Effects of TRH, Ethanol, and TRH-Ethanol Combination on Activity in Rats With Altered Monoamine Content[1]

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BREESE, G. R., S. COYLE, G. D. FRYE AND R. A. MUELLER. *Effects of TRH, ethanol, and TRH-ethanol combination on activity in rats with altered monoamine content.* PHARMACOL BIOCHEM BEHAV **22**(6) 1013–1018, 1985.— Investigations were undertaken with 5,7-dihydroxytryptamine and 6-hydroxydopamine treated rats to see whether activity changes induced by TRH, ethanol and the TRH-ethanol combination would be affected after reduced monoamine function. In keeping with earlier results, TRH increased activity, ethanol reduced activity and the TRH-ethanol combination produced activity counts greater than those for TRH alone. Neither the 5,7-dihydroxytryptamine-induced reduction of brain serotonin nor the 6-hydroxydopamine treatments which reduced brain catecholamines altered the hyperactivity induced by TRH or the TRH-ethanol combination. While reduction of brain serotonin did not affect the ethanol-induced changes in activity, preferential reduction of dopamine as well as reduction of both norepinephrine and dopamine significantly antagonized this measure of ethanol-induced depression. The reduction of dopamine alone produced the greatest effect on this action of ethanol. It can be concluded from the data that the increased locomotion induced by TRH and the TRH-ethanol combination does not depend upon endogenous monoamines, whereas the sedative effects of ethanol are apparently influenced by alterations in brain catecholamine function.

TRH　　Ethanol　　TRH-ethanol combination　　6-hydroxydopamine—dopamine depletion
5,7-Dihydroxytryptamine—serotonin depletion　　Locomotion—ethanol　　Locomotion—TRH

SEVERAL neurotransmitter systems can influence the depressant effects of ethanol. For example, thyrotropin-releasing hormone (TRH) has been shown to antagonize ethanol-induced sedation [6,12] and impairment of the aerial righting reflex [17]. In addition, several studies have suggested that alterations of biogenic amines may influence ethanol-induced depression of the CNS, though the magnitude and even direction of such effects is not clear [25,43].

Recently, we demonstrated that in addition to the antagonism of ethanol suppression of locomotor activity following TRH, TRH seemed to unmask a stimulant action of ethanol in a rat strain [7], which does not usually demonstrate an increase in activity when given ethanol alone [16]. Carlsson *et al.* [9, 10, 11] suggested that the stimulant action induced by ethanol in a selected mouse strain was dependent upon brain dopamine. Similarly, at least some aspects of the behavioral activation induced by TRH is reportedly dependent upon catecholamine function [18, 27, 29, 30]. Endogenous

TRH has been closely associated with serotonin-containing neurons [8,41] and neonatal destruction of serotoninergic neurons has previously been reported to increase the sensitivity to CNS depressants such as inhalational anesthetics [33] and to alter TRH effects on respiration [32].

From these background data, it seemed important to determine if removal of catecholamine-containing fibers with 6-hydroxydopamine (6-OHDA) or reduction of serotonergic fibers with 5,7-dihydroxytryptamine (5,7-DHT) would alter the acute CNS depression induced by ethanol, affect TRH behavioral activation, or influence its analepsis against ethanol-induced impairment of CNS function.

METHOD

Neonatal Sprague-Dawley rats (Charles River Laboratories, Somerville, MA) were treated with saline or the neurocytotoxic agents as previously described [2, 3, 4, 39].

These rats were not used until they had reached 150 g. For destruction of serotonergic fibers, rat pups received 50 μg (10 μl) 5,7-dihydroxytryptamine (5,7-DHT) intracisternally on day 3 one hr after desipramine (20 mg/kg) [2]. These rats received the same dose of ethanol (2.25 g/kg) that had been used to examine dose-response relationships in an earlier study [7]. This dose of ethanol (2.25 g/kg) allowed us to assess for either increases or decreases in motor function over the various doses of TRH and to confirm our earlier findings. For destruction of both norepinephrine and dopamine, rats received 100 μg (10 μl) of 6-hydroxy-dopamine (6-OHDA) intracisternally on day 5 [4]. Dopa-mine was preferentially reduced by pretreating rats with 20 mg/kg desipramine before administering the 100 μg dose of 6-OHDA [39] on day 5. In this case, a dose of 3 g/kg of ethanol was used with the standardized 100 μg dose of TRH to maximize the locomotor stimulant response [7]. Controls run with the various groups that received the neurocytotoxins were treated with vehicle and a portion with desipramine. Since no differences were observed between these treatments, they were combined. Monoamine content was measured in brain after both neurocytotoxic treatments utilizing the method described by Kilts et al. [26]. Rats were killed three weeks after the last experiment and when the rats were approximately 3–4 months of age. By analyzing selected areas of brain, we were able to assess the effectiveness of the neurocytotoxic treatments.

Locomotor activity was quantitated with doughnut-shaped activity monitors housed in sound-attenuated, fan ventilated chambers illuminated with a 7 watt lamp [20]. After being habituated to the chambers, rats were then given various drug treatments. Ethanol (2.25 or 3.0 g/kg) was administered IP at a concentration of 0.1 g/ml to minimize tissue irritation. Saline was administered to control animals in volumes equivalent to the largest volume of ethanol used. Ethanol or saline was administered 5 min before intracisternal administration of either saline or TRH (3, 25, 100 or 200 μg). All drugs were dissolved in sterile 0.9% saline for intracisternal (25 μl volume) or intraperitoneal (IP) administration. Data were evaluated by analysis of variance. A Newman-Keuls' test was used for post-hoc comparisons of the means. Any difference was considered significant if $p < 0.05$.
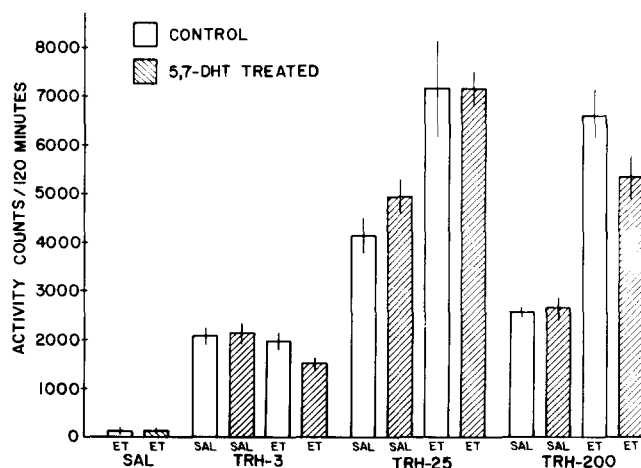

FIG. 1. Effect of destroying serotonergic fibers on the activity changes induced by TRH, ethanol, or the TRH-ethanol combination. Various doses of TRH were administered to rats receiving saline (sal) or ethanol (ET, 2.25 g/kg, IP). Ethanol was administered 5 min before intracisternal injection of TRH and saline. Locomotor activity was recorded for 2 hr and activity counts summed over that period. The 5,7-DHT treatment is defined in the Methods section. Locomotion for the TRH-ethanol group was significantly increased at TRH doses of 25 μg and 200 μg (IC), when compared to TRH alone or to saline ($p < 0.01$). Activity counts for control and 5,7-DHT-treated rats given saline was 724±195 and 943±177 counts/120 min, respectively ($p > 0.1$). All groups represent the mean±SEM of 6–10 rats. Serotonin content for control and 5,7-DHT treated rats is presented in Table 1.

RESULTS

Effect of Desipramine-5,7-Dihydroxytryptamine (5,7-DHT) Treatment on Ethanol, TRH or the TRH-Ethanol Combination Induced Changes in Locomotion

In agreement with earlier findings in control rats, TRH by itself increased activity [43] and all doses of TRH antagonized ethanol's reduction of locomotion [7]. Furthermore, 25 and 200 μg of TRH induced activity in combination with ethanol in control rats that was significantly greater than for

TABLE 1

MONOAMINE CONTENT IN BRAIN OF 5,7-DHT AND 6-OHDA TREATED RATS†

Brain Area	Monoamine	Control	DM1 + 6-OHDA	Neonatal 6-OHDA	Neonatal 5,7-DHT
Striatum	Dopamine	85.1 ± 2.1	4.5 ± 1.9*	1.2 ± 0.8*	78.3 ± 4.1
	Serotonin	4.6 ± 0.2	5.9 ± 0.3*	5.2 ± 0.3*	0.7 ± 0.1*
Olfactory Tubercle	Dopamine	34.5 ± 1.9	4.5 ± 1.4*	1.1 ± 0.6*	38.0 ± 2.4
	Serotonin	10.5 ± 0.5	8.7 ± 0.6	9.8 ± 0.6	0.8 ± 0.1*
Rest of Brain	Dopamine	6.0 ± 0.4	0.8 ± 0.1*	1.0 ± 0.1*	5.8 ± 0.4
	Serotonin	5.2 ± 0.3	5.3 ± 0.3	5.0 ± 0.4	1.3 ± 0.3*
	Norepinephrine	3.1 ± 0.3	3.3 ± 0.2	0.1 ± 0.1*	2.9 ± 0.3

*$p < 0.05$ when compared to corresponding control.

†Values are the mean ng/g protein ± S.E.M. of at least 5 rats from the same litters that were used to derive the behavioral data. Explanation of 6-OHDA-treatment groups ("DM1 + 6-OHDA" and "6-OHDA") are described in the legend to Fig. 2. Representative effects of these treatments on other brain areas can be found in Breese et al. [5].

TABLE 2

EFFECT OF 6-HYDROXYDOPAMINE (6-OHDA) TREATMENTS ON ACTIVITY INDUCED BY TRH, ETHANOL AND THE TRH-ETHANOL COMBINATION

Treatments†	Activity (Counts/2 hr)
A. Control	
-Saline	1625 ± 207
-TRH	4306 ± 724
-Ethanol	292 ± 103
-TRH-Ethanol	7968 ± 504*
B. 6-Hydroxydopamine	
-Saline	1427 ± 215
-TRH	3917 ± 420
-Ethanol	641 ± 141‡
-TRH-Ethanol	8036 ± 838*
C. Desipramine + 6-Hydroxydopamine	
-Saline	1213 ± 264
-TRH	4324 ± 989
-Ethanol	1862 ± 399‡
-TRH-Ethanol	11046 ± 2047*

†Rats received ethanol (3.0 g/kg, IP) 5 min before receiving 100 μg of TRH intracisternally in control (A) and 6-OHDA-treated rats (B and C). The 6-OHDA was administered as described in the Method section; "6-hydroxydopamine" refers to rats with both brain norepinephrine and dopamine reduced and "Desipramine + 6-hydroxydopamine" refers to rats with brain dopamine reduced. Monoamine content for representative groups to demonstrate the effectiveness of the treatment is presented in Table 1. Each value represents the mean ± SEM of 6–11 rats.
*$p<0.05$ when compared to TRH or to ethanol alone.
‡$p<0.05$ when compared to saline-ethanol (group A).

TRH alone (Fig. 1). This result is also consistent with an earlier report [7]. In those rats treated with 5,7-DHT to destroy serotonergic fibers, neither the TRH-ethanol-induced hyperactivity nor TRH-induced activity was altered (Fig. 1). In addition, the reduction of locomotion induced by ethanol was not affected by this treatment. Effects of 5,7-DHT treatment on monoamines in selected areas of brain are presented in Table 1.

Effect of Various Neonatal-6-Hydroxydopamine (6-OHDA) Treatments on TRH, Ethanol and the Ethanol-TRH Combination Induced Alterations in Locomotion

These data demonstrate that the increased dose of ethanol (3 g/kg), in combination with 100 μg of TRH intracisternally, resulted in activity counts greater than that for TRH alone (Table 2). Even though dopaminergic neurons have been implicated in the hyperactivity observed in rat strains demonstrating this response to ethanol, the 6-OHDA treatments did not attenuate the activity induced by the TRH-ethanol combination (Table 2). Neither did these treatments alter the activity response to TRH alone. However, both 6-OHDA treatments reduced the usual sedation produced by ethanol (Table 2, Fig. 2), with the brain dopamine depletion producing a significantly greater antagonism of ethanol-induced locomotion than that induced when both brain catecholamines were reduced (Table 2). Locomotor activity counts observed after ethanol treatment in the 6-OHDA-treated groups are plotted over time in Fig. 2. Monoamines in selected brain areas are presented in Table 1.
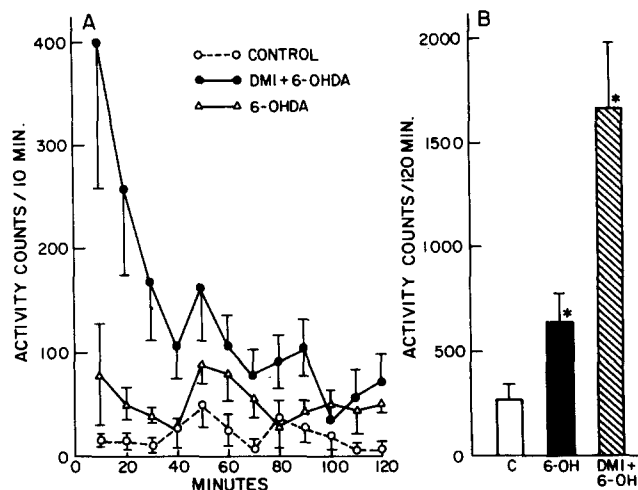

FIG. 2. Time-course of activity after ethanol in rats treated to reduce brain catecholamines or dopamine. Rats were treated with ethanol (3 g/kg, IP) 5 min prior to being placed in the activity chambers. Activity counts at 10 min intervals for the two hour recording period are provided in Panel A. Total counts over the two hour period are presented in Panel B. "DMI + 6-OHDA" refers to rats (N=12) treated to reduce dopamine; "6-OHDA" refers to rats (N=6) treated with 6-hydroxydopamine to reduce both norepinephrine and dopamine. Values represent mean±SEM. *$p<0.01$ when compared to control given ethanol.

DISCUSSION

The data collected in this study reaffirm the analeptic effects of TRH against ethanol depression of CNS motor function [7,12]. Furthermore, the hyperactivity observed by the TRH-ethanol combination reported earlier [7] was clearly evident at doses of TRH above 25 μg. Since this Sprague-Dawley strain shows only depression of motor function when given ethanol [16], this finding is consistent with the view that TRH is revealing a stimulant action of ethanol in this strain [7,16]. However, this view may yet require modification, because impairment of locomotion by ethanol was antagonized by 6-OHDA treatment, yet no hyperactivity of the magnitude noted by the TRH-ethanol combination was noted in these treatment groups.

Even though Carlsson et al. [9,14] presented evidence that brain catecholamines are involved in the stimulant action of ethanol, the absence of an inhibitory effect on the hyperactivity induced by the TRH-ethanol combination after destruction of catecholamine-containing fibers seems to discount an involvement of catecholamines in this response. Similarly, destruction of serotonergic pathways did not affect TRH-ethanol-induced activity. Thus, neural pathways other than these must be responsible for the TRH-ethanol-induced activity in our Sprague-Dawley rat strain. Further, the activity noted by this combination is likely mediated by a different neural mechanism than that observed in the rat strain used by Swedish investigators, because dopamine was clearly implicated in this locomotor stimulation [8, 9, 10, 14].

Reduction of catecholamines in brain with 6-OHDA did not antagonize the locomotor stimulant effect of TRH in agreement with an earlier finding [43], suggesting that brain catecholamines are not involved in this action of TRH. In accord with this result, the profile of TRH to induce behavioral excitation does not resemble that for d-amphetamine

[15,27], a drug associated with dopamine release [20]. For example, drugs like yohimbine and naloxone, block TRH-induced activity, but do not alter the actions of d-amphetamine [27]. Further, TRH does not induce turning in an animal with a unilateral lesion to the substantia nigra [18], as would be expected if dopamine were being released by TRH. d-Amphetamine induces turning after unilateral lesions to the nigrostriatal pathway [42]. Another drug dependent upon intact dopaminergic mechanisms is scopolamine [36]. Whereas the actions of d-amphetamine are antagonized by 6-OHDA treatment [20], the effects of scopolamine are not, unless administered with alpha-methyltyrosine [36]. Perhaps TRH acts on dopamine pathways in such a way that the degree of disruption of dopamine synthesis required to antagonize scopolamine-induced locomotion after 6-OHDA treatment may also be necessary for TRH.

In contrast to the conclusion that brain catecholamines do not support the locomotor effects of TRH, several investigators have provided evidence for the stimulant action of TRH being associated with dopamine-released in the nucleus accumbens [18, 19, 22, 29, 30, 31, 38]. These studies have included administration of TRH directly into this brain area to induce locomotion [18, 19, 31], pharmacological blockade of this TRH response with alpha-methyltyrosine and haloperidol [18, 19, 27, 30] and release of dopamine from slices of rat nucleus accumbens [22, 30, 34]. It is interesting that the locomotor response to peripheral administration of TRH was not antagonized by lesions of the nucleus accumbens [19,31]. It is also worth mentioning that the action of TRH placed in the nucleus accumbens was potentiated by tranylcypromine pretreatment, whereas systemically administered TRH was not affected by this treatment [18]. Nevertheless, a dose of 1 mg/kg haloperidol antagonizes the locomotor response following peripheral injection of TRH [18,19]. While there is evidence that TRH does not act to release dopamine in the caudate [18], an elevation of dopamine metabolites can be noted in ventricular perfusates [35]. Drust and Connor [13] recently reported that shaking behavior was diminished by 6-OHDA pretreatment, but unaffected by 5,7-DHT treatment. It is not presently known what area(s) of brain are necessary for these latter actions. As pointed out above, there is evidence that peripherally injected TRH has a slightly different action from that administered directly into the nucleus accumbens, suggesting that TRH may have multiple sites of action. Since the 6-OHDA treatments did not antagonize the activity induced by TRH, another explanation would be that TRH is exerting an interaction on post-synaptic dopamine-receptive neurons that rely on residual amounts of dopamine. Evidence for this latter possibility is not available. Hopefully, future investigations will permit a better understanding of results concerning the action of TRH on catecholamine-containing neurons.

Even though TRH has been co-localized in neurons containing serotonin within the CNS [21,41], destruction of serotonergic-containing fibers with 5,7-DHT did not alter the locomotor response to TRH at any of the doses tested. Earlier findings from our laboratory have demonstrated that 5,7-DHT treatment can enhance the effect of TRH on respiratory function [32]. Co-localization of serotonin and TRH is most frequently associated with caudal brain stem regions and spinal cord [41]. In more rostral sites in brain, TRH and serotonin-containing neurons are usually independent of each other [41]. 5,7-DHT treatment has been shown to increase TRH receptors in caudal brain structures, but not in rostral forebrain areas, providing an explanation for the enhanced TRH response in 5,7-DHT treated rats [37]. Therefore, in view of these previous data, the present findings suggest that the locomotor stimulant effect of TRH is associated with a brain area where reduction of serotonin does not influence TRH receptors and would appear to discount a role for serotonin in the behavioral activation induced by TRH.

Only a limited number of investigations have been undertaken to examine the effects of monoamine disruption on the intoxicating effect of ethanol. Kiianmaa and Attila [25] examined the effects of peripherally administered neonatal 5,7-DHT treatment on the intoxication produced by ethanol and found no significant change. This result is consistent with the lack of change found after 5,7-DHT treatment. Other reports which utilized p-chlorophenylalanine to reduce serotonin in brain also found no change in the depressant effects of ethanol [1,40]. Since the action of inhalation anesthetics are enhanced by 5,7-DHT treatment [33], it would appear that ethanol has properties different from these compounds on the CNS. Consistent with our present finding that catecholamine reduction in brain antagonized the reduced locomotion induced by ethanol, Wood and Laverty [44] found that 6-OHDA treatment significantly reduced ethanol-induced sleep. These latter workers implicated norepinephrine in this action because a similar change was not observed after specific depletion of dopamine [44]. In keeping with this view, Mason *et al.* [28] reported that lesioning of norepinephrine-containing pathways antagonized the sedation induced by 1 g/kg of ethanol. However, these data would be at odds with our present finding that ethanol-induced reduction in activity is dramatically antagonized in rats treated neonatally to reduce only dopamine. Consistent with our results, Kiianmaa [23] found decreased intoxication following 6-OHDA lesions to ascending dopamine-containing pathways. Further, this latter laboratory has reported that neonatal treatment with 6-OHDA which reduces brain norepinephrine enhances the sedative effects of ethanol [24,25]. In our rats, the fact that reduction of both catecholamines in brain produces significantly less effect than when dopamine alone was reduced in brain probably relates to this latter finding. From these array of data, it can be concluded that catecholamine-containing fibers do indeed influence ethanol narcosis. However, an explanation for the disparate findings in different laboratories as to which catecholamine-containing pathway is of greater importance must yet be determined. Possibilities for the divergent results include the differing ages at which the rats were treated with 6-OHDA [5], the routes by which catecholamine-containing fibers were destroyed among the various studies, as well as the potential for strain differences [16].

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