ing the display size. Rather, our results imply that vision reversal reversed the interpretation of visual information from the exposed portion of the visual field. This change was adaptive, in that it appeared to be directed toward the goal of veridical self-motion perception. The RCV could be demonstrated only when the field of view was limited to or less than the field of view of the goggles. With a wide field stimulus (as in experiment 1), RCV appeared to be overwhelmed by normal vection. In experiment 2, normal CV response to PVF stripe motion was, if anything, enhanced by exposure of the central field to visual reversal. Our findings suggest that visual information from the exposed central visual field is transmitted centrally along pathways separate from those carrying information from the peripheral visual field and that each of these pathways may be separately modified as a result of sensory experience. The occasional presence of alternating normal CV and RCV during early tests during exposure suggests that RCV may not develop gradually. Instead, it is as if a second competitive mechanism develops.

It is not surprising that the RCV velocity magnitudes reported were modest, given the narrow field of view of the goggles, as normal CV can be more effectively elicited if peripheral retinal areas are exposed to the moving display (*13*). Whether a subject demonstrated RCV within the allowed exposure period appeared to be correlated with CV strength produced with a narrow field stimulus. In experiment 2, subjects B1 through B4 showed strong normal CV at least once, either in CVF tests before exposure or during the first four sessions during exposure; they were the only subjects in this experiment to show RCV. Test scheduling constraints limited exposure to 190 minutes in experiment 2. Had the exposure for subjects B5 through B7 been extended, it is conceivable that they, too, would have shown RCV. The exposure duration in experiment 1 was not so constrained, and all five subjects experienced RCV.

In animals, convergence of visual and vestibular head rotation information occurs in neurons of the vestibular nucleus (*14*), which are thought to determine the slow phase velocity of vestibular and optokonetic nystagmus under many conditions. The extent to which vestibular nucleus neurons contribute to rotation perception is unknown, although there seems to be a close relationship between the time course of normal CV in humans (*15*) and the response pattern of some vestibular nucleus neurons in animals (*14, 16*). It would be interesting to know if a reversal in visual sensitivity of vestibular nucleus neurons can be demonstrated in animals after several hours of active exposure to vision reversal. It may be that both CV and VOR (*8*) adaptation are mediated by a common (possibly transcerebellar) mechanism that provides a reversed drive to neurons of the vestibular nucleus. The long latency (1 to 2 weeks) of VOR reversal (*7*) (when contrasted with the rapid CV reversal we found) may result from the presence of a direct, competitive input from primary semicircular canal afferents.

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Ethanol Specifically Potentiates GABA-Mediated Neurotransmission in Feline Cerebral Cortex

Abstract. *Ethanol (ethyl alcohol) potentiates the inhibition of cortical neurons by γ-aminobutyric acid. This effect is specific, since ethanol does not potentiate inhibition by glycine, serotonin, or dopamine. These results have implications for alcoholism because (i) γ-aminobutyric acid mediates anxiolytic mechanisms, and (ii) anxiety is implicated in the etiology of alcoholism.*

Ethanol (ethyl alcohol) is the oldest and most commonly used psychoactive agent. Most people consume alcoholic beverages without apparent harm, but an estimated 9 million Americans suffer from alcoholism (*1*). Ethanol shares many pharmacological effects with benzodiazepines and barbiturates (*2*), drugs which are known to potentiate neurotransmission mediated by γ-aminobutyric acid (GABA) (*3*). Furthermore, ethanol potentiates spinal presynaptic inhibition (*4*), which is also mediated by GABA (*5*). Finally, bicuculline (a specific GABA antagonist) diminishes the behavioral manifestations of ethanol intoxication, whereas amino-oxyacetic acid (an inhibitor of GABA catabolism) markedly increases these behavioral manifestations (*6*). I have therefore studied the interactions of ethanol with various hypothesized synaptic transmitters acting on single feline cortical neurons; ethanol specifically potentiated the inhibitory effects of GABA, but not the inhibitory effects of glycine, serotonin, or dopamine. Ethanol also potentiated the inhibition of single cortical neurons by electrical stimulation of the surface of the cerebral cortex; that inhibition is believed to be mediated by endogenous GABA (*7*).

The experiments were carried out on cats (2.5 to 4 kg, of either sex) anesthetized with Fluothane or methoxyflurane. The same results were obtained in five control experiments with the "isolated cerebrum," unanesthetized preparation (*8*). Multibarreled glass microelectrodes were used to make extracellular recordings from single neurons of the pericruciate cortex (*9*). The recorded action potentials (spikes) were amplified, gated, electronically counted, processed through a peristimulus histogram ana-

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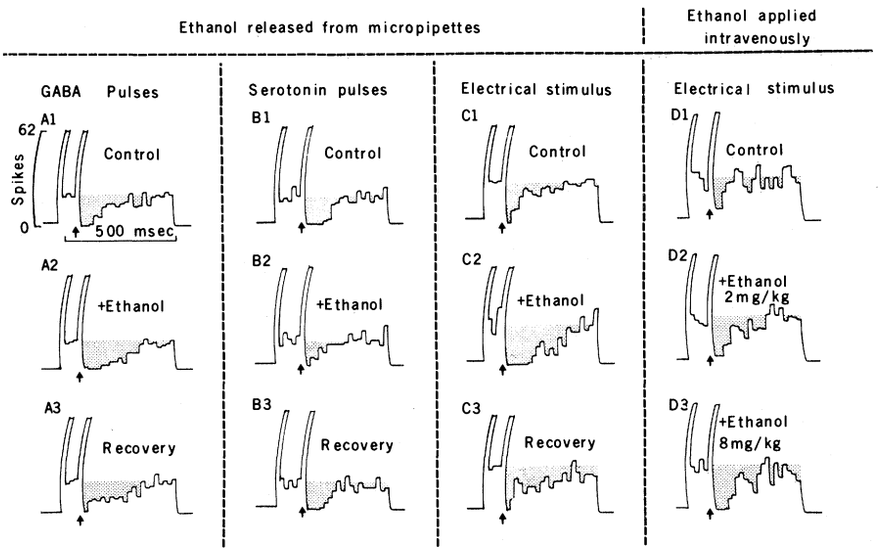

Fig. 1. Peristimulus histograms illustrating typical ethanol-induced potentiation of GABA (A), electrically evoked inhibition [(C) same cell as in (A) and (D) another cell], and typical ethanol-induced antagonism of serotonin [(B) (another cell)]. Each histogram shows the number of spikes occurring during each of the 25 20-msec intervals for 128 consecutive 500-msec periods. Background firing was maintained throughout at steady submaximum rates by continuous release of sodium L-glutamate (20 nA in all cases, except for D_3, where 40 nA was needed to obtain the control firing rates). Whenever ethanol was released from the micropipette (A–C), it was applied continuously throughout the entire period by removing its negative retaining current (10 nA) 15 seconds before the onset of the histogram period. Histograms D_2 and D_3 were obtained 2 minutes after the end of slow intravenous infusions of ethanol (2 mg/kg and 8 mg/kg, respectively) given 5 minutes apart. In each record, note the sequence of events from left to right: (i) the calibration column generated by the peristimulus histogram analyzer (not caused by spikes); (ii) the preliminary control firing (between the two high columns); (iii) at the arrow, the iontophoretic pulse (A_1–A_3; GABA, 200 nA for 15 msec; B_1–B_3; serotonin, 300 nA for 15 msec) or electrical stimulus to the surface of the cerebral cortex (C_1–C_3 and D_1–D_3: 2 Hz; 0.1 msec; 6.5 V) (the column containing the iontophoretic pulse or the electrical stimulus is high because the stimulus artifact is counted); (iv) the firing deficiency due to inhibition; and (v) the recovery of firing. Shading indicates the area of each record lying between the extrapolated mean control firing level and the actual firing after the stimulus. Ethanol influenced the magnitude of inhibition without interfering with control firing before the stimulus.

lyzer, and displayed on an oscilloscope and a pen-recorder. Ethanol (0.3*M* solution in 165 m*M* NaCl) was released from the micropipettes either by removing the negative retaining current of 10 nA or by electroosmosis (*10*) with positive ejecting currents as high as 50 nA (*11*). The other drugs were released according to standard microiontophoretic techniques. The four inhibitory neurotransmitters were applied as iontophoretic pulses (*12*) to induce inhibition comparable to that caused by electrical stimulation of the surface of the cerebral cortex (at a distance 2 to 3 mm from the recording site) (*13*). Monopolar cathodal square pulses (2 Hz, 0.1 msec, various voltages) were delivered through a silver ball electrode. The degree of inhibition of single cortical units, induced to fire less than maximally by continuous application of sodium L-glutamate, was measured from peristimulus histograms of the recorded spikes.

Ethanol released from micropipettes rapidly and reversibly potentiated pulses of GABA (16 cells) (Fig. 1A). This potentiation was specific for GABA since the inhibition produced by pulses of glycine (not shown) was either not affected (seven cells) or antagonized (six cells). Furthermore, ethanol consistently antagonized the inhibitory effects of pulses of serotonin (eight cells) (Fig. 1B) (*14*) and dopamine (nine cells) (not shown). Ethanol in the same electroosmotic doses also potentiated the inhibition of neuronal firing by electrical stimulation of the surface of the cerebral cortex (34 cells) (Fig. 1C). All actions of ethanol occurred within 10 seconds of its release from micropipettes; they were fully reversible within 1 to 3 minutes after it was discontinued. The magnitude of electrical inhibition could be easily varied by changing the intensity of the electrical stimulus; the effect of ethanol on different degrees of inhibition could thus be conveniently studied (Fig. 2).

Potentiation of inhibition, resulting from pulses of GABA and electrical stimulation of the cortex, was also produced by intravenous administration of ethanol (22 cells). Detectable changes were observed in some cells with intravenous doses of ethanol as low as 0.2 mg per kilogram of body weight. However, in "blind" experiments (*15*), the effect of the drug could be always distinguished from that of injected physiological saline only when the dose of ethanol (administered by slow intravenous infusion) was 4 mg/kg or higher. Effective electroosmotic and intravenous (as high as 300 mg/kg) doses of ethanol did not change the spike size (Fig. 2), but often decreased the frequency of spontaneous firing as well as of the firing evoked by

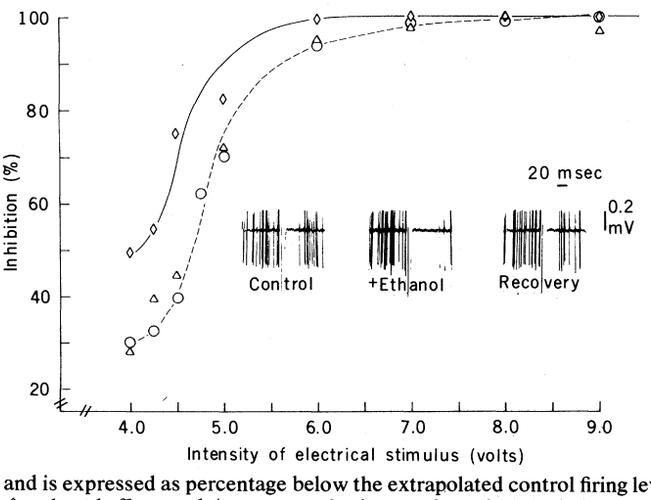

Fig. 2. Effect of ethanol (released from the micropipette by removing its 10-nA negative retaining current) on inhibition during the first 100 msec after the surface of the cerebral cortex was electrically stimulated at various intensities (2 Hz, 0.1 msec). All data were obtained from the same neuron. The degree of inhibition was assessed by measuring the area of the inhibitory period of the histogram and is expressed as percentage below the extrapolated control firing level. Symbols: ○, control; ◇, ethanol effect; and △, recovery 2 minutes after ethanol administration. Inset: photographs of 20 superimposed sweeps of oscilloscope tracings before, while, and 2 minutes after ethanol was released from the micropipette. Spike size was not affected, whereas electrically evoked (2 Hz, 0.1 msec, 6.5 V) cortical inhibition (after the stimulus artifact) was prolonged.

sodium L-glutamate. These effects on excitation (*16*), however, typically occurred at doses two to four times those affecting inhibition, and only doses of ethanol that did not interfere with firing evoked by sodium L-glutamate were used to obtain the results on inhibition reported here.

The ethanol-induced potentiation of the postsynaptic effects of GABA might be due to (i) blockade of GABA uptake, (ii) induction of GABA release, or (iii) a direct effect on the postsynaptic membrane. The possibility that ethanol exerted its effects by preventing GABA uptake appears unlikely, because ethanol (applied by electroosmosis) potentiated even further both GABA pulses and electrically evoked inhibitions that were most enhanced by iontophoretically applied (*17*) nipecotic acid (four cells), which blocks GABA uptake (*18*). Enhancement of GABA release cannot be a significant factor in these experiments, because ethanol exerted its potentiating effects on GABA-mediated inhibition in doses that by themselves had no inhibitory effect on control firing. Moreover, ethanol not only enhanced electrical inhibition but also enhanced the effect of iontophoretically applied GABA. Finally, ethanol selectively enhanced only the effect of GABA and not that of other inhibitory neurotransmitters, as would have been expected if the observed ethanol effects were the result of GABA release of the result of a nonspecific potentiation of all cortical inhibitions. For the same reasons, it is unlikely that ethanol in these experiments exerted its effects by interfering with GABA metabolism and thus by resulting in the availability of more GABA at the postsynaptic site. Thus, the most likely site of action of ethanol is the postsynaptic membrane. The action of ethanol cannot be due to an unspecific effect on Cl^- channels, since the inhibition produced by glycine was either not affected or antagonized. Since ethanol could potentiate GABA-mediated inhibition in doses that by themselves had no inhibitory effect, it is unlikely that ethanol is a direct GABA agonist. Thus the evolving picture is reminiscent of the mechanism of GABA potentiation by benzodiazepines, which probably act on a regulatory site on or near the GABA binding site (*3*). When tested on the same neurons, the effects of flurazepam and chlordiazepoxide (*19*) on GABA—and on electrically evoked cortical inhibition—were identical (within the limits of observation afforded by extracellular recordings) and additive to those of ethanol. Neither ethanol nor the barbiturates, however, bind to the benzodiazepine receptor identified in vitro (*20*). Thus, the exact mechanism through which the interaction between ethanol and the postsynaptic membrane results in potentiation of GABA-mediated neurotransmission remains to be clarified.

The specific potentiation of GABA-mediated neurotransmission by ethanol has implications for the etiology and treatment of alcoholism because (i) the most commonly prescribed anxiolytic drugs enhance GABA-mediated neurotransmission (*3*), and (ii) anxiety is involved in the etiology of alcoholism (*21*). Since long-term ethanol administration (in contrast to short-term administration) decreases GABA concentrations in the brain (*22*), and since long-term ethanol intake alters the density of GABA receptors (*23*), it is possible that long-term users of alcohol are forced to use higher amounts of ethanol in order to obtain the GABA potentiation necessary to achieve an antianxiety effect or to avoid withdrawal symptoms.

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