Pergamon

Pharmacology Biochemistry and Behavior, Vol. 52, No. 1, pp. 43–48, 1995

0091-3057/95 $9.50 + .00

0091-3057(94)00411-0

REM Sleep Deprivation Alters Dopamine D_2 Receptor Binding in the Rat Frontal Cortex

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Received 30 August 1993

BROCK, J. W., A. HAMDI, K. ROSS, S. PAYNE AND C. PRASAD. *REM sleep deprivation and dopamine D_2 receptor binding in the rat frontal cortex.* PHARMACOL BIOCHEM BEHAV 52(1) 43–48, 1995.—REM sleep deprivation (RSD) of rats results in facilitation of dopaminergic behavior and an increase in striatal D_2 receptor density. To determine whether RSD results in changes in D_2 receptor in other brain regions, receptor affinity (K_d) and density (B_{max}) were measured in the anteromediofrontal (AM), cingulate (CN), and sulcal cortex (SL) in four groups of rats: 1), RSD96 group (RSD for 96 h; small pedestal/water tank method), 2) RSD24 group (large pedestals for 72 h then small pedestals for 24 h), 3) tank control group (TC; large pedestals for 96 h), and 4) cage control group. In separate groups, ambulation was recorded for 30 min following treatments. Group RSD96 showed an increase in activity compared to TC, and TC was increased compared to CC ($p < 0.05$ for all). In group RSD24, the AM showed an increase in B_{max} and K_d ($p < 0.05$), but there were no effects by RSD96. In the CN, B_{max} and K_d were decreased by RSD96 ($p < 0.05$) but not RSD24. In the SL, B_{max} was increased by RSD96, but not RSD24, whereas K_d was increased in both RSD groups ($p < 0.05$).

REM sleep deprivation Dopamine receptors Frontal cortex

THE EFFECTS of sleep loss on behavior in humans are most pronounced during problem-solving tasks, especially if the tasks are monotonous or regarded as "uninteresting" by the subject (36). Prolonged sleep deprivation in humans is even known to cause certain mild forms of psychotic disorganization; changes in the perception of time, size of self, space, weight, speed of movement, and the illusion that stationary objects are moving are commonly reported (18). Rats subjected to rapid eye movement sleep deprivation (RSD) for 3–4 days have demonstrated abnormal performance in a number of behavioral tests. The effects of RSD on memory of passive avoidance in rats have been equivocal (17,32,37,45). The effects of RSD on active avoidance behavior are also mixed. Some investigators have observed decreased acquisition of a shuttle-box avoidance task in the REM-deprived rat (46,49), whereas others saw no decrease in acquisition, but observed that the rats were unable to sustain performance of the task (2). In general, the effects of RSD on spontaneous behaviors in the rat, such as passive avoidance and locomotor activity, appear to be dependent upon age (23) and the method used to accomplish RSD (37). However, measures of response to novelty (24,34,37), problem solving (12,22), and sensory information processing (43,52) during REM deprivation agree that RSD produces changes in higher brain function. Rats deprived of REM sleep for 4 days were unable to develop an adaptive coping strategy in response to repeated stress (22). Also within that time, decision making to initiate voluntary movement in the rat was reportedly altered (12).

The neurochemical bases for RSD-induced changes in cognitive function are presently unclear. However, it is well known that dopamine activity in the forebrain is involved in goal-directed behavior, motivational arousal, learning processes (30), sensory information processing (7), and time perception (40); and there is increasing evidence that changes in central dopaminergic activity are an important effect of RSD (3,6,13). REM-deprived rodents demonstrated increased dopamine turnover in the striatum (3), hyperresponsiveness to dopaminergic agonists (5,51), and an increase in D_1 and D_2 receptor densities in the striatum (10,20). Because our own group has recently reported that RSD in rats was associated

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with a significant increase in the density of dopamine D_2 receptors (D_2) in the striatum using [^{3}H]YM-09151-2 binding (20), it is important to determine whether RSD results in changes in dopamine receptors in other forebrain regions that are relevant to locomotor behavior in the rat. In the present study, we compared the effects of 24 or 96 h of RSD in rats to the tank and cage control groups, with regard to 1) spontaneous locomotor activity, and 2) [^{3}H]YM-09151-2 binding in different divisions of the frontal cortex [anteromedial (AM), cingulate (CN), sulcal (SL)]. It is important to analyze different divisions of the frontal cortex separately because there are important anatomical and functional differences between them. For example, all receive innervation from the ventromedial and mediodorsal nuclei of the thalamus; however, the CN division receives additional innervation from the anteriomedial nucleus, whereas the SL division receives additional innervation from the parafascicular nucleus (29). With regard to functional differences, the AM, CN, and SL divisions of the rat frontal cortex show similar responses of DOPAC : DA ratio to foot shock stress (11), but the changes in the AM were larger and more consistent than those in the SL and CN. The heterogeneity in the distribution of dopamine concentrations among various nuclei of the brain (15) and regional variations in its release (1,11) support the theory that dopamine may have different physiological roles from one nucleus to another (30).

The small pedestal/water tank method is the most widely used technique for depriving rats of REM sleep stage without the need for electroencephalographic (EEG) monitoring (53). Although this has been the method of choice for depriving rats of REM sleep in over 80% of such studies performed since 1989, there are some points that must be mentioned. The technique has been validated as depriving rats of the REM sleep stage using EEG recording by different groups [(21,33, 35,39); and most recently by (48)], but there is some loss of non-REM as well (21,39), and there is no clear consensus about the magnitude of the REM decrease; reports range from 50% (33) to 100% decrease (21,39). Although claims of 100% abolishment of REM sleep may be spurious, the technique remains valuable to the extent that the rats residing on small pedestals experience significantly less REM compared to the large-pedestal rats that, in turn, are not significantly different from the cage control rats after 96 h (33). Also, there is a significant amount of stress involved for the rats on the small pedestals (8,23,53), some of which may not be accounted for by the use of large-pedestal controls. Thus, any biological effects observed with the use of the water tank method can only be interpreted to occur in association with REM deprivation, and not necessarily as a result of it. Lastly, the effectiveness of this method in precipitating biological changes, and the degree of stress associated with it, are dependent upon the age of the rat and the ratio of the rat's body size to the size of the pedestal being used (23). All of these factors were taken into account in the design of the present experiment.

We included a group of rats that resided on large pedestals for the first 72 h of the 96 h, then were transferred to small pedestals for the remaining 24 h. This was done to determine whether the effects of more acute REM sleep deprivation could be detected if the animals were allowed more time to acclimate to the novelty of the water tank environment. Locomotor activity was an appropriate behavior to measure in this study because: 1) hyperactivity is one of the salient features of sleep deprivation in rodents (2,4,6,37), thus it provides an indirect validation that our methodology was sufficient to produce the desired effect in the rats, and 2) there is a strong correlation between locomotor behavior and central dopaminergic activity (9,16,41).

METHOD

Preparation

Male Sprague–Dawley rats (211–270 g; Harlan Sprague–Dawley) were housed individually at controlled temperature (22–23°C) and 12L : 12D cycle (light on at 0700 h, both before and during the sleep deprivation protocol) with food and water ad lib. The animals were selectively deprived of REM sleep using the water tank procedure (53). On the day of experimentation, the rats were randomly divided into four groups (N = 6 each) as follows: 1) the RSD96 group, which was subjected to RSD for 96 h by residing in the water tank on small, 6.5-cm diameter pedestals; 2) the RSD24 group, which resided in the watertank on large, 15-cm diameter pedestals for 72 h then small pedestals for 24 h; 3) the tank control group (TC group), which resided in the water tank on large pedestals for 96 h, receiving only controlled water immersions; and 4) the cage control group (CC group), which remained in the home cages for the duration of the study, receiving only controlled handling (5 min/day). After 96 h of treatment, the rats were sacrificed by decapitation during the light cycle, between 1100 and 1200 hours.

Tissue Collection

The brains were dissected and stored at −80°C until binding assays were performed. The frontal cortex of each rat was divided as follows: 1) the anteromediofrontal cortex, which correspond to the FR1, FR2, and FR3 regions described by Zilles (55); 2) the cingulate cortex, which corresponded to regions Cg1 and the caudal aspect of FR2 (55); and 3) the sulcal cortex, an area that constituted the dorsal agranular insular cortex and the lateral orbital cortex (29), which forms the bank of the rhinal fissure.

Radioligand Binding

Binding of [^{3}H]YM-09151-2 to D_2 receptors was carried out using tissue membranes as previously described (19,31,50). Tissues from individual rats were homogenized (Virtishear Polytron, setting at 60 for 20 s) in 5 ml ice-cold buffer A (50 mM Tris-HCl, 8 mM $MgCl_2$, 5 mM EDTA, pH 7.15). The homogenate was centrifuged (48,000 × g for 20 min at 4°C). The homogenization and centrifugation were repeated twice. The final pellet was resuspended in buffer B (50 mM Tris-HCl containing 0.1% ascorbic acid, 10 μmol pargyline hydrochloride, and ions as follows: 120 mM NaCl, 5 mM KCl, 5 mM $MgCl_2$, 1.5 mM $CaCl_2$, 1 mM EDTA, pH 7.4 at 25°C) and used for the binding assay. The incubation mixture (1.5 ml) for D_2 receptor assay contained: 150 μg membrane protein and 10–200 pM (seven different concentrations) of [^{3}H]YM-09151-2 (87 Ci/mmol; New England Nuclear, Boston, MA). The tubes were incubated at 25°C for 90 min in the dark. The membrane-bound radioactivity was separated from the free by rapid filtration under vacuum through Whatman GF/B filters with four 4-ml rinses with ice-cold buffer B (pH 7.4 at 25°C). The membrane-associated radioactivity was measured in 10 ml of Scintiverse II scintillation fluid in a Beckman liquid scintillation counter at an efficiency of 55–60%. The nonspecific binding of [^{3}H]YM-09151-2 was defined in the presence of 30 μM (−)-sulpiride; it represented about 15–36% of total binding.

The specific binding data from each group were analyzed

separately using a nonlinear regression analysis and Scatchard plot (the computer program GraphPAD, ISI Software) to give the estimates of the maximal density (B_{max}) and the affinity (K_d) values. Protein determinations were performed using bicinchoninic acid (BCA) protein assay kit (Pierce Chemical Co.). The specific [^{3}H]YM-09151-2 binding to cortical membranes was of high affinity and saturable for all regions (AM, CN, and SL). Saturation curves were analyzed by nonlinear regression and modeled first to a one-site and then a two-site model. The two-site model was accepted only if the addition of the second site reduced the residual sums of squares of the deviations from regression, as judged by a significant F statistic. The above procedures and Scatchard analysis revealed only a single class of binding sites for the radioligand.

Spontaneous Ambulation

In a separate experiment, the RSD24, RSD96, TC, and CC groups of rats were placed in individual activity cages (46 × 23 × 23 cm) equipped with the Opto-Varimex mini system (Columbus Instruments) following the 96-h procedure. The cage was placed between optical emitters and detectors, which recorded the rat's ambulatory activity for 30 min.

Statistics

All data were analyzed statistically by analysis of variance (ANOVA) followed by unpaired Student's t-test. Significance was accepted at the 95% confidence level (alpha = 0.05, two-tailed test).

RESULTS

The effects of RSD on spontaneous locomotor activity in the rats are presented in Fig. 1. The result of the ANOVA for the ambulatory counts was: $F = 5.56$ (critical $F = 3.52$). The relevant statistical comparisons for hypothesis testing were: 1) group RSD24 vs. TC, 2) group RSD96 vs. TC, and 3) group TC vs. CC. The RSD96 group showed increases in total and ambulatory activity that were statistically significant compared to the TC group ($p < 0.05$). The total and ambulatory activity of the TC group was significantly greater ($p < 0.05$) than the CC group. Although the RSD24 group demonstrated a possible trend toward increased activity, variability in the data prevented the differences from being statistically significant.

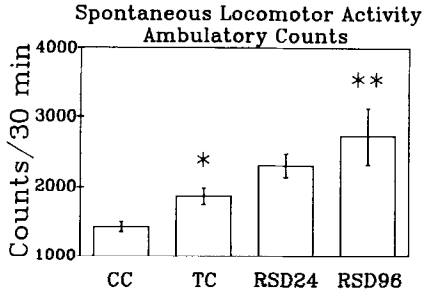

FIG. 1. Spontaneous locomotor activity of rats following 96 h of REM sleep deprivation (RSD), 24 h of REM sleep deprivation (RSD24), tank control group (TC), and cage control group (CC); values are mean ± SEM (ambulatory counts per 30 min). **Indicates $p < 0.05$, compared to TC group; *indicates $p < 0.05$, compared to CC group.

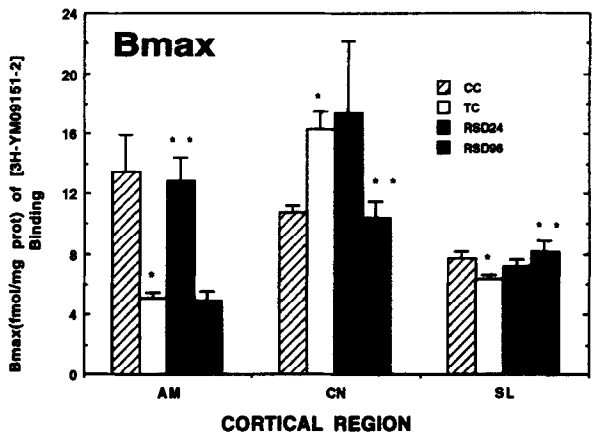

FIG. 2. Maximum binding (B_{max}) of [^{3}H]YM-09151-2 to rat frontal cortical membranes from cage control group (CC) and tank control group (TC), following 24 h of REM sleep deprivation (RSD24), and following 96 h of REM sleep deprivation (RSD96); values are expressed in fmol/mg of protein (mean ± SEM). Anteromedial frontal cortex (AM), cingulate cortex (CN), sulcal cortex (SL). **Indicates $p < 0.05$, compared to TC group; *indicates $p < 0.05$, compared to CC group.

The results of [^{3}H]YM-09151-2 binding to different divisions of frontal cortical tissue following the RSD procedure are presented in Figs. 2 and 3. The results of the ANOVA were as follows (critical $F = 4.08$): for the AM division, (B_{max}) $F = 9.3669$ and (K_d) $F = 4.0853$; for the CN division, (B_{max}) $F = 2.1205$ and (K_d) $F = 4.1086$; for the SL division, (B_{max}) $F = 2.3472$ and (K_d) $F = 3.8317$. In the AM division, tank stress alone (group TC vs. CC) was associated with a statistically significant decrease in D_2 receptor density ($p < 0.05$) and an increase in D_2 receptor binding affinity (decreased K_d, $p < 0.05$). Precisely the opposite effects of water tank stress were seen in the CN division, where D_2 receptor density was

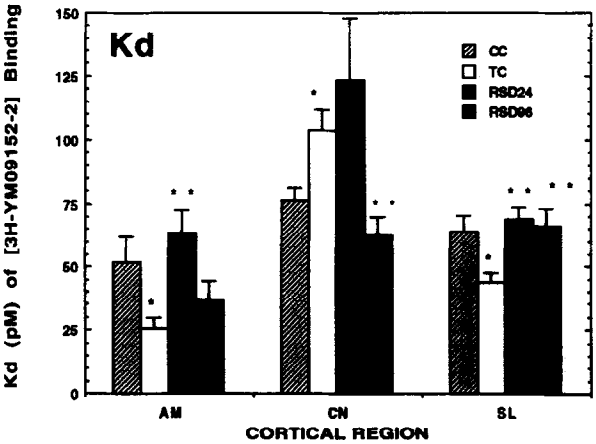

FIG. 3. Binding affinity (K_d) of [^{3}H]YM-09151-2 to rat frontal cortical membranes from cage control group (CC) and tank control group (TC), following 24 h of REM sleep deprivation (RSD24), and following 96 h of REM sleep deprivation (RSD96); values are expressed in pM (mean ± SEM). Anteromedial frontal cortex (AM), cingulate cortex (CN), sulcal cortex (SL). **Indicates $p < 0.05$, compared to TC group; *indicates $p < 0.05$, compared to CC group.

increased ($p < 0.05$) and binding affinity was decreased (increased K_d, $p < 0.05$). In the SL division, water tank stress was associated with a decrease in D_2 receptor density and an increase in D_2 receptor binding affinity (decreased K_d, $p < 0.05$).

When the rats were subjected to RSD for 24 h, the B_{max} was affected only in the AM division, where the D_2 receptor density was significantly increased ($p < 0.05$). RSD24 also was associated with a decrease in D_2 receptor binding affinity in the AM and SL divisions (increased K_d, $p < 0.05$). The characteristics of [^{3}H]YM-09151-2 binding in the CN division were not significantly affected by 24 h of RSD. After 96 h of RSD, the effects in the AM were no longer demonstrable. However, the CN division showed a significant decrease in B_{max} and K_d ($p < 0.05$ for both) in the RSD96 group. In the SL, the RSD96 group was associated with an increase in B_{max} and K_d ($p < 0.05$ for all), compared to the TC group.

DISCUSSION

Water tank stress alone was associated with effects on D_2 receptor bindings, which were most pronounced in the AM and CN. In the AM, there was a decrease in D_2 receptor density and an increase in D_2 receptor sensitivity, whereas the effect in the CN was precisely the opposite. The importance of these diverse effects of stress is presently unclear. In general, alterations in D_2 receptor affinity may be expected to influence dopaminergic neurotransmission, but the biological significance of small changes in receptor affinity are questionable. Others have shown that stress provokes a number of neurochemical effects that appear to selectively influence those dopamine neurons innervating the medial prefrontal cortex (42). For example, nonpainful stressors (swim stress, restraint stress, and conditioned stress) result in an augmentation in prefrontal dopaminergic activity that does not depend on the stress paradigm per se, and suggest that these paradigms share a common component, such as anxiety or fear (42). It was previously shown in mice that restraint stress created an imbalance between dopamine receptors of the D_1 and D_2 subtypes in the striatum, creating an increase in the $D_1 : D_2$ ratio (38). The authors suggested that stress-induced alteration in dopamine receptors may be related to the expression of behavioral strategies of individuals facing aversive experiences.

The results of this study show that RSD initiated specific changes in dopamine receptor regulation in the rat brain that were distinct from the effects of methodological stress. Perhaps the most interesting observations were the increased receptor density and decreased receptor affinity in the AM division of the frontal cortex, indicating a decrease in dopaminergic activity in that area of the frontal cortex after only 24 h of RSD. There were no effects in the CN division of group RSD24, but the SL division also showed a decrease in affinity for the D_2 receptor at that time. These changes in dopamine receptor regulation are thus among the earliest events to occur in the brain during REM deprivation, and appear to precede significant changes in EEG (33) or behavioral measurements [(22); also see Fig. 1]. In the RSD96 group, the absence of an effect in the AM division suggests that dopamine activity in that brain region may have returned to normal. However, dopamine activity may have increased in the CN division, as indicated by the decrease in D_2 receptor density (decreased B_{max}) and increased binding affinity (decreased K_d) by that time. In the SL division, dopamine activity appeared to be decreased, as indicated by the increase in D_2 receptor density and decrease in receptor binding affinity. It is unlikely that significant differences observed in groups RSD24 and RSD96 were simply due to nonspecific stress, because the changes in B_{max} and K_d for group TC were invariably in the opposite direction of those associated with RSD.

A previous study reported that 96 h of RSD had no significant effect on D_2 receptor density in the rat frontal cortex, as measured by [^{3}H]spiperone binding (14). However, in that study, the frontal cortex was dissected differently, having included all cortical tissue in front of the anterior commissure. The tissue analyzed in that study corresponded to an area roughly equal to the AM and SL divisions of the present study combined. The changes observed herein in the AM division would perhaps not have been detected if the tissue had been pooled with the SL during analysis.

The present data suggest that RSD in the rat is characterized by a transient decrease in dopamine activity in the anteromedial area of the frontal cortex within the first 24 h of REM deprivation, followed by a decrease in dopamine activity in the sulcal division and an increase in dopamine activity in the cingulate cortex. We previously reported the effects of RSD on [^{3}H]YM-09151-2 binding in the rat striatum (20), having observed significant increases in both D_1 and D_2 receptor densities after 24 and 96 h of deprivation. Anatomically, both the anteromedial region of the striatum and frontal cortex receive afferents from the mediodorsal thalamic nuclei; the AM division of the striatum also receives afferents from the AM division of the frontal cortex, thus forming a complete, prefrontal neuronal circuit (30). Although our behavioral data reaffirm that hyperactivity is a consistent behavioral feature of RSD in rats (Fig. 1), it is interesting to note that lesions of the rat medial frontal cortex (29) or the striatum (26) also result in hyperactivity. Lesions in the vicinity of the sulcal cortex precipitate hyperactivity (27), abnormal circadian rhythms (27), and an inability to initiate new response strategies (28). It is tempting to hypothesize that dysfunction of dopaminergic mechanisms in these specific brain regions is a causative factor for the expression of hyperactivity in the REM-deprived rat.

Because all three divisions of the frontal cortex have input to the expression of locomotor behavior in rodents, changes in dopamine activity in any of them is likely to alter activity levels in the animal. Hence, increased dopamine activity in the AM region of group TC and in the CN region of group RSD96 may account for the significant differences in locomotor activity shown in Fig. 1. It may be argued that there was a trend toward increased locomotor activity in group RSD24, although no corresponding decreases in D_2 receptor B_{max} were detected in that group (Fig. 2). Significant increases in D_2 receptor binding affinity in the AM and SL regions of group RSD24 (Fig. 3) may have contributed to the phenomena. It is interesting to note that although the behavioral data in Fig. 1 present a simple "dose-response" appearance, such a pattern is conspicuously absent from the receptor binding data, despite the strong correlations between dopamine activity and locomotor activity reported in the literature (9,16,41). This lack of clear consistency underscores the point that RSD is associated with changes in neural mechanisms that are distinct from what would be predicted if the large- and small-pedestal treatments induced nothing more remarkable than different degrees of stress (as might be concluded from Fig. 1 alone).

Differences in receptor binding characteristics among the RSD24 and RSD96 groups reflect the unique, time-dependent changes that take place in specific dopaminergic systems in association with REM deprivation, and/or the initial vs. compensatory effects on those systems. RSD is known to induce

changes in other neurotransmitter systems (e.g., noradrenergic and serotonergic systems) (54), which may modulate dopamine activity in a direct or indirect manner. Nonetheless, the effects of RSD on dopamine receptors reported herein are intriguing because they have the potential to explain a large body of phenomena related to sleep deprivation and mental function. Dopamine activity in the frontal cortex is important for mechanisms of selective attention (7) and rate of learning (25), brain mechanisms that are specifically impaired by sleep deprivation in both humans (36) and rodents (12,46). It is interesting to note that sleep deprivation in normal humans can produce disorganized thinking and abnormal social behavior (36,47), which have been compared to a state of acute psychosis (18); and such behaviors are linked by other lines of evidence to dysfunction of the central dopaminergic system (44).

In summary, alterations in dopamine receptor binding distinguished the effects of stress from the effects of RSD. Changes in dopamine receptor regulation appear to be among the earliest neurochemical events that occur in the rat brain as a result of RSD. These data suggest that differential changes in dopamine receptor regulation in discrete forebrain areas is a mechanism by which REM sleep deprivation influences locomotor behavior, and possibly congition, in rodents.

ACKNOWLEDGEMENTS

This research was supported by the U.S. Army Research and Development Command, grant DAMD-17-88-Z-8023. Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the U.S. Army. In conducting research using animals, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee of Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH), publication #86-23, revised 1985.

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