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Effects of Acute Ethanol Administration on Neocortical Inhibition

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The hypothesis that acutely administered ethanol could interfere with neocortical recurrent inhibition (RI) was supported. The large surface negative wave in response to antidromic stimulation of the cerebral peduncle represents a summation of inhibitory postsynaptic potentials, a measure of RI. In acute experiments on adult rats, blood alcohol levels of less than about 120 mg/100 ml slightly facilitated the surface negative wave. Higher blood alcohol levels always blocked the surface negative response. Stimulation of the somatosensory thalamic relay nuclei produced a cortical response on which ethanol had a moderate blocking effect. Conditioning-test procedures revealed that cerebral peduncle stimulation strongly blocked the thalamocortical (test) response, especially after ethanol, but thalamic stimulation (conditioning) had no effect upon the surface negative wave. This demonstrates a differential effect on the two cortical processes. Cortical RI seems to be especially sensitive to blood alcohol level, but the function of cortical RI is complex. By way of acting on RI, ethanol likely affects control of sensory input and cortical sensory organization as well as selectivity and magnitude of motor discharge.

ETHANOL is known to affect many areas of the brain. A common assumption, based upon behavioral observations in humans, is that it releases the neocortex from inhibitory control (disinhibition[1]). Few neurophysiological data support this assumption, mostly because we know little about possible correlations between commonly measured electrical events, such as evoked potentials and specific cortical functions of excitation and inhibition. For example, an evoked potential recorded from the cortical surface or scalp is a field potential, representing in large part summations of populations of neuronal postsynaptic potentials. Unless the kinds and loci of the postsynaptic potentials are identified, it is not possible to say that a change in evoked potential amplitude under an experimental condition represents more or less excitation or inhibition. To a considerable extent this caution also applies to measures of neuronal unit activity. An extracellular spike can be from either an inhibitory or an excitatory cell.

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Numerous studies have shown that acutely administered ethanol has mixed or inconsistent effects upon various cortical evoked potentials and neuronal unit firing.[2-9] More related to the results of our study is the work of Nestoros[10,11] who found in cat cortex that ethanol potentiated the inhibitory effect of surface stimulation upon neurons as well as γ-aminobutyric acid-mediated inhibition.

We selected a specific measure of cortical inhibition on which to test the effects of ethanol. The neocortex of mammals contains an inhibitory circuit that includes axon-recurrent collaterals of pyramidal tract and other corticifugal cells synapsing on inhibitory interneurons.[12-14] Electrical stimulation of the pyramidal tract produces an antidromically mediated complex field potential recorded at the cortical surface. The largest wave of the potential is surface negative (SN) and likely represents a summation of inhibitory postsynaptic potentials.[12,15,16] The SN wave can be viewed as a measure of one kind of cortical inhibition (recurrent). The functional significance of cortical recurrent inhibition (RI) for motor behavioral expression has been studied. It was found that cortical RI tends to limit the spread of pyramidal tract neuronal activity as well as that of other cortical cells.[17] As in the spinal cord,[18] cortical RI appears to have a neuronal discharge frequency-limiting function.[17] Cortical RI is likely important for controlling a major part of the output from the cortex. The hypothesis for the experiments reported here was that acutely administered ethanol could interfere with a specific cortical inhibitory mechanism, RI, as evaluated by the SN wave.

METHODS

Animals

Data were obtained from experiments on 25 male Sprague-Dawley rats (Charles River) weighing between 410 and 560 g. They had been housed in the animal colony for at least 3 weeks with ad libitum water and standard rat pellet chow. In preliminary experiments it was found that a combination of ketamine HCl and xylazine gave the most physiologically stable preparations and had no discernible interactive effect with ethanol doses. An initial intramuscular dose of 13 mg/kg of xylazine was given 10 min prior to an injection of 90 mg/kg of ketamine (intraperitoneally). Supplementary doses were: 13 mg/kg of xylazine every 4 hr and 30–50 mg/kg of ketamine every 1-1.5 hrs. Rats were placed in a stereotaxic apparatus and the dorsal cortical surface exposed under warm mineral oil. Temperatures of the body and the cortical oil pool were maintained by a heating pad and heat lamp.

Electrodes

For antidromic stimulation of the motor projection pathway, a concentric bipolar depth electrode was inserted at the level of the cerebral peduncle (CP) where the corticifugal fibers are farthest from the medial lemniscus (rostral, −1.8; lateral, 2.75; depth, 8.75; System B, Pellegrino et al.[19]). In larger animals like the cat, antidromic stimulation of corticifugal fibers is best done by isolating the pyramidal tract which prevents stimulating current spread to sensory afferent fibers in the medial lemniscus.[20] Such isolation is not routinely possible in the small brain of the rat and therefore it was assumed that CP stimulation could lead to some orthodromic effects and activate the somatosensory pathway. For this reason we chose to stimulate the somatosensory thalamic relay area deliberately to produce a thalamocortical (TC) response. This cortical potential could be interacted with the SN wave in a conditioning-test procedure in order to evaluate contributions of neurons commonly shared in the two pathways activated.

For stimulating and recording from the somatosensory relay in the thalamus,[21,22] a concentric bipolar electrode was aimed for the ventral nucleus-posterior nucleus complex (rostral, −3.2; lateral, 2; depth, 6.75).[19] A platinum ball recording electrode was placed on the sensorimotor cortex[22,23] at the location of best antidromic response to stimulation of the ipsilateral CP. A reference electrode was attached to a screw in the rostral skull. Foot shock was via needles inserted in a foot pad. At the conclusion of each experiment, current was passed through the depth electrodes and loci were determined by histological examination (Weil stain) as necessary.

Blood Alcohol Level

The procedure for the enzymatic determination of blood ethanol (Sigma Chemcial Co. No. 332-UV) was modified to use small capillary tubes to collect blood samples from the cut end of a rat's tail. Each sample set for blood alcohol level (BAL) measurements was compared with a control standard. In preliminary experiments, BAL data from this procedure were equivalent to those from the Sigma procedure requiring 0.5 ml for each blood sample. It was possible to take blood samples every few minutes without serious blood loss since only about 180 μl of blood were needed for each determination. Blood ethanol equilibrates rapidly with brain[24] and we wanted to observe possible biphasic effects which could start within a few minutes after administration. Ethanol was usually administered in 2 g/kg amounts as a 66% (v/v) solution in order to keep the volume to about 2 ml since repeated doses would be given in some experiments.

Experimental Procedure

The response characteristics of the antidromically elicited surface negative wave, the cortical response to thalamic stimulation, the primary cortical potential evoked by foot shock, and the thalamic potential in response to foot shock were established in preliminary experiments. Input-output functions showed that the most reliable response data were obtained by using intensity of stimulation sufficient to produce near maximal responses. Electrical stimulation pulse durations were kept between 0.1 and 0.5 msec and the intensity was varied as necessary but kept constant after optimal responses were obtained in a particular experiment. For SN elicitation, repetitive shocks were sometimes more effective than single shocks. Standard electrophysiological equipment was used with computer averaging of responses during 50–200-msec sweeps. The number of sweeps averaged was 5–15 depending upon response variability. Stimulation rate was 1 Hz. Since rate of ethanol uptake varied it was not possible to pool data and therefore individual response curves are presented.

RESULTS

In preliminary experiments response amplitudes, latencies, and durations were measured but only response amplitudes of the negative waves seemed to vary reliably with BAL and thus this was the exclusive measure. The three principal cortical field potentials are shown in Fig. 1. Note that preceding the SN wave there are one or two positive deflections. These have been identified by others as probably representing pyramidal tract neuron responses (earliest positivity[25]) and/or soma or postsynaptic activity (second positivity in cat[12]). In only a few preparations could we identify two positive deflections as in Fig. 1B; more usually there was only one as in Fig. 1A. The TC and foot shock evoked potentials consisted of positive-negative components (Fig. 1C). Other succeeding wave components were observed, especially in response to foot shock, but they were too variable for study. Amplitude measurements were made of the major negative wave peaking at 8–10 msec for the SN wave, 10–15 msec for the TC response, and about 15 msec for the potential evoked by foot shock. Since the thalamic response to foot shock was usually small and attenuated, it proved to be of little use in helping to determine if the thalamic-stimulating electrode (central pole for recording) was in the somatosensory relay area.

Ethanol depressed the SN wave but the effect upon the positive deflection varied (compare Fig. 1A2 and Fig. 1B2). Ethanol at 2 g/kg completely eliminated the potential evoked by foot shock within 5–10 min and there was no, or only slight, recovery after about 1 hr (not illustrated). This effect was in contrast to that seen on the SN wave and TC responses where negative potential amplitudes were more slowly depressed. Reduction of the SN wave depended upon the rate of ethanol uptake and BAL. Data in Fig. 2 were obtained from two separate experiments. BAL was measured five times during slow uptake after the initial intraperitoneal injection in one of the

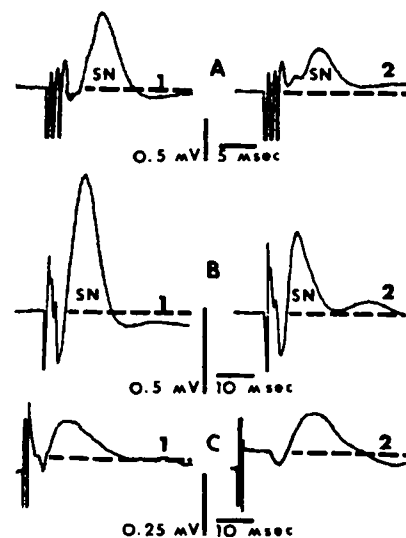

Fig. 1. Cortical surface recordings after stimulation of cerebral peduncle (A, repetitive; B, single shock), thalamus (C1), and foot (C2), in animals A, B, and C. CP stimulation control SN responses are in A1 and B1. A2 is 11 min after 2 g/kg of ethanol (intraperitoneally) and B2, 18 min after ethanol. Stimulation intensities for just maximal responses. Surface postivity down. Amplitudes measured from the peak of negative potentials to indicated baseline.

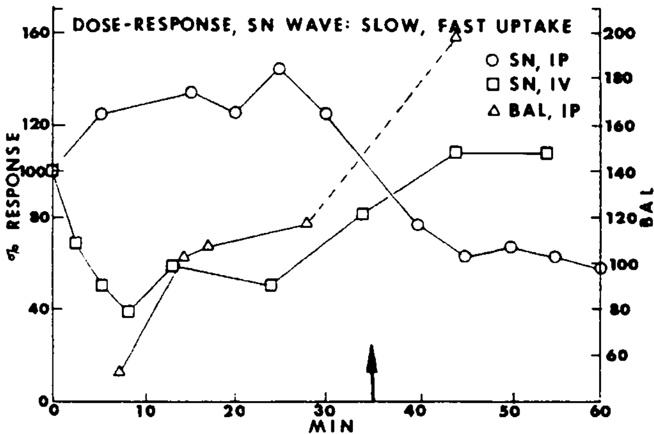

Fig. 2. Effect of ethanol on the SN wave. SN wave amplitudes after slow and fast ethanol uptake compared in two animals, intraperitoneal administration in one, intravenous in the other. BAL for the intraperitoneal experiment only. Two intraperitoneal injections of 2 g/kg, the first completed at time zero, the second given at arrow. Intravenous injection, 2 g/kg completed at time zero, duration of injection 2 min. Control SN amplitude taken as 100%. BAL in mg/100 ml. These are only "dose-response" effects in terms of BAL; the curves can be called time-responses.

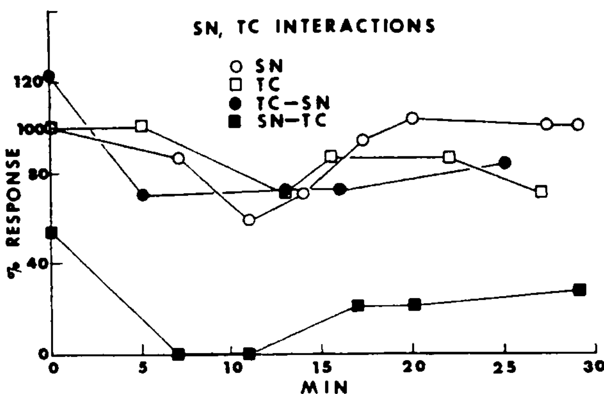

Fig. 3. SN and TC response amplitudes after 2 g/kg of ethanol (intraperitoneal) given during 2 min prior to time zero. Control responses, just prior to ethanol, indicated at zero time. No BAL determinations. SN and TC waves were depressed similarly with maximal effect of about 35% around 12 min. ●, ■, conditioning-test interactions, stimultion separation 30 msec.

animals. A biphasic effect was seen. Below about 120 mg/100 ml the SN wave amplitude increased, but following a second intraperitoneal injection, 35 min after the first, there was about a 55% amplitude decrease while BAL was increasing to 200 mg/100 ml. Following intravenous injection, where ethanol uptake into brain would be relatively rapid, there was a 50–60% reduction in SN wave amplitude for about 25 min following which the SN wave "recovered." Such recovery was frequently seen in about 1 hr after a single intraperitoneal injection when the BAL had begun to fall toward 120 mg/100 ml. In some experiments there was an indication that "tolerance" could develop since amplitude of the SN wave showed an increase from its smallest point before the BAL began to decrease.

In an experiment in which BAL was not determined, ethanol seemed to have an equal effect upon TC and SN responses (Fig. 3). However, when the responses were interacted, reciprocal blocking effects were not found. Prior to ethanol administration, thalamic stimulation seemed to facilitate the SN wave about 20% (TC-SN, Fig. 3), but this is an artifact since it could be explained by this unusual TC response's long duration (more than 30 msec) which algebraically summated with the SN wave. In all experiments where the thalamic electrode was correctly located in somatosensory relay structures, thalamic conditioning stimulation had no significant effect upon the SN wave (Fig. 4). The weak effect of thalamic stimulation (conditioning) upon the SN wave (test) was totally different from that seen when CP stimulation preceded that to the thalamus. Prior to ethanol, CP stimulation reduced the TC response by about 50%; after ethanol, it blocked it completely from about 7–11 min (Fig. 3).

Figs. 4 and 5 show the relationships between the effects of a single ethanol dose and electrophysiological responses

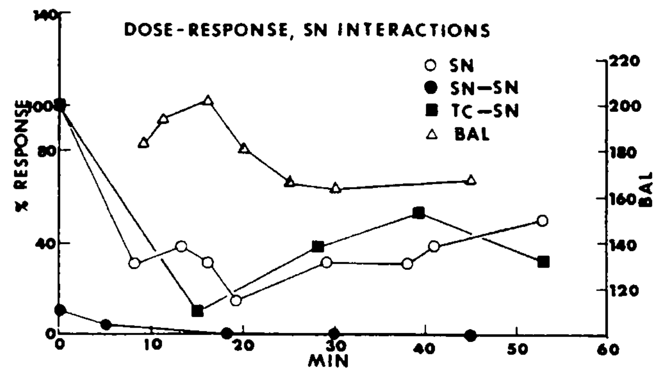

Fig. 4. BAL and SN wave amplitudes after a single intraperitoneal injection of 2 g/kg during 2 min prior to time zero. Control SN amplitude taken as 100%. Rapid block of SN wave occurred with BAL rising above 180 mg/100 ml within 8 min. The SN wave started to recover slightly by 50 min even though BAL leveled off around 165 mg/100 ml. Dual shocks to CP (SN-SN), separated by 110 msec, resulted in 90% SN wave block prior to ethanol and total block after. Thalamic stimulation (TC) preceding CP stimulation (SN) by 50 msec had no additional effect upon the SN wave. Dose-response: see Fig. 2.

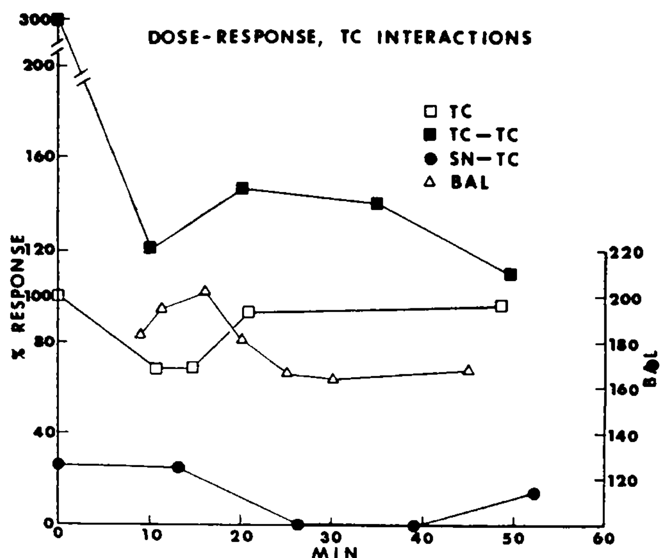

Fig. 5. Same experiment as in Fig. 4, but TC response emphasized. TC response decreased 32% 11 min after 2 g/kg of ethanol (intraperitoneal). However, TC response was greatly facilitated when dual thalamic shocks spaced 110 msec were given. Conditioning stimulation to CP preceding thalamic stimulation by 110 msec totally blocked the TC response by 26 min. Dose-response: see Fig. 2.

obtained during seven BAL determinations made over the same time period. Fig. 4 clearly shows the usual observation of SN wave blockade by BAL above 160 mg/100 ml and that activation of the TC pathway with a conditioning shock had no additional effect upon the SN wave. Note the total refractoriness of the SN wave, after ethanol, when dual shocks to CP were given. In Fig. 5 two other consistent findings are illustrated. First, in nine experiments where histology verified the thalamic-stimulating location as being in or near the posterior nucleus, the ventral nucleus, or the medial lemniscus, 2 g/kg of ethanol reduced the TC response amplitude an average of 45% within 11–25 min. Second, in contrast to the absence of TC effect upon the SN wave, stimulation of CP reduced the TC response to zero by 26 min. There were no exceptions to this nonreciprocal blocking relationship between TC and SN responses (Figs. 3, 4, and 5). In the majority of experiments, ethanol had a greater blocking effect upon the SN wave than it did upon the TC response. Also of note, in contrast to SN refractoriness with dual CP shocks (Fig. 4), dual stimulation of the thalamus resulted in facilitation of the TC response (Fig. 5).

DISCUSSION

The hypothesis for these experiments was supported by finding a consistent relationship between BAL above about 120 mg/100 ml and the amplitude of a negative cortical potential which is a measure of recurrent inhibition. BAL below above 120 mg/100 ml occasionally slightly facilitated the antidromically elicited SN wave, but always blocked it at higher BALs. This biphasic effect has been described for other ethanol effects on the brain.[26] The other cortical responses evoked by foot shock and thalamic relay stimulation also responded to ethanol. The potential evoked by foot shock was quickly blocked and showed little recovery, while the TC response could be reduced about 45% with marked recovery of tolerance even though BALs were not dropping. This apparent tolerance was also observed with the SN wave, but less frequently. Conditioning-test pairings revealed that ethanol had different effects on the two cortical systems, as represented by the TC response and the SN wave.

CP stimulation (conditioning) producing the SN wave, strongly blocked the TC response (test), and even more so after ethanol. The reverse, TC block of the SN wave, was not found. These differential effects can be explained by assuming two different cortical circuits are involved. It has already been pointed out that the SN wave likely represents summations of synchronous inhibitory postsynaptic potentials in a recurrent inhibitory circuit.[12,15] The basis for the TC response is much less definite. Cortical surface potentials are field potentials, reflections of summations of synchronized postsynaptic potentials and fiber activity rather than neuronal action potentials.[15,27,28] It is theoretically possible to identify the loci of inhibitory and evoked postsynaptic potential generators associated with evoked field potentials and to draw conclusions about which components of an evoked potential represent excitation or inhibition. However, as pointed out by Humphrey[15] and Towe,[28] experimental results are exceedingly difficult to obtain. Creutzfeldt et al.[29] in experiments on cats, showed that the large, early surface negativity in response to stimulation of the ventral-lateral nucleus of the thalamus, represents both excitatory and inhibitory postsynaptic potential activity at different locations on neurons in upper cortical layers (vertically elongated pyramidal cells). The TC negative wave, in our experiments, is likely a mixture of synchronized depolarizations in apical dendrites of pyramidal cells below the recording electrode and hyperpolarizations in the region of their somas. In the cat, Towe[28] implicated pyramidal cells in layers II and III as receiving somatosensory input from the thalamus. In our experiments, ethanol depressed the TC negative wave by 45%, but there is no way of proving whether the block was on deep hyperpolarizations (block of inhibition) or on superficial depolarizations (block of excitation). However, since ethanol also depressed the SN wave (above a BAL of 120 mg/100 ml) it is suggested that ethanol has only one kind of action on the TC and SN responses, a block of postsynaptic inhibition. That two different neural circuits are involved in mediating the SN wave and TC response is also supported by the observations that dual shock produced inhibition of the SN wave and facilitation of the TC response.

Our observations and interpretations are based upon the use of ketamine-xylazine for anesthesia. Although we did note that SN wave depression after ethanol occurred without dependence upon the depth of anesthesia, the observations on the SN wave should be confirmed in other species and under different conditions, such as, without general anesthesia. The present data on ethanol block of the TC response and the potential evoked by foot shock do confirm similar studies by others on evoked potentials with and without anesthesia.

Story et al.[30] found that 2 g/kg of ethanol, in unanesthetized cats, blocked the large cortical negative wave (peak at about 10 msec latency) to thalamic sensory relay stimulation and the visual cortex response (not illustrated) to optic tract stimulation. Perrin et al.[4] observed that ethanol blocked the early (within about 25 msec) complex auditory-evoked cortical response in unanesthetized cats, but only if BAL reached about 50 mg/100 ml. Hetzler et al.[31,32] studied positive and negative cortical potentials during about 300 msec, in response to photic stimulation, in unanesthetized rats. Late and early waves were depressed but one positive wave was enhanced by ethanol (1.0–2.5 g/kg). BAL was not given. From a review of many studies[26] it is obvious that ethanol has multiple loci of effects in the brain; some of these are in the neocortex.

The previous reports of ethanol effects on evoked neocortical potentials have not considered the neuronal bases

for the observations. One does not know whether ethanol affected processes of excitation or inhibition in those experiments and thus conclusions about function cannot be made. As a result of relating the evoked TC response to the SN wave in the present experiments, it can be suggested that two different circuits were affected by ethanol in different degrees, both circuits contained some shared inhibitory interneurons, and the interaction between activity in the circuits was in one direction only. It may be concluded that acutely administered ethanol above about 120 mg/100 ml blocks neocortical inhibitory processes and this occurs via inhibitory interneurons. If BAL is low and rises slowly toward 120 mg/100 ml, an initial effect may be a slightly increased amount of recurrent inhibition, but since ethanol infrequently increased the SN wave amplitude we tend to discount this observation.

Low doses of ethanol caused neocortical desynchronization and high doses synchronization and delta waves.[26] These effects have been interpreted as evidence for cortical excitation and inhibition on the afferent side. Low doses of ethanol increased spontaneous locomotor activity and high doses inhibited it[33]; these are efferent effects. We view ethanol block of neocortical RI as one effect which could lead to increased motor discharge from the cortex. Although the function of RI in the cortex is unknown it may act to limit the frequency and the selectivity of discharge from cortical motor cells, analogous to its possible function in the spinal cord.[34] Another effect of ethanol may be upon other inhibitory neurons[35] which normally fine tune smaller cortical regions and circuits. The total effect could be a loss of selectivity of cortical motor control and an increased excitation of lower motor neurons. Although in the following paper,[36] we suggest that chronic ethanol treatment results in loss of inhibition upon cortical excitatory processes, it seems too restrictive to explain the effect of acute ethanol upon the cerebral cortex as "disinhibition." Ethanol blocks RI in the hippocampus,[37] a nonmotor structure. It is likely that RI in both hippocampus and neocortex may also function to control the proper distribution of neuronal activity initiated by afferent input.[36]

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