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The Effects of Various Doses of Alcohol on Sleep in the Rat[1]

MARC H. BRANCHEY, HENRI BEGLEITER, and BENJAMIN KISSIN

Department of Psychiatry, Downstate Medical Center, State University of New York, Brooklyn, New York 11203

Sleep records were monitored for 24 hr after a single intraperitoneal injection of a placebo, 0.5 and 1.5 g/kg of ethyl alcohol, in 12 chronically implanted rats. A sedative effect of alcohol, evidenced by an increase in non-REM sleep, was observed with the low dose, as well as with the high dose. REM sleep, on the other hand, was decreased by the high dose but was not greatly modified by the low dose.

INTRODUCTION

It is well known that the administration of alcohol, in human and animals, induces changes in behavior, described as sedation or sleep and modifications of the electrical activity of the cortex and other brain structures, similar to those observed during normal sleep (Engel and Rosenbaum, 1945; Story, Eidelberg, and French, 1961). More recently, the inhibitory effect of alcohol on rapid eye movement (REM) sleep has been reported by a number of investigators. Gresham, Webb, and Williams (1963) observed that a dose of 1.0 g of alcohol/kg body wt, given at bed time, induced a moderate decrease in REM sleep in humans. Yules, Freedman, and Chandler (1966) studied the effects of the same dose of alcohol administered at bed time, on 5 consecutive days, in humans. They observed a decrease in REM sleep on the first night, but, on subsequent nights, REM sleep gradually increased and eventually exceeded control levels. In the cat, Yules *et al.* (1966) investigated the effect of 1.0 g of alcohol/kg body wt given on 4 consecutive days. REM sleep decreased on the first 3 days and returned to normal values on the 4th day. These recent studies, however, did not investigate the possibility that alcohol would induce an increase in sleeping time. In one human study (Gresham *et al.*, 1963) only the first 5 hr of the night were investigated. In the other human study (Yules *et al.*, 1966) the subjects were awakened in the morning. In the study of Yules *et al.* (1966), cats were administered alcohol immediately after a period of sleep deprivation and, as a consequence, slept during virtually the whole recording period.

It seems, thus, that the effects of alcohol on total sleeping time and on non-REM (NREM) sleep have not been adequately studied. A study was therefore undertaken in the rat with the purpose of determining eventual modifications in the amounts of NREM and REM sleep under the influence of alcohol.

METHODS

Twelve male Sprague-Dawley rats, weighing between 400-450 g, were implanted, under pentobarbital anesthesia, with stainless steel screws placed unilaterally over the frontal and occipital cortices and over the olfactory bulb, a single bipolar stainless steel electrode in the hippocampus and two small solder disc electrodes under the skin on the neck muscles. All leads were soldered to a miniature connector, and the assembly was fastened to the skull with acrylic cement.

The animals were allowed 2 weeks to recover from surgery. They were housed, for the duration of the experiment, in a cage placed in a soundproof chamber with a lighting schedule of 12 hr of darkness (from 6 PM to 6 AM) and 12 hr of light (from 6 AM to 6 PM). The skull pedestal was attached to a cable connected to a mercury pool swivel, allowing the animals freedom of movement. They were adapted to this situation for

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at least 2 days prior to recording. The electrical activity of the cortex, the hippocampus and the olfactory bulb, and the electromyogram of the neck muscles were recorded on a Beckman polygraph at a speed of 1 mm/sec. Each half minute of recording was scored as wakefulness, NREM or REM sleep, according to criteria described in a previous study (Branchey and Branchey, 1970).

All animals were injected on 3 consecutive days at 6 PM according to a counterbalanced design. They received an intraperitoneal injection of a placebo, 0.5 and 1.5 g alcohol/kg body wt. The placebo consisted of 0.63 cc/100 g body wt of physiologic saline (0.9% sodium chloride). The alcohol doses consisted of an equivalent amount of a 10% or 30% (v/v) ethanol solution in physiologic saline. Sleep was monitored for 24 hr after each injection.

Each 24-hr record was divided into successive 3-hr periods for which the percentages of NREM and REM sleep were computed. The differences observed in the amounts of NREM and REM sleep after the high or low dose of alcohol when compared to the placebo were evaluated by three-way analyses of variance (Effect of Alcohol X Time X Animal). If the effect of alcohol or the interaction effect of Alcohol X Time were significant, the effect of alcohol in each of the successive 3-hr periods was evaluated by a two-tailed t test.

RESULTS AND DISCUSSION

Figure 1 shows the modification in NREM and REM sleep following the injection of 0.5 g alcohol/kg body wt. This dose of alcohol induced an increase in NREM sleep ($F = 4.14$, 1 and 77 df, $p < .05$) but had no noticeable effect on REM sleep. The graph shows that most of the increase in NREM sleep occurred during a period of 3 hr following the injection of alcohol ($p < .025$ for 0-3 hr).

The changes in the two types of sleep occurring after the injection of 1.5 g alcohol/kg body wt can be seen on Fig. 2. An increase in NREM sleep for approximately 6-9 hr following the injection was induced by this dose (F for the interaction of effect of Alcohol X Time was 3.25, 7 and 77 df, $p < .01$. The effect of

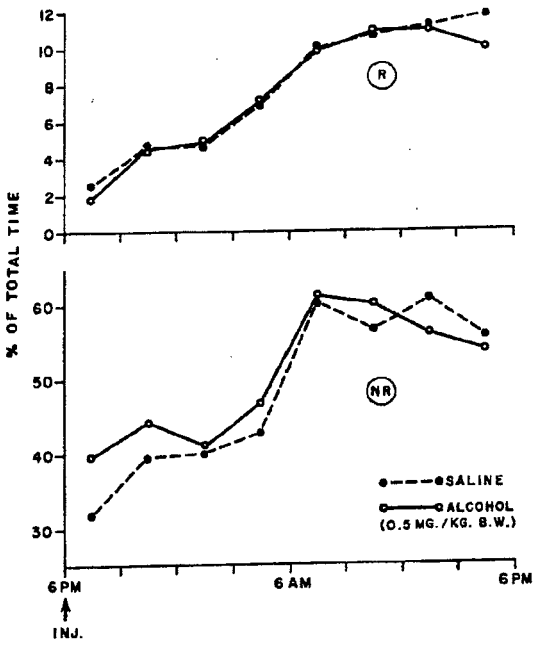

Fig. 1. Percentages of NREM (NR) and REM sleep (R) during the 24 hr following the administration of 0.5 g/kg body wt of alcohol or an equivalent amount of saline.

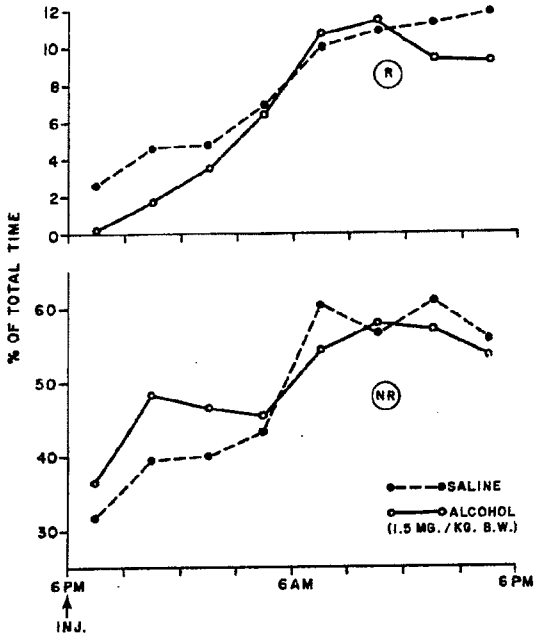

Fig. 2. Percentages of NREM (NR) and REM sleep (R) during the 24 hr following the administration of 1.5 g/kg body wt of alcohol or an equivalent amount of saline.

alcohol was found to be significant in the three 3-hr periods following the injection, at a level of $p < .025$ for 0-3 hr, $p < .005$ for 3-6 hr, and $p < .025$ for 6-9 hr). A marked reduction in REM sleep ($F = 12.77$, 1 and 77 df, $p < .001$) could also be observed for at least 6 hr after the administration of the drug ($p < .005$ for 0-3 hr and $p < .005$ for 3-6 hr).

The results of this study confirm the assumption that alcohol has a sedative effect. A dose of 0.5 g/kg body wt which did not induce any noticeable decrease in REM sleep increased significantly the amount of NREM sleep. A larger dose of 1.5 g/kg body wt induced a more prolonged increase in NREM sleep. These results support the generally accepted notion that alcohol, in adequate dosage, is a depressant of the central nervous system. A number of investigators have demonstrated that alcohol, at doses similar to the ones used in this study, has a depressant effect on evoked potentials recorded from various cortical and subcortical structures (Himwich and Callison, in press). Most of the cortical areas were found to be more sensitive to alcohol than the reticular formation. We have recently completed a study of visual evoked potentials in rats implanted with cortical and subcortical electrodes. The animals received the same alcohol doses as in the present experiment, and our results also indicate that cortical areas appear to be more sensitive to alcohol than subcortical areas (Begleiter, Branchey, and Platz, in preparation). It could be hypothesized that the general decrease in the activity of the central nervous system, and more specifically of the cortex, is accompanied by a diminution of the stimulation that reaches the reticular formation. This, in turn, would induce a decrease in the level of arousal (Jones, Bobillier, and Jouvet, 1969).

The decrease in REM sleep observed after administration of 1.5 g alcohol/kg body wt confirms previous studies done in humans (Gresham *et al.*, 1963; Yules *et al.*, 1966). However, this inhibitory effect on REM sleep is dose related. At the lower dosage used in this study, a sedative effect was obtained that was not accompanied by a decrease in REM sleep. A similar dose-related effect on REM sleep has been observed with other sedative drugs. Studies done in the cat with chlorpromazine (Hishikawa *et al.*, 1965) and promethazine (Jewett, 1968) have shown that a low dosage of these drugs induced only an increase in NREM sleep while at a higher dose, the sedation induced by the drug was accompanied by a decrease in REM sleep. In humans, the same drugs did not induce a decrease in REM sleep at low dosages, while they did at higher dosages (Lewis

and Evans, 1969; Kales *et al.*, 1969). The effect of alcohol and these phenothiazines is thus intermediate between that of sedative drugs which have a strong inhibitory effect on REM sleep even at low dosages, such as gluthetimide and secobarbital (Kales *et al.*, 1969), and that of other sedative drugs which do not have any effect on REM sleep, even at relatively high dosages, such as chloral hydrate (Kales *et al.*, 1969). The degree of inhibition of REM sleep induced by alcohol and other sedative drugs does not appear therefore to be a good indicator of their addictive potential.

Various authors (Oswald, Evans, and Lewis, 1969; Kales *et al.*, 1969) have pointed out that drugs with addictive potentials are characterized not only by their inhibitory effect on REM sleep but also by the fact that a rebound in REM sleep is observed after their withdrawal. Such a rebound following alcohol withdrawal has been described in humans by Yules *et al.* (1966). They observed an increase in REM sleep during the recovery nights following a few days of administration of alcohol. This increase exceeded by far the loss in REM sleep which had occurred during the administration of alcohol. The marked rebound observed after a few days of administration of alcohol was in sharp contrast with the absence of rebound after the first administration of this substance, observed in the same study as well as in various other studies in humans (Gresham *et al.*, 1963; Knowles, Laverty, and Kuechler, 1968) and in animals (Yules *et al.*, 1966). This absence of rebound after the first administration has been tentatively explained by persistent high blood levels of alcohol during the recording period (Knowles *et al.*, 1968). However, such an explanation is not supported by our findings. In spite of the fact that a dose of 1.5 g of alcohol/kg body wt is usually metabolized after 6 hr in the rat (Owens and Marshall, 1965), we did not observe a rebound in REM sleep during a period of 24 hr following its administration. Therefore, it can be hypothesized that the rebound in REM sleep observed after alcohol withdrawal is not a simple compensation for the loss of REM sleep but is an indication of the physical dependence induced by the prolonged administration of the drug. A number of authors (Greenberg and Pearlman, 1967; Gross and Goodenough, 1968; Johnson, Burdick, and Smith, 1970) have indeed reported that sleep recordings taken during episodes of delirium tremens following alcohol withdrawal in chronic alcoholics are characterized by a considerable increase in REM sleep. A better understanding of the sleep modifications induced by the administration and withdrawal of alcohol may help to elicit some of the mechanisms by which physical dependence to this drug is established.

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