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Changes in Monoamines and Their Metabolite Concentrations in REM Sleep-Deprived Rat Forebrain Nuclei

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FAROOQUI, S. M., J. W. BROCK AND J. ZHOU. *Changes in monoamines and their metabolite concentrations in REM sleep-deprived rat forebrain nuclei.* PHARMACOL BIOCHEM BEHAV 54(2) 385-391, 1996. – Rapid eye movement sleep deprivation (REMSD) is a potent stressor in rats. Behavioral abnormalities such as passive and active avoidance, locomotor activity, problem solving, sensory information processing, and the development of adaptive copping strategy in response to repeated stress are among the earliest obvious symptoms of REMSD, the mechanism for which remain largely unknown. The aim of this study was to determine whether 96 h of REMSD causes changes in monoamine neurotransmitters concentrations in rat forebrain regions (frontal cortex, FC; parietal cortex, PC, and striatum) that are involved in mediating higher brain functions such as attentional mechanisms, sensory information processing, and locomotor activity, which are severely affected in REMSD conditions. Rats were subjected to 96 h of REMSD using inverted flower pot water tank technique. To account for the stress associated with water tanks, a tank control group (TC) was included where the animals could reside comfortably on a large pedestal in the water tank. Regional brain concentrations of norepinephrine (NE), dopamine (DA), dihydroxyphenyacetic acid (DOPAC), L-3,4-dihydroxyphenylalanine (L-DOPA), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT), and 5-hydroxyindoleacetic acid (HIAA) were determined by electrochemical detection using high-performance liquid chromatography. The concentrations of serotonin and its metabolite, HIAA, was reduced in the frontal and parietal cortexes of REMSD rats compared with TC or cage control (CC) group. NE, DA, DOPAC, and HVA concentrations in FC and PC of REMSD animals were remained unchanged compared with TC or CC rats. A significant increase in the concentrations of DA metabolites was observed in the striatum of REMSD rats when compared with CC and TC rats. There was a 29 and 31% increase in the concentration of striatal DA in REMSD group compared to the TC and CC groups, respectively; however, these percentages were not statistically different. Striatal NE, 5-HT, and HIAA concentrations were not significantly different among the three groups. These results suggest that 96 h of REMSD alters dopaminergic and serotonergic systems in different locations in rat brain. The effect of REMSD on the serotonergic systems are localized in the cerebral cortex, whereas dopaminergic metabolism is increased in the striatum.

REM sleep deprivation Catecholamines Dopamine HVA DOPAC 5-HT HIAA HPLC Electrochemical detection Cortex Striatum

RATS subjected to REM sleep deprivation for 3-4 days have demonstrated abnormal performance in a number of behavior tests. The effect of REM sleep deprivation on passive (15,37, 45,52), and active avoidance (2,54,55) have been equivocal. In general, the effect of REMSD on spontaneous behaviors in the rat, such as passive avoidance and locomotor activity, appears to be dependent upon age (23) and the method used to accomplish REMSD (45). However, measures of response to novelty (42,45), problem solving (12,20), sensory information processing (51,60), and the development of adaptive copping strategy in response to repeated stress (5,20) agree that REMSD produces changes in the higher brain function in the

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rat. The neural mechanism that mediate these changes are currently under investigation.

It is widely accepted that the effects of sleep deprivation on brain functions are associated with decreased functional catecholamine neurotransmission (39,53). Nonetheless, there is no consensus as to what effect sleep deprivation has on the concentrations of monoamines in the brain (46,47). Early studies observed no changes in brain concentration of the monoamine neurotransmitter 5-hydroxytryptamine (5-HT) (22), despite the fact that 5-HT is implicated in the genesis of sleep (28) and lesions of the raphe nuclei coincide with suppression of sleep and a decrease in the forebrain 5-HT levels (29). Investigators have attempted to link a large body of sleep deprivation-induced abnormalities to changes in the regulation of central noradrenergic systems (53). However, the importance of the central noradrenergic system as a mediator of direct effects of sleep deprivation has been challenged by more recent findings. Instead of the expected downregulation of adrenergic receptors by total sleep deprivation, radioligand binding studies revealed upregulation of adrenergic receptors in rat hypothalamus and cerebellum (58), and to complicate the picture further, the same group found no change in the central catecholamines concentrations (48). A more recent study on rapid eye movement (REM) sleep deprivation in rats has suggested that changes in the central norepinephrine (NE) concentration are more related to physiological adaptation to the methodological stress than to specific effect of sleep deprivation (5,61). By comparison, the central dopaminergic systems have not received as much attention by investigators in sleep research (7,55). Twelve days of REM sleep deprivation in cats can produce an increase in dopamine (DA) concentration in the midbrain (22). In mice, 48 h of REM sleep deprivation significantly increased DA turnover in the striatum and nucleus accumbens (2). Moreover, prolonged sleep deprivation in rats resulted in a decreased turnover of NE in hypothalamus, decreased NE with no change in turnover rate in hippocampus, and no change in the striatal DA (46). We have also recently reported that 4 days of REM sleep deprivation in rats is associated with significant increases in the density of both dopamine D_1 and D_2 receptors in striatum (19) and frontal cortex (6). The implication is that central DA concentrations are depleted in the REMSD rats, but this hypothesis must be tested. Differences in the species studied, and the method and duration of sleep deprivation employed makes it impossible to extrapolate from the findings of others in addressing this issue.

The present study was performed to determine whether 96 h of REMSD in rats causes a depletion of monoamine neurotransmitter concentrations in some selected regions of the forebrain (frontal cortex, FC; parietal cortex, PC; and striatum). These brain regions were chosen because of their known importance in mediating higher brain functions, such as attentional mechanisms (34), sensory information processing (35), memory (57), and locomotor activity (33). The importance of catecholamine involvement in these brain mechanisms is widely recognized (8), as is the phenomenon that these mechanisms are altered by REMSD (12,15,44,51).

METHOD

Eighteen male Sprague–Dawley rats purchased from Harlan Sprague–Dawley (Indianapolis, IN) were housed individually in metalcages, with food and water ad lib. All animals were on a normal rat diet that consisted of 20% protein, 65% carbohydrate, 5% fat, and contained 3.85 Kcal/g for dry weight (14). When animals were 60 days old they were divided into three groups: a) the REM sleep-deprived group (REMSD, $n = 6$) animals resided on small pedestals in the water tank for 96 h; b) the tank control group (TC, $n = 6$) animals resided on large pedestals in the water tank for 96 h, but were subjected to control immersions; and c) the cage control group (CC, $n = 6$), that remained in their home cages but were subjected to controlled handling (5 min/day).

REM Sleep Deprivation

The inverted flower pot or platform technique is the most frequently used method for producing REM sleep deprivation in rats (5,12,24,38,40,50). The animals were placed in individual acrylic chambers containing a 6.5 or 15 cm diameter platform surrounded by water. The water level in the tank remained constant at 3 cm below the tops of the pedestals. The sleep deprivation and tank control chambers were cleaned and filled with water daily. The ambient room and water temperature was kept constant at 25°C, within the thermoneutral zone for Sprague–Dawley rats. All the animals had free access to food and water through the lid of the deprivation chamber, approximately 14 cm above the pedestals. Animals residing on the small pedestals experienced wakefulness and non-REM sleep, but not REM sleep, because the diameter of the pedestals were so small that with a loss of the posture muscle tone at the onset of each REM episode, the animals were awakened as they started to fall in the water. The control rats residing on the large pedestals (TC), which allowed them to acquire REM sleep as well as non-REM sleep and wakefulness (13,62). This method has been used reliably and most extensively to accomplish selective REM sleep deprivation in rats (12,24,38, 40). While this method is specific for producing REM sleep deprivation (36), it also exerts some degree of stress to the animals resulting from isolation, motor restriction, novel environment, and frequent startling falls in the water. To make up for this additional stress associated with the water tank and startling falls, TC control rats were subjected to a number of control immersions equal to the average number of immersions experienced by the REMSD group. The controlled immersions were accomplished by video tape monitoring of the REMSD rat during each series of rats undergoing the treatment (which included at least one animal of each group at a time). The REMSD rat was recorded on a 8-h cassette tape during the first 8 h of the dark cycle. On the following day investigators analyzed the video tape off line and counted the number of falls encountered by the REMSD rat during the 8-h period, multiplied that number by 3 to estimate the total number of falls in the past 24 h, then treated the TC rat to the same number of immersions. All controlled immersions of rats in the TC group occurred during the first 8 h of the light cycle, as did the controlled handling of the rats in the CC group. Likewise, rats in the CC group were handled daily to account for the amount of noise and handling stress experienced by the TC and REMSD group during the daily cleaning of the water tank.

Brain Dissections and HPLC Analyses

After residing in the water tanks or home cages for 96 h the animals were sacrificed by decapitation and their brains were removed and immediately dissected on a cold surface to remove frontal cortex, parietal cortex, and striatum. The tissue samples were weighed individually and homogenized by sonication in 500 μl of extraction solution (0.1 M perchloric acid containing 0.4 mM sodium metabisulfite and 0.1 mM EDTA)

as described earlier (14). The homogenates were centrifuged at 15,000 × *g* for 10 min, then filtered through a 0.22 μm membrane filter and transferred to sealed vials for HPLC analysis. The PCA precipitates were dissolved in 0.1 N NaOH and an used for protein estimation using BSA as protein standard and BCA protein determination kit (Pierce Chemical, Rockford, IL). The monoamines concentration in the samples were determined using HPLC equipped with catecholamine HR-80 RP C18 column and electrochemical detector (ESA, Inc., MA) as described earlier (14,31). Each sample was analyzed twice for concentrations of norepinephrine (NE), dopamine (DA), and its metabolites, dihydroxyphenyacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT), and 5-hydroxyindoleacetic acid (HIAA). In some brain samples the recovery of analytes was determined by adding a fixed concentration of analyte before homogenization and centrifugation or by adding fixed concentration of internal standard, DHBA (range 1-10 ng). Analysis of the difference chromatogram together with internal standard comparisons resulted in recoveries of 95% or greater for each component. Thus, no further recovery corrections were made when quantifying samples other than internal standard corrections performed by the coulochem 5100A integrator automatically. The final values were expressed as nanogram of amine per mg protein. The average amine concentration for each brain area was statistically analyzed by one-way analysis of variance (ANOVA) followed by unpaired Student's *t*-test or Duncan's test, and the statistical significance was accepted at the 95% confidence level.

RESULTS

The concentrations of serotonin, norepinephrine, and dopamine and their metabolites in cerebral cortical areas are given in Figs. 1 and 2. In frontal cortex, 96 h of REMSD significantly reduced HIAA concentrations when compared with either TC or CC group (REMSD vs. TC, 0.81 ± 0.16 vs. 2.07 ± 0.42; $p < 0.05$; REMSD vs. CC, 0.81 ± 0.16 vs. 3.95 ± 0.5, $p < 0.01$; concentrations of analytes are in ng/mg protein). There was also a significant decrease in frontal cortex HIAA content in TC group compared with CC ($p < 0.01$). Although there was 44 and 54% decrease in 5-HT levels in the frontal cortex of REMSD rats compared to TC and CC rats, respectively (REMSD, 0.73 ± 0.20; TC, 1.29 ± 0.38; CC, 1.57 ± 0.40 ng/mg protein); however, these changes did not achieve a statistical significance. There were no significant differences in the concentrations of NE, DA, DOPAC, HVA, and L-DOPA in FC of REMSD rats when compared with either CC or TC groups (Fig. 1).

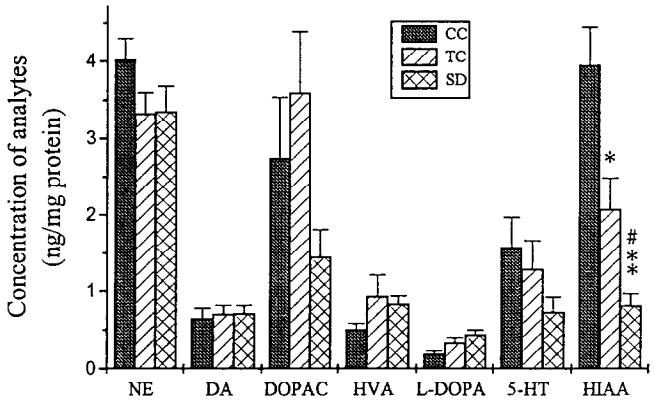

FIG. 1. Monoamine concentrations in frontal cortex of REM sleep-deprived (REMSD), stress-control (TC), and cage-control (CC) rats. Each value indicate mean ± SE of six rats and expressed as ng of neurochemical/mg tissue protein. The asterisks above the horizontal bar represent the statistical significance between the two groups compared. *Compared to CC and # compared to TC. *#$p < 0.05$, **$p < 0.01$.

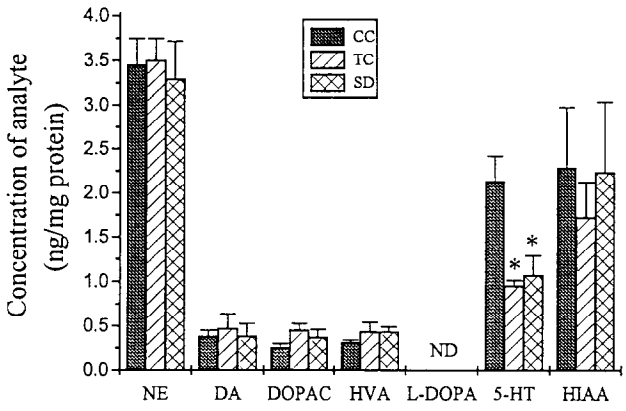

FIG. 2. Monoamine concentrations in parietal cortex of REM sleep-deprived (REMSD), stress-control (TC), and cage-control (CC) rats. Each value indicate mean ± SE of six rats and expressed as ng of neurochemical/mg tissue protein. The asterisks above the horizontal bar represent the statistical significance between the two groups compared. *Compared to CC, *$p < 0.05$. ND, (not determined.)

As shown in Fig. 2, a significant decrease ($p < 0.01$) in the concentrations of 5-HT in parietal cortex of REMSD and TC group was observed compared to CC (REMSD, 1.07 ± 0.22; TC, 0.95 ± 0.06; CC, 2.13 ± 0.29 ng/mg protein). Despite a significant decrease in 5-HT levels in the PC, HIAA concentrations were not markedly different among CC, TC, and REMSD groups (Fig. 2). In addition, REMSD and TC animals showed no significant differences in NE, DA, DOPAC, and HVA concentrations in PC when compared with CC group.

Shown in Fig. 3 are the effects of 96 h of REMSD on striatal concentrations of catecholamines. Statistical analysis of the data revealed no significant effect of REMSD on NE, 5-HT, and HIAA concentrations when compared with CC or TC groups. However, HVA concentration was significantly elevated ($p < 0.01$) in 96 h REMSD rats compared to CC group (REMSD, 20.08 ± 3.19; TC, 17.29 ± 2.37; CC, 2.59 ± 0.8; Fig. 3). Striatal DOPAC concentration was also significantly increased in REMSD rats when compared with either TC ($p < 0.05$) or CC ($p < 0.01$) groups (REMSD, 35.42 ± 4.15; TC, 27.55 ± 1.84; CC, 17.92 ± 3.31 ng/mg protein). There was a tendency for striatal DA concentration to be elevated in REMSD and tank control rats compared to CC (29 and 31% increase in TC and SD group compared with CC, respectively). However, upon analysis the differences did no revealed a statistically significant differences between the three groups.

The DA metabolite data were also analyzed in terms of DOPAC/DA and HVA/DA ratios (14), which are regarded as sensitive indices of DA metabolism in rat brain (3). Under nonsteady state conditions, the concentration of DA metabolites may not be correlated with actual DA release (3); how-

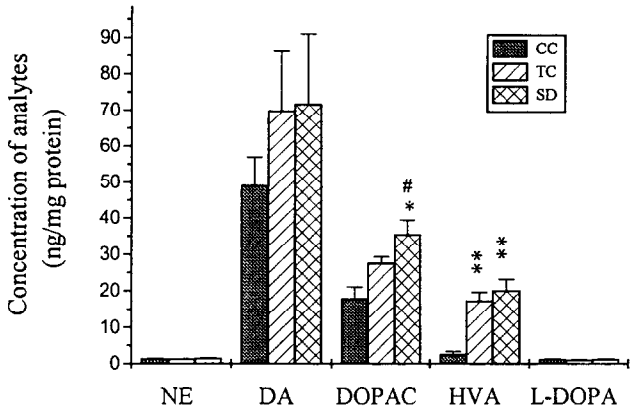

FIG. 3. Concentrations of monoamines and their metabolites in striatum of REM sleep-deprived (REMSD), tank-controls (TC), and cage-control (CC) rats. Each value indicate the mean ± SE of six animals in each group and expressed as ng of neurochemical/mg tissue protein. The asterisks above the horizontal bar represent the statistical significance between the two group compared. *Compared to CC, **$p < 0.01$, #Compared to TC, #$p < 0.05$.

ever, simultaneous measurement of DA metabolites ratios and the DA concentrations may provide insight into the biological implications of the data. An observed increase in one of the variables (DA, DOPAC/DA ratio, or HVA/DA ratio) would indicate that dopaminergic neuronal activity had increased in that brain region, specially if the other two variables were increased or unchanged. On the contrary, a decrease in these parameters will require extra caution for interpretation. For example, a postmortem decrease in DA concentration may be due to decrease in DA synthesis or depletion of the neurotransmitter as result of excessive neuronal activation; the later possibility would also cause a concomitant increase in the metabolite ratios. Paradoxically, other scenarios where both DA and its metabolites are decreased or DA remain unchanged but metabolites were decreased or when DOPAC/DA and HVA/DA ratios changed in the opposite directions, the interpretation and implication of the data for dopaminergic neurotransmission will be far less clear.

The effect of 96 h REMSD on the ratios of DOPAC/DA and HVA/DA in frontal cortex, parietal cortex, and striatum are depicted in Fig. 4. Ninety-six hours of REMSD was not associated with significant changes in DA concentrations in the brain regions studied. However, the metabolite concentrations and metabolite/DA ratios were significantly affected. The DOPAC/DA and HVA/DA ratios were significantly increased in striatum and parietal cortex of REMSD and TC groups when compared with CC group (Fig. 4A and B). In the frontal cortex, only the HVA/DA ratio was significantly increased in REMSD group when compared with CC, but this difference was abolished when the comparisons were made between REMSD and TC group.

DISCUSSION

Statistical analysis of the neurochemical data revealed significant sleep deprivation effects on the concentration of 5-HT in parietal cortex, 5-HIAA in the frontal cortex, and DOPAC in striatum. The factors responsible for the alterations in the monoamine levels in cerebral cortex and striatum cannot be determined from the present study. Previous studies from this laboratory and others have shown that there is a certain amount of stress associated with introduction of rats into the water tank environment, regardless of pedestal size. In this study we tried to exclude these confounding factors by including a stress control group. It is important to emphasize that the nonspecific stress associated with REM sleep methodology also had robust effect on serotonergic as well as dopaminergic neurotransmission in the brain that possibly masked some of the specific effects of REMSD in these studies. It is well known that when rats are deprived of REM sleep using the small-pedestal/water tank method, they undergo adaptive changes to the water tank environment. Included among those changes is an increase in daily caloric intake in REMSD group, compared to both TC and CC groups (5). A general increase in food consumption and an increase in energy expenditure has been reported in REM sleep-deprived rats (4,32). The EEG recordings have demonstrated that even rats residing on the large pedestals experience less REM sleep at the beginning of the experiment (4,34). However, rats on the large pedestal adapted to the novel condition of the water tank by 96 h, as indicated by a complete restoration of their EEG activity. In contrast, the rats residing on small pedestals showed a significant decrease in their REM sleep episodes only after 96 h compared to those on the large pedestals (40). It is relevant to note that restraint stress for a short duration of 10 min could cause persistent increase in norepinephrine turnover in extended brain regions during the nonstressed periods following stress (17). Similarly, the decrease in the 5-HT and HIAA levels in cerebral cortex of the rats residing on large pedestal in this study may be the reminiscent of the initial diminished REM sleep often experienced by these animals. It is unclear why 5-HT and HIAA concentrations in the tank control group is decreased; various forms of stress generally increase rather decrease the concentrations of 5-HT and HIAA in cerebral cortex (11,41,42).

Although 5-HIAA primarily reflect the intraneuronal me-

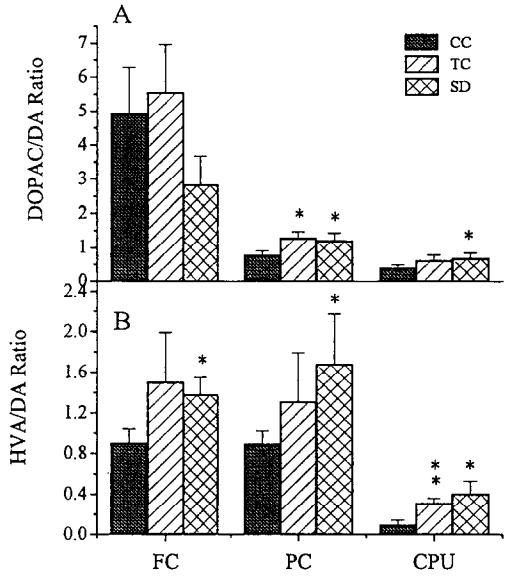

FIG. 4. Effect of REMSD on striatal DOPAC/DA and HVA/DA ratios in REM sleep-deprived (REMSD), tank-control (TC), and cage-control (CC) rats. Each ratio value indicate the mean ± SE of six animals in each groups. The asterisks above the horizontal bar represent the statistical significance between the two group compared. *Compared to CC, *$p < 0.05$, **$p < 0.01$.

tabolism of 5-HT and not its release (10,30,31), it is possible to draw inferences about the serotonergic activity and utilization of 5-HT by examining the concentrations of both substances in the nerve terminals (18,56). The levels of 5-HT and 5-HIAA will depend on the degree of serotonergic activity in the nerve terminals. Hence, a decrease in the concentration of 5-HIAA in the cortex of REMSD animals compared to CC and TC would suggest decreased serotonergic activity and metabolism of 5-HT in the two areas of the cerebral cortex. The raphae nuclei of the midbrain project serotonergic inputs primarily in the medial forebrain bundle to an array of rostral sites including cerebral cortex (27). The dorsal raphae nucleus projects most strongly to the frontal cortex, where serotonin release is best characterized by activation of 5-HT_2 receptors (9). The decreased levels of 5-HT and its metabolites in cerebral cortex may reflect a decreased serotonergic outflow from raphae nuclei in REMSD animals. However, according to methodology employed in these studies, a decrease in 5-HT concentration only suggests, but does not prove, a local decrease in the serotonergic activity in the raphae nuclei or cerebral cortex.

Although the concentration of DA degradation products may be less correlated with the actual release of DA under nonsteady-state conditions (3), simultaneous measurements of DA metabolites and DA metabolite/DA ratios may provide insight into the biological implication of the data (21). The changes in DA metabolite ratios in striatum, frontal cortex, and parietal cortexes implicate alteration in the dopaminergic neurotransmission in mesocortical system (14). The DA metabolism to HVA was increased in REMSD group in striatum, frontal, and parietal cortexes, whereas, DA metabolism to DOPAC in parietal cortex was increased in both REMSD and TC group. The factors responsible for these changes in dopamine metabolism cannot be determined from the present study. One possible mechanism may be a close link between activation of hypothalamic-pituitary-adrenal axis in response to stress and stimulation of various neurotransmitter systems (16,26,49). For example, restraint stress can enhance the release of dopamine and acetylcholine from limbic and cortical areas of conscious rats (25). The activation of DA and acetylcholine release in limbic and cortical areas in REMSD animals might be a neurochemical correlate of emotional arousal produced by changes in the environmental stimuli, irrespective of their aversive (REMSD) and nonaversive (Tank controls) condition.

Earlier, we have shown that stress associated with water tank methodology for inducing REM sleep deprivation decreased the number of striatal D_1 and D_2 receptors, whereas REMSD attenuated such decrease in the B_{max} of these receptors (19). In the present study we have observed a 29 and 31% increase in striatal DA concentrations in TC and REMSD animals. The downregulation of striatal dopamine receptors in TC group may be associated with an increased release of DA in TC group. One of the interesting observation made in this study was the effect of REM sleep deprivation on DA utilization in the striatum, which was contrary to what we expected from previous receptor binding data (19). Based upon the reported increase in B_{max} for D_1 and D_2 receptors in the striata of REM sleep-deprived rats compared to tank controls rats, one would have expected that DA utilization was either decreased in the REMSD group or increased to the point of depletion of the neurotransmitter. However, the results of the present study show that DA utilization was not decreased; neither was DA concentration depleted, in the striata of REM sleep-deprived rats. Although there is no clear explanation for these findings at this time, it is possible that REMSD may be associated with an uncoupling of DA receptor density regulation by its endogenous ligand in the striatum. Thus, an increase in DA release in REMSD group will exhibit greater dopaminergic-mediated effects due to upregulation of dopamine receptors in the striatum of REM sleep-deprived rats compared to TC rats. These data confirm earlier hypothesis that was previously proposed by others (7,59), and is consistent with the behavioral effects of dopaminergic stimulants in the REM sleep-deprived animals (2,8,59). It is pertinent to mention that other additional changes in the dopaminergic neurotransmission at postreceptor level may also be responsible for enhanced dopaminergic neurotransmission in these animals. Moreover, alterations in other neurotransmitters (5-HT and norepinephrine) will also modulate dopaminergic neurotransmission in direct or an indirect way.

In summary, our results suggest that REM sleep deprivation in rats produce changes in serotonin metabolism in cerebral cortex and dopamine metabolism in striatum. The increased DA metabolism in REMSD group may also reflect an increase in mesofrontocortical and mesoparietocortical dopaminergic neurotransmission that may be responsible for hyperactivity and hyperarousal often observed in these rats.

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