) of acetaldehyde.

3.4 Ethanol brain concentration

Figure 5 reveals the concentration of ethanol in the NAC after i.p. administration at the doses of 1 and 2 g/kg in rats

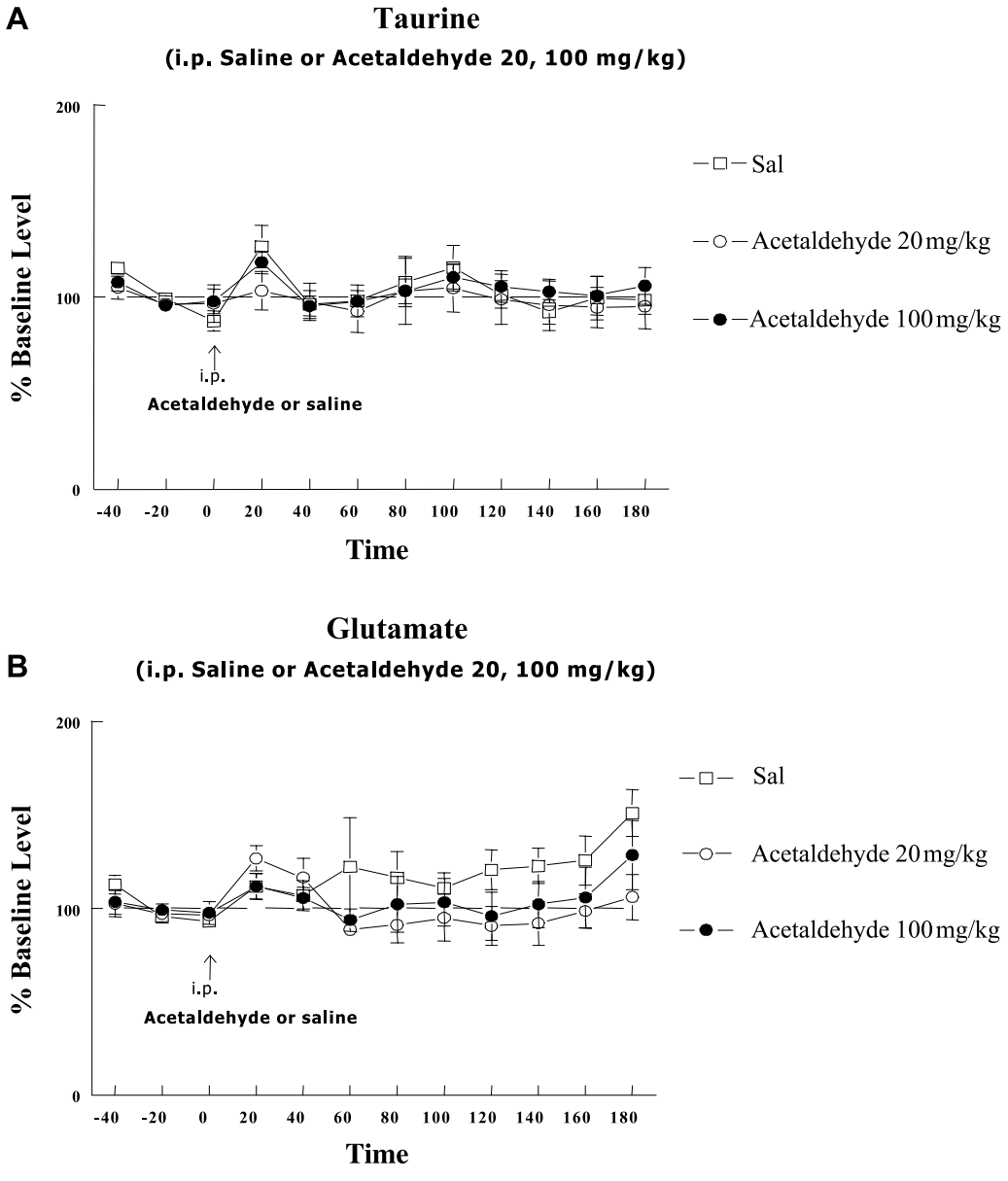

Fig. 3. Effects of an acute injection of acetaldehyde (20 or 100 mg/kg) or saline on extracellular taurine (**A**) and glutamate (**B**) levels in the NAC microdialysate. No statistical differences were found

that were pretreated with either AT or saline. The brain concentration of ethanol significantly increases since 60 minutes after i.p. administration of both doses and further till end of this measurement. Global ANOVA found no significant effects of AT on ethanol brain concentration ($p = 0.36$).

Discussion

In the present studies, an *in vivo* microdialysis technique was applied to evaluate the excitatory and inhibitory amino acids content in the NAC of freely moving male rats during the first 3 h after acute and chronic i.p. administration of acetaldehyde.

Results showed that acute and chronic i.p. administration of acetaldehyde did not affect the content of amino acids in the NAC. As it was noted above, it is not clear whether acetaldehyde penetrates the blood-brain barrier (Baranova et al., 1987; Eriksson and Sippel, 1977) and whether any detectable residual brain acetaldehyde was merely as a result of local ethanol metabolism either by inducible P450IIEI system (Hansson et al., 1990) or by brain catalase (Oshino et al., 1973).

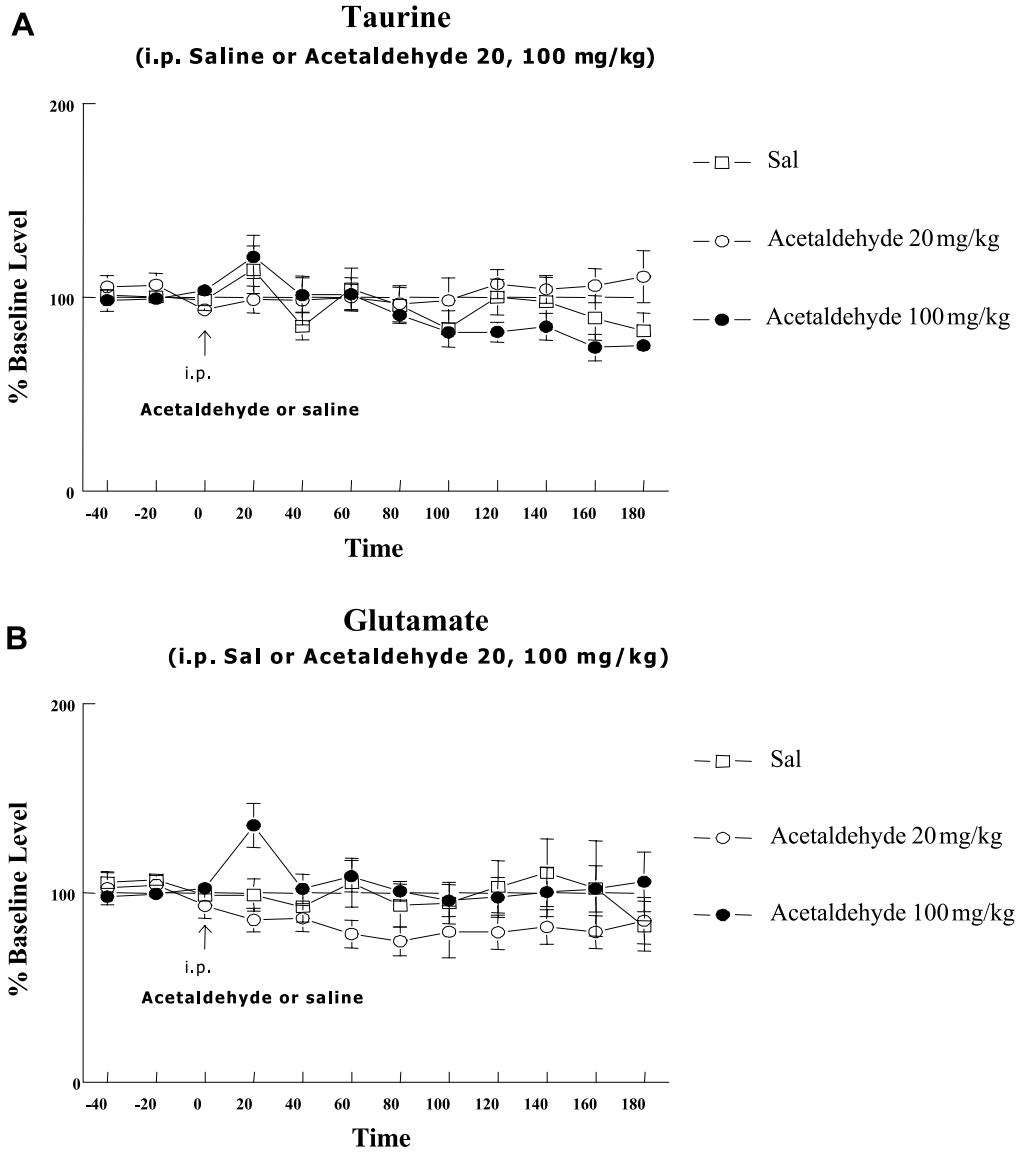

Fig. 4. Effects of chronic injections of acetaldehyde (20 or 100 mg/kg) or saline on extracellular taurine (**A**) and glutamate (**B**) levels in the NAC microdialysate. No statistical differences were found

However, the demonstration of the rewarding effects of acetaldehyde after intracerebroventricular injection (Smith et al., 1984) clearly indicates the role for this major ethanol metabolite in the rewarding action of ethanol. One of our contributions to the field is that administration of acute ethanol increases the level of the sulphonated amino acid taurine in many rat brain regions including nucleus accumbens (Dahchour et al., 1994; 1996), hippocampus, frontal cortex (Dahchour et al., 1998) and amygdala (Quertemont et al., 1998; 1999).

Another part of this study addressed the amino acids concentration in the NAC, following the acute administration of ethanol with and without pre-treatment with AT.

The increase in extracellular taurine levels during the first 20–40 minutes after ethanol administration can be viewed as a physiological adaptation to acute alcohol inducing a fluidification of the membrane structure by stabilizing the plasmic membrane (Sturman et al., 1978) and by maintaining the brain osmotic regulation (Baxter et al., 1986).

In our previous studies (Dahchour et al., 1994; 1996) we have shown that acute ethanol administration to naive rats caused a transitory increase in extracellular taurine NAC microdialysate content, which was dose-dependent and could be related to changes in osmolarity caused by ethanol injection and restored by taurine release.

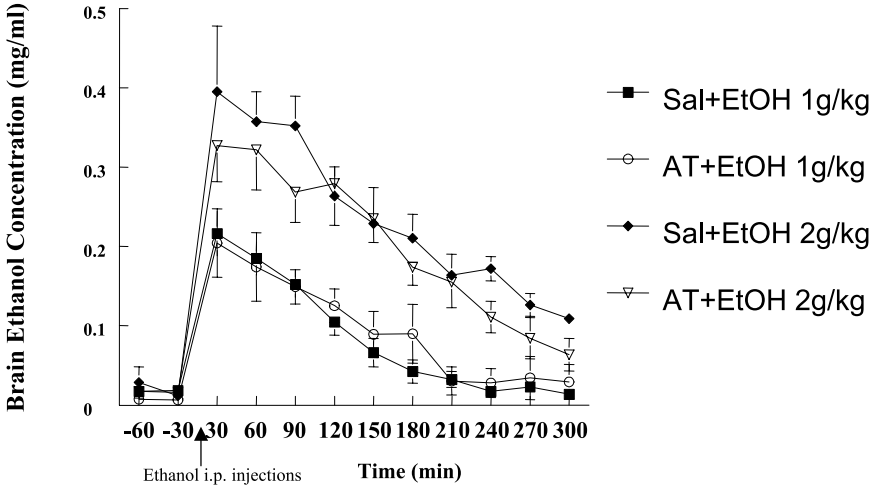

Fig. 5. Effects of an acute injection of ethanol (1, 2 g/kg body weight, IP) on extracellular brain ethanol content of the microdialysate from the nucleus accumbens after pre-treatment of 3-amino-1,2,4-triazole (AT) or saline ethanol-treated rats. Error bars are not shown for all data points. No statistical differences were obtained following AT pre-treatment

The presence of a sulfonic group confers on taurine the capacity of increasing the alcohol metabolism (Iida and Hikichi, 1976; Sprince, 1985). Taurine would thus enhance oxidation of the first alcohol metabolite, acetaldehyde, by activating its degradation enzyme, ALDH (Aragon et al., 1992; Watanabe et al., 1985).

Previously, Ward et al. (1997) published a very small transient increase of taurine in the NAC of adolescent rats after acetaldehyde injection. The present experiment performed on adult rats using the same procedure failed to obtain any extracellular taurine increase following acetaldehyde injection.

Furthermore, after statistical processing of the obtained data, it became clear that there was no significant effect of AT pre-treatment on ethanol-induced increase of taurine content. More specifically, administration of AT five hours prior to ethanol significantly increases taurine concentration in the NAC like ethanol alone did. Such results were predicted based on the evidence that increased ethanol concentration in the brain (e.g., by the blockade of catalase activity) leads to increased taurine content.

Effects of taurine on ethanol metabolism may also be discussed in the context of its modulatory effects. Previous studies have clearly demonstrated that taurine, when administered either i.p. or intragastrically at various doses, had no effect on peripheral ethanol metabolism (Aragon and Amit, 1993; Watanabe et al., 1985). However, taurine may enhance the metabolism of acetaldehyde, the major metabolite of ethanol, by activating the hepatic enzyme ALDH and thereby reducing blood acetaldehyde levels. Indeed, taurine (0.5 g/kg) given orally significantly reduced the elevated blood and liver acetaldehyde concentrations following ethanol loading (1.5 g/kg) (Watanabe et al., 1985).

Obviously, acetaldehyde has an important role in modulating the effects of ethanol. Eriksson (2001) reviewed some aspects of the role of acetaldehyde in the actions of alcohol. Our present results clearly indicate that acetaldehyde is not a pre-element in the ethanol–taurine–glutamate system. The present results provide some evidence for the notion that the putative reinforcing metabolite of ethanol, acetaldehyde, does not play a role in the interaction previously observed between taurine and ethanol.

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