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GABA Turnover in the Brain of Rat Lines Developed for Differential Ethanol-Induced Motor Impairment

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HELLEVUO, K. AND K. KIIANMAA. *GABA turnover in the brain of rat lines developed for differential ethanol-induced motor impairment.* PHARMACOL BIOCHEM BEHAV **34**(4) 905–909, 1989.—The role of GABAergic neurons in the differential sensitivity to ethanol between the AT (Alcohol Tolerant) and ANT (Alcohol Nontolerant) rat lines developed for low and high degree of motor impairment from ethanol, was studied by comparing the effect of ethanol (2 or 4 g/kg, IP) on GABA turnover in different regions of the brain in these rat lines. GABA turnover was estimated from the accumulation of GABA after inhibition of GABA aminotransferase with aminooxyacetic acid (AOAA, 50 mg/kg, IP) given 10 min after administration of ethanol. The rats were killed two hours after the AOAA treatment with focused microwaves. The concentrations of GABA, aspartate, glutamate, glutamine and taurine were analyzed with HPLC. The saline-treated ANT rats were found to have a higher concentration of GABA in the striatum and a higher rate of GABA accumulation in the cerebellum than the AT rats. Ethanol suppressed the accumulation of GABA in both lines, but the suppression was significantly greater in the AT rats than in the ANT rats. In specific regions, this line difference was significant in the cerebral cortex and cerebellum with the higher ethanol dose. No line differences were found in the brain or tail blood ethanol concentration. AOAA increased the concentration of glutamine, decreased that of aspartate and glutamate, and did not modify that of taurine. The AOAA-induced changes in the concentrations of these amino acids were, however, minor relative to those found in the concentrations of GABA. The results that GABAergic mechanisms are involved in the differential sensitivity to the motor-impairing effects of ethanol between the AT and ANT rats.

Ethanol Intoxication GABA Genetics Selected lines Amino acid neurotransmitters

A role for GABAergic mechanisms in the actions of ethanol is suggested by several behavioral, electrophysiological and neurochemical studies. For instance, γ-aminobutyric acid (GABA) antagonists, such as picrotoxin and bicuculline, have been shown to potentiate the locomotor stimulatory effects of ethanol, but to antagonize ethanol-induced motor impairment and to decrease the duration of the loss of the righting reflex (9, 14, 22, 27). Similarly, increasing the concentration of GABA with aminooxyacetic acid (AOAA), and the GABA agonist, muscimol, has been found to enhance the sedative effects of ethanol (3, 9, 14, 27). In electrophysiological studies, ethanol has been shown to augment GABA-mediated inhibition in the cerebral cortex and substantia nigra (28,30). Neurochemical studies indicate that ethanol reduces GABA accumulation (3, 36, 38) and increases $GABA_A$ receptor-linked chloride flux in brain synaptoneurosomes in a picrotoxin-sensitive manner [cf. (37)].

Animal lines selected for ethanol-related behaviors have been widely used to elucidate the mechanisms for actions of ethanol [cf. (13)]. In our laboratory, selective outbreeding has been used to develop the AT (Alcohol Tolerant) line of rats with very low sensitivity to the motor-impairing effect of 2 g/kg ethanol in the tilting plane test and the ANT (Alcohol Nontolerant) line with high sensitivity to this effect (7,19). Further studies have shown that these rat lines also differ in the same way in their sensitivity to the behavioral effects of two GABAergic drugs, barbital and lorazepam, the AT rats showing significantly less motor impairment than the ANT rats (16,34). These findings suggest that GABAergic neuronal mechanisms may be involved in the differential sensitivity to ethanol between these rat lines. This supports the hypothesis of a role for GABAergic mechanisms in the expression of ethanol-induced motor impairment, and suggests furthermore, that the functioning of the GABAergic system is influenced by genetic factors.

The purpose of the present study was to elucidate the involvement of the GABA neuronal systems in the differential sensitivity to ethanol between the AT and ANT rats by comparing the effects of ethanol on GABA accumulation in the brain of these rat lines. In addition, it was hoped to get information about the role of the presynaptic GABAergic mechanisms in ethanol-induced motor impairment. Changes in GABAergic activity were examined by measuring the rate of GABA accumulation after inhibition of GABA metabolizing enzyme GABA aminotransferase (GABA-T)

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with AOAA after ethanol administration. To evaluate the specificity of the AOAA treatment, the concentrations of aspartate, glutamate, glutamine, and taurine were also analyzed. We also checked whether differences in brain ethanol levels might play a role in the differential effect of ethanol in the lines.

METHOD

Male AT and ANT rats of generation F_{32} were used in the experiments. The body weights were 389 ± 4 g (mean $\pm$ SEM, $N = 40$) in the AT rats and 377 ± 4 g ($N = 40$) in the ANT rats. The animals were housed in stainless steel wire mesh cages in groups of 4–6 rats with free access to tap water and standard R 3 rat food (Ewos Ab, Södertälje, Sweden). The ambient temperature was 22 ± 2°C, relative humidity 50–55%, and light/dark cycle 12 hr/12 hr (lights on at 6:00 a.m.).

Neurochemical Studies

GABA turnover was estimated from the accumulation of GABA after inhibition of GABA-T by AOAA. Saline or ethanol [2 g/kg (12% v/v in saline) or 4 g/kg (15% v/v)] was administered intraperitoneally 10 min prior to saline or AOAA (50 mg/kg, IP, in a concentration of 12 mg/ml in saline). In pilot experiments this dose of AOAA caused a linear increase of about 250% in the brain GABA concentration in 3 hours. The rats were killed 120 min after AOAA with focused microwaves (NJE 2603, 10 kW microwave device, New Japan Radio Co. Ltd., Tokyo, Japan).

The head was allowed to cool in crushed ice and then the brain was dissected into cerebral cortex, striatum, limbic forebrain (containing tuberculum olfactorium, nucleus accumbens and septum), and cerebellum. The tissue samples were stored at -80°C until the amino acid assay with high performance liquid chromatography.

The sample preparation and chromatographic procedures were modified from methods published earlier (8, 20, 32). The tissue samples were sonicated for 3×2 sec in 10 volumes of 0.2 M perchloric acid (PCA) (Sonifier B 12, Branson Sonic Power Company, Danbury, CT), and centrifuged at $16{,}000 \times g$ at $+4$°C for 20 min. The internal standard, 100 µl of 1.25 mM norvaline in absolute methanol, was added into 100 µl of the supernatant, and diluted with absolute methanol up to 2.2 ml. This dilution fitted within the linear range of the fluorescence detector (10–600 pmol/amino acid/injection). The chromatographic analyses were performed immediately after tissue extraction.

Amino acid standards containing GABA, aspartate, glutamate, glutamine and taurine were constructed from stock solutions of individual amino acids (10 mM in 0.2 M PCA stored at -80°C). The mixture of amino acids was constructed from 100 µl of each stock solution, which was then diluted with absolute methanol up to 4.8 ml. To obtain a standard curve, 100 µl of 1.25 mM norvaline (internal standard) was added to 55, 110, 220 and 440 µl of the amino acid mixture and the solutions were filled up to 2.2 ml with absolute methanol.

The concentrations of the amino acids were analyzed as precolumn o-phthaldialdehyde (OPA) derivatives by high performance liquid chromatography with fluorescence detection. The derivatization reagent was made weekly from 50 mg OPA, 5 ml absolute methanol, 5 ml saturated H_3BO_3-buffer pH 9.5 and 50 µl 2-mercaptoethanol. The samples were automatically derivatized and run by a Waters Intelligent Sample Processor, WISP 710B, equipped with an OPA valve using the Auto.Tag OPA method (32). The two Model 510 pumps were controlled by an Automated Gradient Controller (Waters Associates, Milford, MA). The detector was a Waters 420AC Fluorescence Detector, equipped with a standard UV lamp, a 338 nm excitation filter, and a 455 nm emission filter.

The samples were first run through a glass-bead column to insure a proper mixing of the derivatized samples, followed by a Bondapak C_{18} precolumn (Waters Associates) and finally separated by an Altex Ultrasphere ODS 5 µm (250 × 4.6 mm i.d.) column (Beckman Instruments Inc., San Ramon, CA) during a gradient run using phosphate- and phosphate-acetonitrile buffers described by Korpi and Wyatt (20). The gradient profile was adjusted to separate the amino acids of interest.

Brain and Blood Ethanol Concentration

The AT and ANT rats were injected with 2 g/kg of ethanol (12% v/v, IP). Blood samples of 100 µl were collected from the tip of the tail after 30 min. The rats were immediately decapitated and their brains removed. The ethanol concentration was determined by head space gas chromatography (5) from the supernatants after protein precipitation with 0.6 M perchloric acid and centrifugation.

Drugs

The amino acid standards, γ-aminobutyric acid (free), L-aspartic acid (free), L-glutamic acid (free), L-glutamine, L-taurine, L-norvaline, aminooxyacetic acid hemihydrochloride, and o-phthaldialdehyde were purchased from Sigma Chemical Co. (St. Louis, MO). All other reagents were of analytical grade.

Statistical Analysis

Differences between the groups were studied using Student's *t*-test or analysis of variance followed by the Student-Newman-Keuls test.

RESULTS

The concentration of GABA was significantly higher in the striatum of the ANT rats than in that of the AT rats (Fig. 1). No significant differences between the rat lines in the concentration of GABA were found in the cerebral cortex, the cerebellum, or the limbic forebrain (Fig. 1).

The AOAA-induced accumulation of GABA was significantly higher in the cerebellum of the ANT rats than in that of the AT rats, as indicated by a significant rat line × AOAA effect interaction, $F(1,32) = 5.93$, $p = 0.0206$ (Fig. 1). There were no significant line differences in the accumulation of GABA in other brain parts.

The ethanol-induced reduction in the GABA accumulation was generally greater in the AT line than in the ANT line (Fig. 1), as indicated by a significant rat line × ethanol effect interaction over all brain areas together, $F(2,28) = 3.93$, $p = 0.0312$. Additional analyses of variance showed that this line difference reached significance in the cerebral cortex, $F(1,28) = 5.68$, $p = 0.0242$, and cerebellum, $F(1,28) = 4.96$, $p = 0.0341$, with the 4 g/kg dose and approached significance in the striatum, $F(1,30) = 4.08$, $p = 0.0525$, and cerebral cortex, $F(1,28) = 3.42$, $p = 0.0752$, with the 2 g/kg dose.

The effect of ethanol on the concentrations of aspartate, glutamate, glutamine, and taurine in the different brain regions of the AT and ANT rats treated with AOAA is shown in Table 1. AOAA alone decreased significantly the concentrations of aspar-

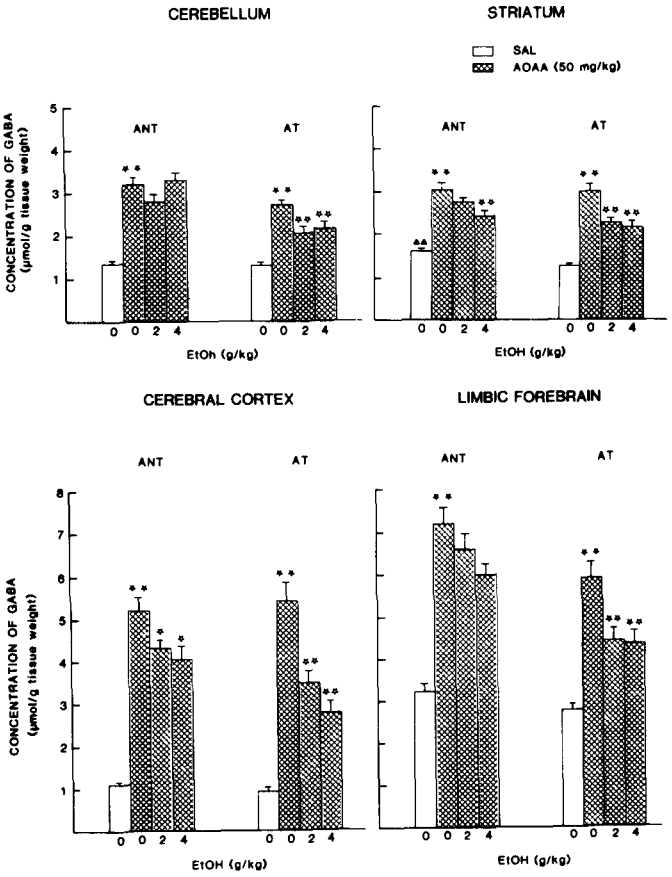

FIG. 1. The concentrations of GABA in different parts of the brain of the AT and ANT rats treated with saline (SAL) or ethanol (EtOH) without or with aminooxyacetic acid (AOAA) administration. A significant rat line × AOAA effect interaction was found in the cerebellum, and significant rat line × ethanol effect interactions were found in all areas together, and specifically in the cerebral cortex and cerebellum (see the Results section). Mean ± SEM of 8–10 rats are given. ▲▲ $p<0.01$ from the AT line (t-test); ★★ $p<0.01$ from the saline-saline control; ☆☆ $p<0.01$, ☆ $p<0.05$ from AOAA-saline control (Newman-Keuls test).

tate and glutamate in the cerebellum and limbic forebrain of both rat lines, but increased the concentration of glutamine in every analyzed region of the brain. A significant rat line × AOAA-effect interaction was found in the striatum, in which AOAA increased the concentration of glutamine, $F(1,30)=7.97$, $p=0.0084$, and taurine, $F(1,30)=7.27$, $p=0.0114$, significantly more in the AT rats than in the ANT rats. Otherwise, the concentration of taurine was not modified by AOAA.

Ethanol further decreased significantly the concentration of aspartate in the cerebellum of both rat lines (Table 1). The higher dose of ethanol significantly raised the concentration of glutamine in every analyzed brain part of the ANT rats. The rat lines did not, however, differ significantly in this effect. A line difference in response to ethanol was found in the concentration of taurine in the cerebral cortex, $F(2,42)=5.25$, $p=0.0092$, although the ethanol-induced changes were not significant.

There were no significant differences between the AT and ANT rats in ethanol concentrations in the brain or in the tail blood (Table 2).

DISCUSSION

The functional relationship between ethanol-induced changes in GABA neurotransmission and impairment of motor performance during ethanol intoxication was studied using two rat lines selected for differential sensitivity to ethanol. The concentration of GABA in the striatum and the AOAA-induced GABA accumulation in the cerebellum were higher in the ethanol-sensitive ANT rats than in those of the ethanol-insensitive AT rats, suggesting higher GABAergic tone in the cerebellum of the ANT rats.

Ethanol was found to reduce GABA accumulation after AOAA. This finding is in agreement with most previous studies (3, 36, 38), but see (9,10), using similar ethanol doses to those used in this study and measuring GABA accumulation after AOAA, γ-allenyl-GABA, or gabaculine in the brains of rats and mice. With a different method, using a radioactive glucose precursor, ethanol did not, however, affect the rate of GABA synthesis (31).

The ethanol-induced reduction in GABA accumulation after AOAA was greater in the ethanol-insensitive AT line than in the ethanol-sensitive ANT line. This effect cannot be accounted for by differences in the distribution of ethanol, because brain ethanol concentrations were found to be similar in both rat lines. Interestingly, significant differences in the basal concentrations of GABA and after AOAA were found only in the cerebral cortex, striatum, and cerebellum, i.e., brain parts closely related to the control of motor performance (11,18).

The rate of GABA accumulation after inhibition of GABA metabolism with AOAA has been used as an index of the utilization of the GABA releasing neurons, and thus of the amount of GABA released into synaptic clefts (23, 26, 39). If this is correct, ethanol suppresses GABA release more in the brain of the ethanol-insensitive AT rats than in that of the ethanol-sensitive ANT rats. On the other hand, both in electrophysiological and in vitro slice studies, ethanol has been found to suppress GABAergic activity more in the brain of the ethanol-sensitive long-sleep (LS) than ethanol-insensitive short-sleep (SS) mice, developed for differences in the duration of ethanol-induced loss of righting reflex (17,35). An explanation for the contrasting results between the AT/ANT rats and LS/SS mice is difficult to give.

The assumption that the level of GABA accumulation after AOAA reflects the amount of GABA release can be criticized. The level of GABA accumulation after AOAA probably reflects GABA in other compartments in addition to that released as a transmitter, and for this reason may not be an accurate measure of the absolute rate of GABA release (1, 12, 24). Nevertheless, it should be correlated to the rate of GABA release and suitable for making a comparison between the AT and ANT rats. Consequently, the conclusion that AT rats have a greater ethanol-induced decrease in GABA release than do ANT rats seems to be justified even if the figures do not represent the absolute release rates.

The estimation of GABA release from the accumulation of GABA can also be justified by the present finding that AOAA had considerably less effect on the concentrations of aspartate, glutamate, glutamine, and taurine than that of GABA. Thus, the dose of AOAA used in this study inhibited GABA-T much more than other enzymes, in spite of being a nonspecific enzyme inhibitor (29,39).

AOAA causes hypothermia (3) and thus could affect GABA accumulation through the change in body temperature. It should be noted, however, that the AT and ANT rats are not differentially sensitive to the hypothermic effects of ethanol (6,21).

The ability of ethanol to reduce the accumulation of GABA is probably not caused by a direct inhibitory effect of ethanol on

TABLE 1

THE EFFECT OF ETHANOL ON THE CONCENTRATIONS OF ASPARTATE (Asp), GLUTAMATE (Glu), GLUTAMINE (Gln) AND TAURINE (Tau) IN DIFFERENT AREAS OF THE BRAIN OF THE AT AND ANT RATS TREATED WITH AOAA

	EtOH (g/kg)	Cerebral Cortex ANT	Cerebral Cortex AT	Cerebellum ANT	Cerebellum AT	Limbic Forebrain ANT	Limbic Forebrain AT	Striatum ANT	Striatum AT
Asp									
	0	91 ± 5 (8)	91 ± 7 (8)	69 ± 7 (8)[a]	87 ± 6 (8)	69 ± 6 (8)[a]	69 ± 9 (7)[a]		
	2	86 ± 6 (8)	86 ± 7 (8)	58 ± 6 (8)	60 ± 5 (8)[b]	78 ± 9 (8)	73 ± 6 (8)	N.D.	
	4	100 ± 9 (8)	89 ± 8 (8)	30 ± 5 (8)[b]	58 ± 7 (8)[b]	61 ± 8 (8)	72 ± 12 (7)		
Glu	0	100 ± 11 (8)	103 ± 11 (8)	74 ± 4 (8)[a]	86 ± 4 (8)	92 ± 5 (8)	75 ± 7 (8)[a]		
	2	95 ± 9 (8)	99 ± 10 (8)	81 ± 4 (8)	89 ± 3 (8)	111 ± 8 (8)	76 ± 4 (8)	N.D.	
	4	75 ± 6 (8)	94 ± 13 (8)	67 ± 5 (8)	88 ± 5 (8)	98 ± 3 (8)	84 ± 7 (8)		
Gln									
	0	145 ± 8 (8)[a]	142 ± 9 (8)[a]	156 ± 9 (8)[a]	152 ± 5 (8)[a]	130 ± 7 (8)[a]	132 ± 9 (8)[a]	126 ± 3 (8)[a]†	149 ± 4 (8)[a]
	2	133 ± 10 (8)	138 ± 8 (8)	132 ± 7 (8)	146 ± 9 (8)	124 ± 6 (8)	121 ± 5 (8)	118 ± 3 (8)	130 ± 6 (10)
	4	229 ± 21 (7)[b]	171 ± 12 (7)	194 ± 16 (8)[b]	174 ± 17 (8)	171 ± 9 (8)[b]	145 ± 9 (8)	145 ± 7 (8)[b]	158 ± 12 (9)
Tau									
	0	101 ± 3 (8)	98 ± 3 (8)	101 ± 3 (8)	96 ± 3 (10)	101 ± 4 (8)	105 ± 6 (8)	98 ± 3 (8)*	114 ± 3 (8)[a]
	2	95 ± 4 (8)‡	101 ± 3 (8)	95 ± 4 (10)	100 ± 6 (10)	101 ± 4 (8)	101 ± 4 (8)	91 ± 3 (8)	110 ± 3 (8)
	4	109 ± 4 (8)‡	94 ± 4 (8)	110 ± 4 (10)	106 ± 6 (10)	101 ± 3 (8)	98 ± 5 (8)	89 ± 3 (7)	107 ± 3 (8)

Results are expressed as percent of the saline-saline control [mean ± SEM, (N)]. N.D. = not determined. The concentrations (μmol/g tissue weight) of the amino acids of the saline-treated AT and ANT rats, respectively, were: cerebral cortex: Asp 4.2 ± 0.4 (8), 3.7 ± 0.2 (8); Glu 5.8 ± 0.6 (7), 5.8 ± 0.5 (8); Gln 4.3 ± 0.2 (8), 3.5 ± 0.2 (8); Tau 5.4 ± 0.2 (8), 5.8 ± 0.2 (8); cerebellum: Asp 3.6 ± 0.3 (8), 3.7 ± 0.2 (8); Glu 11.6 ± 0.9 (8), 12.5 ± 0.7 (8); Gln 4.9 ± 0.3 (10), 4.7 ± 0.3 (10); Tau 6.1 ± 0.4 (8), 7.0 ± 0.2 (8); limbic forebrain: Asp 3.3 ± 0.3 (7), 2.7 ± 0.2 (6); Glu 9.4 ± 0.3 (7), 7.7 ± 0.9 (7); Gln 6.0 ± 0.2 (8), 5.4 ± 0.2 (8); Tau 5.1 ± 0.3 (8), 5.7 ± 0.2 (8); striatum: Gln 2.8 ± 0.1 (8), 2.8 ± 0.1 (10); Tau 6.1 ± 0.2 (8), 7.4 ± 0.2 (10). [a]$p<0.01$ difference from saline-saline control; [b]$p<0.01$ difference from AOAA-saline (Newman-Keuls test); *$p<0.05$, †$p<0.01$ AOAA effect × rat line interaction; ‡$p<0.01$ ethanol effect × rat line interaction (ANOVA).

GAD, since the activity of the enzyme has not been found to be decreased (15,36). Based upon the suggestion by Frye and Fincher (10), the reduced GABA accumulation produced by ethanol may, however, involve the negative-feedback produced by presynaptic GABA autoreceptors, although it is not clear whether they are of type $GABA_A$ or $GABA_B$ (2,4). There is evidence suggesting that ethanol potentiates $GABA_A$ receptor-mediated chloride influx [cf. (33,37)]. If it also potentiates or mimics GABA actions on autoreceptors it would decrease GABA release. Consequently, if the AT rats have more autoreceptors than the ANT animals, the AT rats would show a greater reduction of GABA release when given ethanol and thus would show less overt intoxication. In support of this hypothesis, less GABA release (in this study) and a larger total number of muscimol binding sites in the AT rats than in the ANT rats has been found in the cerebellum (25).

TABLE 2

BRAIN AND TAIL-BLOOD ETHANOL CONCENTRATIONS IN THE AT AND ANT RATS

Rat Line	Ethanol Concentration (mM) Brain	Tail-Blood
AT	43.2 ± 1.4 (6)	48.2 ± 1.9 (6)
ANT	41.1 ± 2.0 (5)	46.0 ± 2.7 (5)

Mean ± SEM (n) are given. The determinations were made 30 min after administration of ethanol 2 g/kg IP.

The present study has provided further evidence that there are genetically determined differences in central GABAergic mechanisms between the AT and ANT rats, and that the mechanisms differ in their sensitivity to ethanol. This is in accord with the earlier findings showing that the ANT rats are more sensitive than the AT rats to the motor impairing effects of barbital and lorazepam (16,34), suggesting a role for GABAergic mechanisms in the differential sensitivity to ethanol between the lines and in ethanol-induced motor impairment.

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REFERENCES

1. Bernasconi, R.; Maitre, L.; Martin, P.; Raschdorf, F. The use of inhibitors of GABA-transaminase for the determination of GABA turnover in mouse brain regions: An evaluation of aminooxyacetic acid and gabaculine. J. Neurochem. 38:57–66; 1982.
2. Bonanno, G.; Fontana, G.; Raiteri, M. Phaclofen antagonizes GABA at autoreceptors regulating release in rat cerebral cortex. Eur. J. Pharmacol. 154:223–224; 1988.
3. Dar, M. S.; Wooles, W. R. GABA mediation of the central effects of

acute and chronic ethanol in mice. Pharmacol. Biochem. Behav. 22:77–84; 1985.
4. Ennis, C.; Minchin, M. C. W. Modulation of the GABA autoreceptor by benzodiazepine receptor ligands. Neuropharmacology 27:1003–1006; 1988.
5. Eriksson, C. J. P.; Sippel, H. W.; Forsander, O. A. The determination of acetaldehyde in biological samples by headspace gas chromatography. Anal. Biochem. 80:116–124; 1977.
6. Eriksson, C. J. P.; Sarviharju, M. Motor impairment, narcosis and hypothermia by ethanol: Separate genetic mechanisms. Alcohol 1: 59–62; 1984.
7. Eriksson, K.; Rusi, M. Finnish selection studies on alcohol-related behaviors: General outline. In: McClearn, G. E.; Deitrich, R. A.; Erwin, G., eds. Development of animal models as pharmacogenetic tools. Proc. Workshop, Boulder, CO, 1978, NIAAA Res. Monograph No. 6. Washington, DC: U.S. Government Printing Office; 1981: 87–117.
8. Fernstrom, M. H.; Fernstrom, J. D. Rapid measurement of free amino acids in serum and CSF using high-performance liquid chromatography. Life Sci. 29:2119–2130; 1981.
9. Frye, G. D.; Breese, G. R. GABAergic modulation of ethanol-induced motor impairment. J. Pharmacol. Exp. Ther. 223:750–756; 1982.
10. Frye, G. D.; Fincher, A. S. Effect of ethanol on γ-vinyl-GABA-induced GABA accumulation in the substantia nigra and on synaptosomal GABA content in six rat brain regions. Brain Res. 449:71–79; 1988.
11. Garcia-Rill, E. The basal ganglia and the locomotor regions. Brain Res. Rev. 11:47–63; 1986.
12. Geddes, J. W.; Wood, J. D. Changes in the amino acid content of nerve endings (synaptosomes) induced by drugs that alter the metabolism of glutamate and γ-aminobutyric acid. J. Neurochem. 42: 16–24; 1984.
13. Goldstein, D. B. Animal models developed by selective outbreeding: some questions raised and a few answered. In: Kiianmaa, K.; Tabakoff, B.; Saito, T., eds. Genetic aspects of alcoholism, The Finnish Foundation for Alcohol Studies, vol. 37. Helsinki: Painokaari Oy; 1989:229–238.
14. Häkkinen, H.-M.; Kulonen, E. Ethanol intoxication and γ-aminobutyric acid. J. Neurochem. 27:631–633; 1976.
15. Häkkinen, H.-M.; Kulonen, E. Ethanol intoxication and the activities of glutamate decarboxylase and γ-aminobutyrate aminotransferase in rat brain. J. Neurochem. 33:943–946; 1979.
16. Hellevuo, K.; Kiianmaa, K.; Juhakoski, A.; Kim, C. Intoxicating effects of lorazepam and barbital in rat lines selected for differential sensitivity to ethanol. Psychopharmacology (Berlin) 91:263–267; 1987.
17. Howerton, T. C.; Collins, A. C. Ethanol-induced inhibition of GABA release from LS and SS mouse brain slices. Alcohol 1:471–477; 1984.
18. Ito, M. The cerebellum and neural control. New York: Raven Press; 1984.
19. Kiianmaa, K.; Hellevuo, K.; Korpi, E. R. The AT (Alcohol Tolerant) and ANT (Alcohol Nontolerant) rat lines selected for differences in sensitivity to ethanol: An overview. In: Kuriyama, K.; Takada, A.; Ishii, H., eds. Biomedical and social aspects of alcohol and alcoholism. Amsterdam: Elsevier; 1988:415–418.
20. Korpi, E. R.; Wyatt, R. J. Effects of chronic D-amphetamine and phenylethylamine on the concentrations of neurotransmitter amino acids in the rat brain. Int. J. Neurosci. 18:239–246; 1983.
21. Lê, A. D.; Kiianmaa, K. Initial sensitivity and the development of acute and rapid tolerance to ethanol in the AT and ANT rats. In: Kiianmaa, K.; Tabakoff, B.; Saito, T., eds. Genetic aspects of alcoholism, The Finnish Foundation for Alcohol Studies, vol. 37. Helsinki: Painokaari Oy; 1989:147–155.
22. Liljequist, S.; Engel, J. Effects of GABAergic agonists and antagonists on various ethanol-induced behavioral changes. Psychopharmacology (Berlin) 78:71–75; 1982.
23. Lindgren, S.; Andén, N.-E. Effect of the normal nerve impulse flow on the synthesis and utilization of GABA in the rat substantia nigra. J. Neural Transm. 61:21–34; 1985.
24. Löscher, W.; Vetter, M. In vivo effects of aminooxyacetic acid and valproic acid on nerve terminal (synaptosomal) GABA levels in discrete brain areas of the rat. Biochem. Pharmacol. 34:1747–1756; 1985.
25. Malminen, O.; Korpi, E. R. GABA/benzodiazepine receptor/chloride ionophore complex in brains of rat lines selectively bred for differences in ethanol-induced motor impairment. Alcohol 5:239–249; 1988.
26. Mao, C. C.; Peralta, E.; Morini, F.; Costa, E. The turnover rate of γ-aminobutyric acid in the substantia nigra following electrical stimulation or lesioning of the strionigral pathways. Brain Res. 155: 147–152; 1978.
27. Martz, A.; Deitrich, R. A.; Harris, R. A. Behavioral evidence for the involvement of γ-aminobutyric acid in the actions of ethanol. Eur. J. Pharmacol. 89:53–62; 1983.
28. Mereu, G.; Gessa, G. L. Low doses of ethanol inhibit the firing of neurons in the substantia nigra, pars reticulata: A GABAergic effect? Brain Res. 360:325–330; 1985.
29. Metcalf, B. W. Inhibitors of GABA metabolism. Biochem. Pharmacol. 28:1705–1712; 1979.
30. Nestoros, J. N. Ethanol specifically potentiates GABA-mediated neurotransmission in feline cerebral cortex. Science 209:708–710; 1980.
31. Noto, T.; Hepler, J. R.; Myers, R. D. Profile of amino acid synthesis in rat hippocampus during push-pull perfusion of ethanol or morphine. Neuroscience 13:367–376; 1984.
32. Pfeifer, R. F.; Hill, D. W. High performance liquid chromatographic analysis of amino acids: Ion exchange and reverse phase strategies. Adv. Chromatogr. 22:37–69; 1983.
33. Schwartz, R. D. The $GABA_A$ receptor-gated ion channel: Biochemical and pharmacological studies on structure and function. Biochem. Pharmacol. 37:3369–3375; 1988.
34. Sinclair, J. D.; Rusi, M.; Airaksinen, M. M.; Altschuler, H. L. Relating TIQ's, opiates and ethanol. In: Bloom, F. E.; Barchas, J.; Sandler, M.; Usdin, E., eds. Beta-carbolines and tetrahydroisoquinolines. New York: Alan R. Liss; 1982:365–376.
35. Sorensen, S.; Palmer, M.; Dunwiddie, T.; Hoffer, B. Electrophysiological correlates of ethanol-induced sedation in differentially sensitive lines of mice. Science 210:1143–1145; 1980.
36. Supavilai, P.; Karobath, M. Ethanol and other CNS depressants decrease GABA synthesis in mouse cerebral cortex and cerebellum in vivo. Life Sci. 27:1035–1040; 1980.
37. Ticku, M. K.; Kulkarni, S. K. Molecular interactions of ethanol with GABAergic system and potential of RO 15-4513 as an ethanol antagonist. Pharmacol. Biochem. Behav. 30:501–510; 1988.
38. Wixon, H. N.; Hunt, W. A. Effect of acute and chronic ethanol treatment on gamma-aminobutyric acid levels and on aminooxyacetic acid-induced GABA accumulation. Subst. Alcohol Actions Misuse 1:481–491; 1981.
39. Wood, J. D.; Peesker, S. J. The role of GABA metabolism in the convulsant and anticonvulsant actions of aminooxyacetic acid. J. Neurochem. 20:379–387; 1973.