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Suppression of Ethanol-Induced Locomotor Stimulation by GABA-Like Drugs

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Summary. Ethanol (2.4 g/kg) was given intraperitoneally to mice and was found to cause a marked increase in spontaneous locomotor activity. When mice were pretreated with low doses of agents which mimic or augment the action of GABA (γ-hydroxybutyric acid, baclophen, or aminooxyacetic acid) the ethanol-induced locomotor stimulation was completely eliminated. Baclophen (10 mg/kg) was found to cause an initial increase followed by a later decrease in synthesis of catecholamines, as measured by the accumulation of dopa after inhibition of central aromatic L-amino acid decarboxylase, in dopamine-rich areas of rat brain. These data are consistent with previous findings that baclophen, as well as other agents which enhance the activity of GABA systems, reduce the firing of dopamine neurons, thus causing enhanced synthesis of dopamine via feedback mechanisms. These findings also indicate a potential interaction between GABA-like drugs and alcohol in man, and may be of heuristic value in the treatment of chronic alcoholism. The possibility that the mechanism of the inhibition of ethanol-induced locomotor stimulation by GABA-like drugs may be due to a selective interference with ethanol-induced dopamine release is discussed.

Key words: Ethanol – Locomotor activity – Dopamine – GABA.

INTRODUCTION

Behavioural stimulation from small doses of ethanol is a well known phenomenon which has been demonstrated in several species including man (Weiss and Laties, 1964; Read et al., 1960; Carlsson et al., 1972b; Ahlenius et al., 1973; Engel and Carlsson, 1976). This stimulation appears to involve enhanced catecholamine (CA) activity since low doses of α-methyltyrosine (α-MT), a specific inhibitor of tyrosine hydroxylase, cause a rather selective inhibition of ethanol-induced locomotor activation (Carlsson et al., 1972b). Furthermore, this inhibition of ethanol-induced stimulation can be partially reversed by L-dopa (Engel et al., 1974).

Acute administration of ethanol has been shown to affect CA metabolism by several different biochemical methods. Corrodi et al. (1966) and Hunt and Majchrowicz (1974) reported that ethanol enhanced the depletion of norepinephrine (NE) after inhibition of CA synthesis with α-MT in rat brain. Cott (1975) reported on accelerated disappearance of both NE and DA after pretreatment with α-MT in mouse brain. An enhanced accumulation of dopa after inhibition of central aromatic amino acid decarboxylase was found by Carlsson and Lindqvist (1973). In addition, an enhanced formation of ^{3}H-NE (Pohorecky and Jaffe, 1975) and of both ^{3}H-NE and ^{3}H-DA (Carlsson et al., 1973; Svensson and Waldeck, 1973; Waldeck, 1974) from ^{3}H-tyrosine has been demonstrated.

Thus it appears that ethanol-induced central stimulation may be related, either directly or indirectly to the effects of ethanol on CA metabolism. Recent literature suggests that both acute and chronic administration of ethanol may also interact with γ-aminobutyric acid (GABA) systems in brain (Roth, 1970; Goldstein, 1973; Sutton and Simmonds, 1973; Sytinsky et al., 1975). In addition, there is a growing body of experimental evidence indicating that GABA-carrying neuronal pathways exert an inhibitory control over central DA neurons (Roth and Suhr, 1970;

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Andén, 1974; Stevens et al., 1974; Carlsson, 1975a; Fuxe et al., 1975a, b). Since these DA neurons appear to be of primary importance in the expression of ethanol-induced locomotor stimulation, it was of interest to investigate the effect of drugs which mimic or enhance the effects of GABA on this behavioral activation.

METHODS

a) Subjects and Drugs. Female mice of the N.M.R.I. strain, weighing approximately 20 g, were used for the behavioural studies. Male Sprague-Dawley rats weighing 200–325 g were used for the biochemical experiments. Animals were fed ad libitum and were housed under a 12 h light/dark cycle. The following drugs were used: Ethanol 99.5%; baclophen (β-[4-chlorophenyl]-γ-aminobutyric acid, Lioresal®, Ciba-Geigy, Mölndal, Sweden); γ-hydroxybutyric acid (GHBA, sodium form, Sigma Chemical Co., St. Louis, Mo.); aminooxyacetic acid hemichloride (AOAA, Sigma); DL-α-methyltyrosine methylester HCl (α-MT, Hässle, Mölndal, Sweden); NSD 1015 (3-hydroxybenzylhydrazine HCl, synthetized in this department by Dr. Per Martinson). Ethanol was given intraperitoneally (i.p.) as a 15% v/v solution with saline in a volume of 20 ml/kg. All other drugs were dissolved in 0.9% NaCl, and were administered i.p. in a volume of 10 ml/kg. The doses given refer to the forms mentioned above.

b) Behavioural Studies. Locomotor activity was measured using the "M/P 40 Fc Electronic Motility Meter" (Motron Products, Stockholm) (see Ahlenius et al., 1974). Every 10th interruption of the photocell beams registered one count. Ethanol, 2.4 g/kg, was given immediately before placing the mice (in groups of 3) into the activity chambers. Baclophen (5 mg/kg) was given 20 min before, GHBA (200 mg/kg) immediately before, and AOAA (40 mg/kg) 90 min before activity was measured. Control animals received saline injections. Activity was recorded every 5 min for 60 min.

c) Biochemical Studies. Tyrosine and tryptophan hydroxylase activity was estimated in vivo by measuring the accumulation of dihydroxyphenylalanine (dopa) and 5-hydroxytryptophan (5-HTP) respectively, after inhibition of aromatic L-amino acid decarboxylase with NSD 1015 (Carlsson et al., 1972a). Rats received baclophen (0.5–20 mg/kg) 45 min to 8 h before and NSD 1015 (100 mg/kg) 30 min before death. Control animals received only NSD 1015.

The rats were killed by decapitation and the brains were quickly removed and placed on a glass plate over ice. The following parts of the brain were taken for analysis: 1) corpus striatum, 2) limbic forebrain including the olfactory tubercle, nucleus accumbens (medial part) and nucleus amygdaloideus centralis, and 3) rest of the hemispheres (referred to as "hemispheres"). For details on the dissection, see Carlsson and Lindqvist (1973). Immediately after dissection the brain parts were placed on dry ice. The parts of 3 brains were pooled and weighed.

The brain parts were homogenized in 10 ml 0.4 N perchloric acid containing 5 mg $Na_2S_2O_5$ and 20 mg EDTA. The extract was purified on a strong cation exchange column (Dowex 50) (Kehr et al., 1972a). The following spectrophotofluorimetric analyses were performed: tyrosine (Waalkes and Udenfriend, 1957), dopa (Kehr et al., 1972a), tryptophan (Bédard et al., 1972) and 5-hydroxytryptophan (Atack and Lindqvist, 1973).

d) Statistics. For all statistical calculations analysis of variance (with one criterion of classification) followed by *t*-test, was used.

RESULTS

A. Effects of GABA-Like Agents on Ethanol-Induced Locomotor Stimulation

Mice receiving 2.4 g/kg ethanol (i.p.) immediately before activity measurements showed a significant increase in locomotor activity over saline injected controls during the entire 60-min session (Figs. 1, 2, and 3). Pretreatment with the GABA-transaminase inhibitor AOAA (Wallach, 1961) (40 mg/kg) 90 min before ethanol completely antagonized the ethanol-induced locomotor stimulation, while having no effect on saline treated animals (Fig. 1). In fact, during the first part of the recording session, mice receiving both ethanol and AOAA showed a significant suppression of locomotion when compared with saline controls.

Pretreatment with the GABA-derivative, baclophen (5 mg/kg), 20 min before ethanol administration also produced an inhibition of ethanol-induced locomotor stimulation, but had no significant effect on saline treated mice (Fig. 2). The activity of these animals was again significantly lower than saline controls during the first part of the session. A partial recovery of ethanol stimulation was noted toward the end of the session (Fig. 2).

Mice which received the GABA analogue, GHBA (200 mg/kg), immediately before ethanol administration also showed reduced activity during the first 45 min of the session (Fig. 3). Although GHBA inhibited saline treated animals during the first part of the session, it was necessary to give this large dose since its effects are quite short-lived as evidenced by the complete return of ethanol-induced activation during the last 10 min of the session.

Administration of all of the GABA-like agents tested produced a qualitative difference in the appearance of mice treated with low doses of ethanol, as determined by gross observation. Instead of the usual ethanol-induced behavioural stimulation with spontaneous running and slight ataxia, the animals appeared to be sedated and quite ataxic. These observations prompted the authors to try a simple experiment with slightly higher doses of baclophen and ethanol. When 15 mice were injected with 10 mg/kg baclophen and 3 g/kg ethanol, they lost their righting reflex and appeared to be completely anaesthetized for 69 ± 4 min. In contrast, animals receiving only baclophen (10 mg/kg) appeared almost normal with a slight muscular hypotonicity, while others receiving only ethanol (3 g/kg) were markedly stimulated for almost 2 h.

B. Effect of Baclophen on Monoamine Synthesis

The dose-response effects of baclophen on the accumulation of dopa after NSD 1015 are shown in

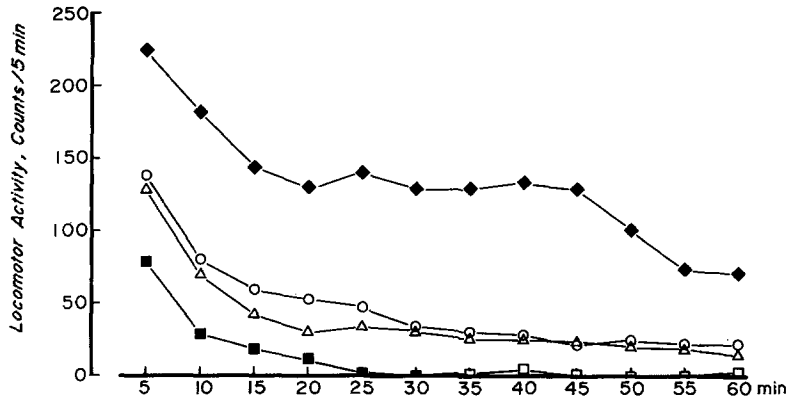

Fig. 1
Suppression of ethanol-induced locomotor stimulation by AOAA. Ethanol (2.4 g/kg i.p. 1 min before recording, ◇——◆) was given to mice alone or in combination with AOAA (40 mg/kg i.p. 90 min before recording, □——■). Control animals received saline (i.p. 1 min before recording, ○——○) or AOAA (40 mg/kg i.p. 90 min before recording, △——▲). Shown are the means of 8 values per experimental group each comprising 3 animals. Filled symbols represent significant difference from saline control at $P < 0.05$ or less

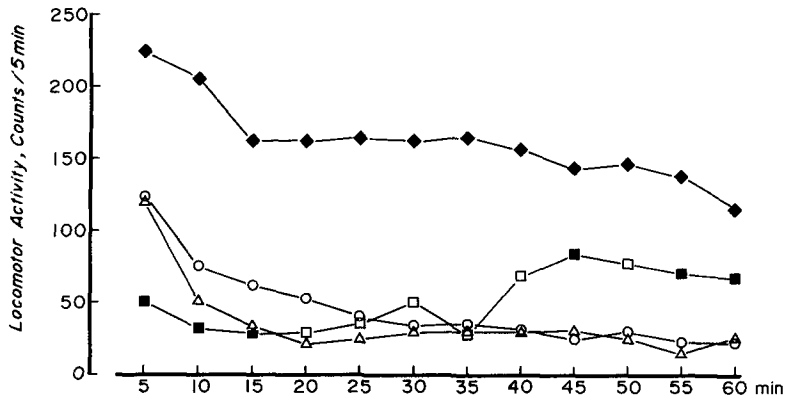

Fig. 2
Suppression of ethanol-induced locomotor stimulation by baclophen. Ethanol (2.4 g/kg i.p. 1 min before recording, ◇——◆) was given to mice alone or in combination with baclophen (5 mg/kg i.p. 20 min before recording, □——■). Control animals received saline (i.p. 1 min before recording, ○——○) or baclophen (5 mg/kg i.p. 20 min before recording, △——▲). Shown are the means of 8 values per experimental group, each comprising 3 animals. Filled symbols represent significant difference from saline control at $P < 0.05$ or less

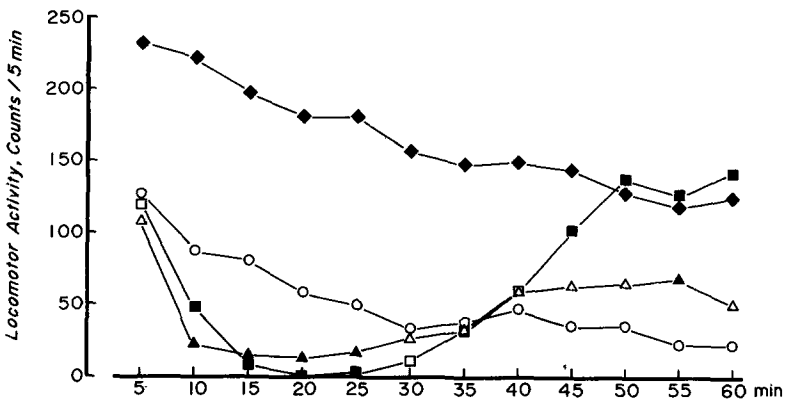

Fig. 3
Suppression of ethanol-induced locomotor stimulation by GHBA. Ethanol (2.4 g/kg i.p. 1 min before recording, ◇——◆) was given to mice alone or in combination with GHBA (200 mg/kg i.p. 1 min before recording, □——■). Control animals received saline (i.p. 1 min before recording, ○——○) or GHBA (200 mg/kg i.p. 1 min before recording, △——▲). Shown are the means of 7 values per experimental group, each comprising 3 animals. Filled symbols represent significant difference from saline control at $P < 0.05$ or less

Table 1. Baclophen in doses of 5–20 mg/kg caused a significant increase in the formation of dopa over NSD 1015 control values in both the striatum and the limbic areas, however, the effects were more pronounced in the striatum. In addition, 0.5 mg/kg baclophen caused a small increase and 2.5 mg/kg a small decrease in the limbic forebrain.

There were no significant baclophen-induced changes of dopa formation in the NE predominated hemispheres, of the levels of tyrosine or tryptophan, or of the accumulation of 5-HTP in any of the brain parts investigated (data not shown).

The time course of the effects of 10 mg/kg baclophen is shown in Table 2. A 35% increase in dopa formation was found in the striatum after 45 min, followed by a linear decrease between 2.5 and 4 h, the dopa value being 30% below control level at 4 h. At 8 h the dopa levels had returned to control values.

Table 1. Effect of various doses of baclophen on dopa formation in rat striatal and limbic regions. Baclopen was injected 45 min and NSD 1015 (100 mg/kg i.p.) 30 min before death. Control rats received NSD 1015 only. Shown are the means ± S.E.M. Figures in parentheses indicate number of experimental groups, each comprising pooled brain parts of 3 rats

Baclophen, mg/kg i.p.	Dopa, ng/sample	
	Striatum	Limbic
Controls	360 ± 5 (26)	197 ± 3 (26)
0.5	377 ± 19 (3)	209 ± 11* (3)
1.25	357 ± 5 (4)	181 ± 11 (4)
2.5	360 ± 13 (5)	180 ± 7* (5)
5	432 ± 13** (6)	218 ± 7** (6)
10	481 ± 19** (4)	213 ± 4* (4)
20	432 ± 40** (2)	228 ± 7** (2)

* Differs from corresponding control group, $P < 0.05$
** Differs from corresponding control group, $P < 0.01$ or less

Table 2. Effect of baclophen (10 mg/kg i.p.) on dopa formation in rat striatal and limbic regions: time course. All rats received NSD 1015 (100 mg/kg i.p.) 30 min before death. Shown are the means ± S.E.M. Figures in parentheses indicate number of experimental groups, each comprising pooled brain parts of 3 rats

Interval baclophen-death	Dopa, ng/sample	
	Striatum	Limbic
Controls	360 ± 5 (26)	197 ± 3 (26)
45 min	481 ± 19** (4)	213 ± 4* (4)
1.5 h	351 ± 15 (4)	195 ± 8 (4)
2.5 h	317 ± 14** (3)	180 ± 12 (3)
4 h	260 ± 27** (3)	155 ± 8** (3)
8 h	345 ± 14 (3)	199 ± 10 (3)

* Differs from corresponding control group, $P < 0.05$
** Differs from corresponding control group, $P < 0.001$

In the limbic forebrain, there was a similar biphasic effect with a significant increase in dopa after 45 min and a significant decrease after 2.5 and 4 h (Table 2). Again, the dopa levels had returned to normal control values after 8 h.

After baclophen, there were no significant differences in dopa formation in the hemispheres, in the level of tryptophan, or in the accumulation of 5-HTP in any of the brain parts studied (data not shown). However, in the striatum, there was a small but significant decrease in the level of tyrosine at 1.5 h (15%) and 2.5 h (18%) and an increase at 8 h (15%). In the limbic forebrain a 13% decrease was observed at 2.5 h. No significant differences in tyrosine levels were found in the hemispheres (data not shown).

DISCUSSION

The results of this investigation show that agents which mimic or augment the actions of GABA (GHBA and AOAA) inhibit the locomotor stimulation produced by small doses of ethanol. These data also indicate that baclophen may have GABA-mimetic characteristics since its effects are very similar to those of GHBA and AOAA in this respect. Pretreatment with baclophen or AOAA, not only prevents the ethanol-induced excitation, but also produces a significant locomotor inhibition, leading to a qualitative change in the behavioural effects of ethanol. Such a qualitative difference is further supported by the finding that slightly higher doses of baclophen and ethanol than were used in the behavioural studies produce complete anaesthesia when administered together. These data suggest a hypothesis that ethanol administration may result in two opposing behavioural effects – a stimulatory effect which is only evident after small doses and a depressant effect after large doses which outweighs the stimulatory effect. The fact that pretreatment with GABA-like drugs results only in behavioural depression after ethanol administration may indicate that these drugs cause a selective elimination of the stimulatory effect of ethanol thereby unmasking a depressant effect.

This observation may be of clinical importance since baclopen is commonly used in man as an antispastic agent and might result in toxic effects if taken with alcohol. The possibility also exists that the interaction of ethanol and GABA-like drugs such as baclophen might be of heuristic value in the treatment of chronic alcoholism.

Previous investigations into the mechanism of ethanol-induced locomotor stimulation have indicated a probable involvement of enhanced CA activity (cf. Introduction). In addition, other experiments carried out in this laboratory (Engel and Carlsson, 1976) show that compounds which antagonize the effect of ethanol on CA neurons also antagonize ethanol-induced behavioural stimulation. For example, α-MT in doses which do not suppress control activity, produced an inhibition of ethanol-induced hyperactivity. This inhibition can be partially reversed by bypassing the α-MT-induced metabolic blockade with L-Dopa. Further support for this hypothesis was provided by the findings that low doses of the dopamine receptor agonists, apomorphine and ET 495, and the monoamine oxidase inhibitor, nialamide, also inhibit ethanol-induced locomotor stimulation, presumably mediated by a type of feed-back mechanism involving presynaptic DA receptors (autoreceptors, Carlsson,

1975a, b) resulting in a reduced synthesis and release of DA.

Recent reports indicate the probable presence of GABA-ergic striato-nigral neurons which inhibit the firing of DA-nigro-striatal neurons (Roberts, 1974; Carlsson, 1975c; Hornykiewicz et al., 1976; Dray and Straughan, 1976). Other investigators have postulated a similar inhibition of the meso-limbic DA system by GABA neurons (Andén, 1974; Carlsson, 1974; Fuxe et al., 1975b). Exogenous administration of the GABA congener, GHBA, has been shown to increase brain concentrations of DA (Gessa et al., 1966; Aghajanian and Roth, 1970; Hutchins et al., 1972). It has been proposed that this increased level of brain DA is due to an increased DA synthesis in combination with a decreased DA release as a consequence of the interruption of nerve impulse flow, in the DA neurons, caused by GHBA (Roth and Suhr, 1970; Roth et al., 1973; Stock et al., 1973). These biochemical effects of GHBA are in all probability mediated via an activation of GABA receptors since intraventricular administration of GABA has also been found to increase DA levels and stimulate DA synthesis in the striatum and limbic forebrain (Biswas and Carlsson, to be published). Furthermore, the local application of both GHBA and GABA into the substantia nigra produces an increase in striatal DA levels (Andén and Stock, 1973).

Recent evidence suggests that baclophen, another GABA congener, may also inhibit the activity of DA neurons (Fuxe et al., 1975a, b), and thereby cause an increase in brain DA, possibly due to a GABA-like action, (Andén and Wachtel, 1976). These data are in agreement with the present findings in which baclophen was found to cause an initial increase in the formation of dopa in DA-rich areas followed by a decrease for up to 4 h. The initial increase in DA synthesis may be the consequence of an inhibition of DA neurons, while the latter decline in DA synthesis may result from an end product inhibition of tyrosine hydroxylase due to increasing levels of DA in the DA-containing neurons (Carlsson et al., 1976). This hypothesis is supported by the discovery that there is an increase in DA synthesis after cessation of impulse flow in DA neurons (Kehr et al., 1972b; Carlsson, 1974; Roth et al., 1974; Carlsson, 1975a, b). In addition, it has been reported that there are similar increases in brain DA levels after axotomy and after administration of GHBA (Stock et al., 1973). Thus, the present biochemical findings are in agreement with the proposal that at least some of the effects of baclophen may be GABA-like.

It should be noted, however, that recent reports regarding the electrophysiological effects of baclophen indicate that this GABA-derivative has actions that cannot be explained by a simple mimicking of the endogenous transmitter (Curtis et al., 1974; Davis and Watkins, 1974) e.g. baclophen-induced inhibition of single cell firing is not antagonized by the GABA-antagonist, bicuculline. Thus, further work must be done in order to elucidate the precise mechanism of the effects of baclophen.

The previous reports concerning the effect of ethanol on DA metabolism and the interaction of DA and GABA systems together with the present studies suggest that the mechanism by which the GABA-like agents inhibit ethanol-induced locomotor stimulation may be: 1) ethanol acts directly on DA neurons, causing an enhanced transmitter release which is then suppressed by an inhibitory action of the GABA-like agents on the DA cell body, or 2) ethanol, in low doses, causes an indirect release of DA due to an inhibition of certain inhibitory GABA neurons; the GABA-like agents then result in a reversal of this process by stimulation of GABA receptors on the DA neurons, or 3) ethanol causes a release of DA by an unknown neuronal mechanism which is antagonized by stimulation of inhibitory GABA receptors on DA cell bodies by the GABA-like agents. Further studies, however, will be necessary to further define the biochemical actions of GABA-mimetic agents on the interaction of ethanol and CA systems. These studies are now in progress.

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