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Research report

Nociceptor and age specific effects of REM sleep deprivation induced hyperalgesia

Michael E. May[a], Mark T. Harvey[a,b], Maria G. Valdovinos[b], Robert H. Kline IV[c,d], Ronald G. Wiley[c,d], Craig H. Kennedy[a,b,e,*]

[a] *Department of Special Education, Vanderbilt University, Nashville, TN, USA*
[b] *John F. Kennedy Center, Vanderbilt University, Nashville, TN, USA*
[c] *Veteran's Administration Medical Center, Nashville, TN, USA*
[d] *Department of Neurology, Vanderbilt University Medical Center, TN, USA*
[e] *Department of Pediatrics, Vanderbilt University Medical Center, TN, USA*

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Abstract

REM sleep deprivation (REMSD) has been shown to increase rates of negatively reinforced operant behavior, but not operant responding maintained by positive reinforcement. The reason for this differential effect is currently unknown. We hypothesize that REMSD can increase sensitivity to noxious stimuli. In the present study, we sought to determine if REMSD was associated with a change in response to noxious heat (i.e., altered nociceptive sensitivity). Two groups of rats, aged 6 and 22 months, were subjected to hotplate algesia testing at two different temperatures (44 and 52 °C). Initially, baseline numbers of responses and total response time were obtained at 44 °C. Animals then were exposed to 48 h of REMSD or control conditions. The frequency and duration of hindpaw responses (licking and guarding) increased for young animals only after REMSD and none of the control conditions. Old rats showed increased duration of nocifensive responding after REMSD and tank control conditions without a change in the number of responses at 44 °C. Latency to first nocifensive response was significantly longer in the 44 °C hotplate tests, but decreased to levels observed throughout the 52 °C hotplate tests following REMSD and TC conditions. These findings suggest that REMSD increases nociceptive sensitivity under conditions of sustained, selective C nociceptor activation (42 °C), but not under conditions of phasic A-delta activation (52 °C). The findings also indicate that age can be a significant variable in REMSD studies.

Keywords: REM sleep deprivation; Hyperalgesia; Negative reinforcement; Hotplate; Rat

1. Introduction

More than a century after the empirical investigation of sleep began, research continues to reveal its complex psychological and biological effects [1,2]. One strategy used by researchers to study the effects of sleep is the elimination of this behavioral state. By selectively depriving subjects of sleep, changes in behavioral, cognitive, and/or physiological variables can be analyzed [3]. To date, the majority of sleep deprivation research has focused on the role of slow-wave and rapid-eye movement (REM) sleep in memory consolidation and related processes [4,5].

Less attention has been given to how sleep deprivation influences more rudimentary learning processes, such as negative and positive reinforcement [6,7]. Such learning processes involve selectionist regulation of how environmental feedback governs the acquisition and maintenance of behavior [8,9]. In the case of negative reinforcement, behavior functions to avoid, or escape, noxious stimuli. For positive reinforcement, behavior functions to produce rewarding stimuli. As long as these contingencies continue and stimuli maintain their aversive or hedonic value, responding is reinforced.

* Corresponding author. Tel.: +1 615 322 8178; fax: +1 615 343 1570.
E-mail address: craig.kennedy@vanderbilt.edu (C.H. Kennedy).

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Experiments have shown that operants isolated using negative reinforcement schedules increase in response rate following REM sleep deprivation (REMSD) [10,11]. For example, lever pressing maintained on a free-operant avoidance schedule in which brief electrical shocks are postponed by each response, increases by 50% following 48 h of REMSD and then returns to baseline levels following ad libitum access to sleep. However, at lower levels of REMSD, avoidance responding is no affected by sleep deprivation. Typically, the increases in negatively reinforced responding observed following 48 h of REMSD are nonadaptive for the subject in that the behavior does not significantly increase shock avoidance proficiency.

The mechanisms responsible for increased avoidance behavior under REMSD conditions are unclear. One possibility is that REMSD increases sensitivity to noxious stimuli resulting in the electrical shocks used to motivate responding being perceived as more noxious. An experiment by Dinsmoor and Winograd [12] demonstrated that rates of responding maintained on a schedule of free-operant avoidance increased as the shock amperage was increased. These findings suggest that behavior maintained by free-operant avoidance is sensitive to the intensity of noxious stimulation. If REMSD does induce hyperalgesia, then increased rates of negatively reinforced responding may be a result of sleep deprivation altering the animal's motivation to avoid noxious stimuli.

One means of testing this hypothesis would be to analyze whether exposure to REMSD alters the pain threshold of subjects. Results consistent with this hypothesis were obtained by Onen et al. [13] who showed that following REMSD, pain thresholds decreased when animals were tested using mechanical stimulation. In the current experiment we sought to extend the findings of Onen et al. in three ways to determine under what conditions nociceptive responding is increased by REMSD. First, we used a hotplate algesia test to establish the robustness of the Onen et al. findings. Second, we used two different levels of hotplate stimulation to determine if there was a differential effect on responses to low and high intensity noxious heat. Finally, we analyzed young and old rats to assess possible developmental changes associated with sleep deprivation and nociception. Previous research on sleep deprivation had anecdotally suggested age-related effects [14].

2. Methods

2.1. Subjects

Sprague–Dawley male rats were obtained from Harlan Inc. and individually housed in standard vivarium cages for the duration of the experiment. Rats were either 6 months of age ($n = 7$) or 22 months of age ($n = 7$) at the start of the experiment. All rats had ad libitum access to food and water outside of the experimental sessions. A 12:12 h light/dark cycle (lights on 6:00) was in effect and all experimental sessions occurred during the lighted cycle. The protocol was reviewed and approved by the Vanderbilt Animal Care and Use Committee and followed National Institutes of Health guidelines.

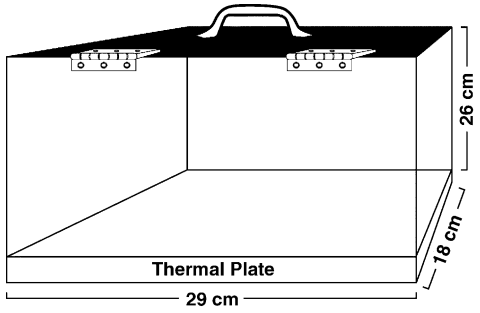

Fig. 1. Drawing of the hotplate apparatus used to test nocifensive responses in young and old rats. Animals were placed in the apparatus with all four paws in contact with the heated surface.

2.2. Apparatus

2.2.1. Thermal stimulation

An aluminum thermal plate was used to test hyperalgesia [15]. The thermal plate (18 cm × 29 cm) was 2 cm thick and contained internal fluid channels to keep temperature uniform across the entire plate surface (see Fig. 1). The plate was connected to a Neslab RTE-111 temperature controlled liquid system (Neslab Instruments). Temperature was regulated to within +1 °C of the set temperature. The thermal plate was topped by a vented Plexiglas enclosure (18 cm × 29 cm × 26 cm). A separate aluminum plate was connected to another Neslab RTE-111 temperature system and used as a warm-up plate to control the temperature of the rat's paws before being exposed to the thermal plate. Behavior on the thermal plate was continuously observed by a research assistant and simultaneously captured using custom computer software and a standard PC computer. Although forelimbs could simultaneously be placed on the thermal plate, only hindlimbs were observed for a behavioral response. The computer software captured the frequency and duration of hindlimb withdrawals from the thermal plate when the research assistant pressed a designated key on the computer keyboard.

2.2.2. REMSD and control conditions

REMSD was accomplished using the pedestal-over-water method [16]. REMSD tanks were cylindrical containers, 1 m high and 0.5 m wide. Two platforms were placed in each tank, between which the rat could move back and forth. Each platform measured 7.5 cm in diameter and was positioned 9 cm from other platforms and the tank wall. The top of each platform was raised 1 cm above 15 cm of water. Rat chow and water were available ad libitum through a wire mesh screen placed 15 cm above the platforms. This arrangement selectively deprives animals of 90–99% of REM sleep, but less than 10% of slow-wave sleep (see [17]).

A tank control (TC) apparatus was also used. The TC apparatus was identical to the REMSD tank, except that two pedestals were placed in the tank that was each 15 cm in diameter. This procedure exposed rats to the same aquatic environment as the REMSD procedure, but allowed ad libitum access to slow-wave and REM sleep. Core body temperature was checked during baseline and at the end of the REMSD and control conditions. No difference in body temperature was found.