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The Disappearing Slow Wave Activity of Hibernators

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High and monotonically declining levels of EEG slow wave activity (SWA) occur following arousal from hibernation. Similar profiles of SWA occur in mammals including humans during sleep following periods of prolonged wakefulness, and have been interpreted as reflecting a homeostatic process regulating NREM sleep. It was proposed that even though hibernation appears to be an evolutionary extension of NREM sleep, the low brain temperatures during hibernation are not compatible with sleep restorative processes, and therefore sleep debt accumulates during hibernation and may be a factor triggering periodic arousal. In the present study, golden-mantled ground squirrels were sleep deprived by gentle handling following arousal from hibernation. If the SWA peaks following bouts of hibernation reflect a homeostatic response to an accumulated sleep debt, sleep deprivation should simply displace the SWA which would then occur, and be augmented, during subsequent sleep. In contrast, when animals were sleep deprived following arousal from hibernation, the anticipated SWA peak did not occur during subsequent sleep. It is suggested that the SWA following arousal from hibernation does not represent homeostatic regulation of NREM sleep, but instead some other neurological process involved in the recovery of brain function from an extended period at low temperature.

CURRENT CLAIM: The intense EEG slow wave activity normally seen after hibernation at low temperature is eliminated without rebound if the animals are sleep deprived during the first 4 hours of euthermia.

The slow wave activity (SWA, 1.0-4.0 HZ) of the cortical EEG has been used as a measure of sleep homeostasis because SWA reflects sleep/wake history. SWA is high in NREM sleep following long periods of wakefulness, indicating an accumulated sleep debt. During sleep, high SWA accompanies large reductions of sleep debt and low SWA accompanies small reductions of sleep debt (Achermann et al., 1993; Dijk and Daan, 1989). The relationship between the peak SWA in NREM sleep and the duration of prior wakefulness has been shown in a variety of different species, including humans, rats, chipmunks, and hamsters (Achermann et al., 1993; Borbely, 1982; Daan et al., 1984; Deboer and Tobler, 1994; Dijk and Daan, 1989; Tobler and Borbely, 1986; Tobler and Jaggi, 1987). Peak SWA in recovery sleep following sleep deprivation increases as an exponential saturating function of the duration of the previous wakefulness (Tobler and Borbely, 1986). In rats, 3-, 6-, and 12-hour sleep deprivations result in progressively higher peak SWA levels in recovery sleep.

Sleep following arousal from hibernation bears a striking resemblance to recovery sleep in non-hibernating animals following periods of extended wakefulness (Daan et al., 1991; Deboer and Tobler, 1994; Deboer et al., 1994; Larkin and Heller, 1996; Trachsel et al., 1991). Both are characterized by a high incidence of NREM sleep and by high initial SWA which falls during the subsequent hours of sleep (Larkin and Heller, 1996; Strijkstra and Daan, 1995; Trachsel et al., 1991). The resemblance of sleep in these two conditions has led to speculation that they are functionally similar; namely, that the high SWA following arousal from hibernation may reflect a sleep debt which accumulated during the hibernation bout.

It has also been proposed that accumulated sleep debt may itself provoke arousal from hibernation to euthermia and that the reduction of an accumulated sleep debt may be a necessary function of the interbout euthermic interval (Barnes et al., 1993; Daan et al., 1991; Trachsel et al., 1991). Hibernating animals periodically arouse to euthermia. These interbout euthermic intervals typically last less than a day each but are responsible for up to 90% of the energy consumed during the hibernation season (Lyman et al., 1982). The identity of the physiological process driving the periodic arousal from hibernation is unknown, but the relationship between the frequency of arousal and temperature and metabolic rate during hibernation suggests that the process is temperature-dependent (French, 1985, 1988; Geiser and Broome, 1993; Lyman et al., 1982). Recent work has shown that the peak SWA following arousal from hibernation is temperature-sensitive, suggesting that sleep homeostasis during hibernation may also be temperature-sensitive (Larkin and Heller, 1996).

If sleep homeostasis is a necessary function of the interbout euthermic interval, then perturbations in sleep homeostasis should affect the intensity of sleep following the termination of the sleep deprivation and the timing of re-entrance into hibernation. The purpose of this study was to investigate sleep homeostasis during the euthermic intervals between hibernation bouts. We sleep deprived squirrels during the first three hours of euthermia, when SWA and incidence of NREM

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sleep is highest, to determine whether sleep is regulated homeostatically during this time. It was expected that sleep deprivation at this time of apparent maximal sleep pressure would result in an increase in sleep intensity, marked by a rebound of SWA, and an increase in sleep duration, marked by a lengthening of the euthermic interval.

METHODS

Golden-mantled ground squirrels (*Spermophilus lateralis*) were caged individually in environmental chambers (5°C, 12L:12D) year round. Surgical implantation of EEG and EMG electrodes and thermocouple reentrant tube to measure brain temperature (T_{br}) followed methods previously described (Trachsel et al., 1991). Hibernation status was assessed by daily visual checks of animals in their home cages. EEG recordings during the hibernation season were taken from animals that had been in hibernation consistently for a minimum of a month.

For recording sessions, animals were placed in 12-inch diameter Plexiglas cages and provided with wood chips and cotton nesting material. Food (Purina rat chow and sunflower seeds) and water were available *ad libitum*. Recording cages were in an environmental chamber with air temperature (T_a) maintained at 5-11°C and a photoperiod of 24L:0D (20 lux). During recordings animals were connected to a Grass model 7 polygraph by a commutator which allowed full range of movement. They were assumed to have acclimated to the recording apparatus when they re-entered hibernation.

Data acquisition and analysis

The EEG signal was low pass filtered at 35.0 Hz and high pass filtered at 0.3 Hz. The EMG signal was low pass filtered at 75 Hz and high pass filtered at 3 Hz, and was integrated over 2.0 s intervals. The EEG signal for each animal was calibrated to a 200mV signal at the start of the recording. T_{br} was measured by a thermocouple inserted into the reentrant tube. The EEG signal, integrated EMG, T_{br} , and T_a were recorded every 10 s on a computer. Vigilance state of each 10s epoch during euthermia was determined by visual analysis to be NREM sleep, rapid eye movement (REM) sleep, or wake. Epochs containing artifacts were not included in the spectral analysis that was performed by fast Fourier transformation. SWA was calculated as the mean power density (1.0-4.0 Hz) in NREM sleep per hour. SWA was not calculated for a given hour if less than 5% of that hour was spent in NREM sleep. Mean T_{br}, percent vigilance states, and SWA were calculated for each hour of recording. For each animal SWA was normalized to the mean values in NREM sleep during baseline euthermic interval (T_{br} > 34°C) in winter euthermic animals. NREM sleep bout duration and number of brief interruptions of NREM sleep (nBA, defined as one or two epochs of either wake or REM sleep) were calculated by computer routines. NREM sleep bout length was determined for all NREM sleep bouts ≥ six epochs. The NREM sleep bout was determined to have ended if it was followed by three consecutive epochs of either wake or REM sleep.

During the hibernation season, animals were permitted several (3 to 5) undisturbed euthermic intervals and hibernation bouts to establish baseline data on sleep patterns, hibernation bout length and euthermic interval length. Animals (N = 10) were then sleep deprived (SD) following spontaneous arousal to euthermia. SD by gentle handling was initiated when T_{br} rose above 33.5°C and lasted for the first 3 to 4 hours of euthermia. Squirrels were not disturbed during the remainder of the euthermic interval following the SD. SD by gentle handling consisted of removing the cotton nesting material and adding fresh cedar shavings and a fresh supply of food (sunflower seeds and Purina rat chow). When EEG showed

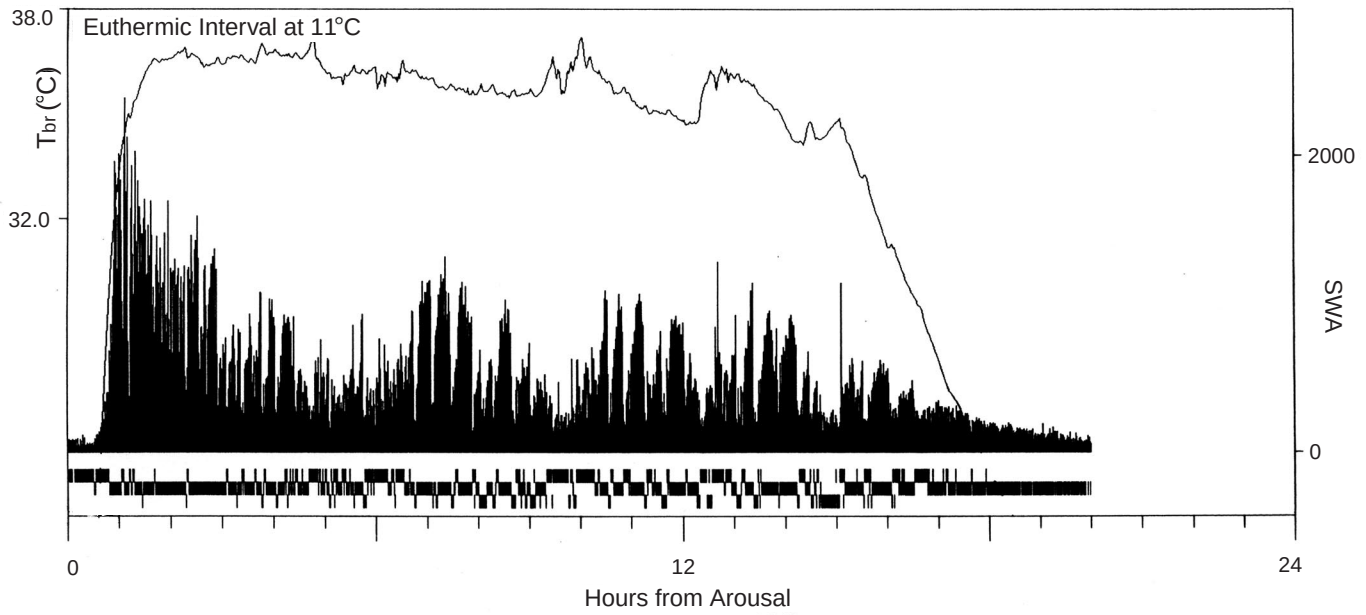

Figure 1. Typical SWA and vigilance state distribution during an interbout euthermic interval in a ground squirrel. Profiles of SWA (heavy lines), T_{br} (light lines), and vigilance states in euthermic intervals at T_a of 11°C.

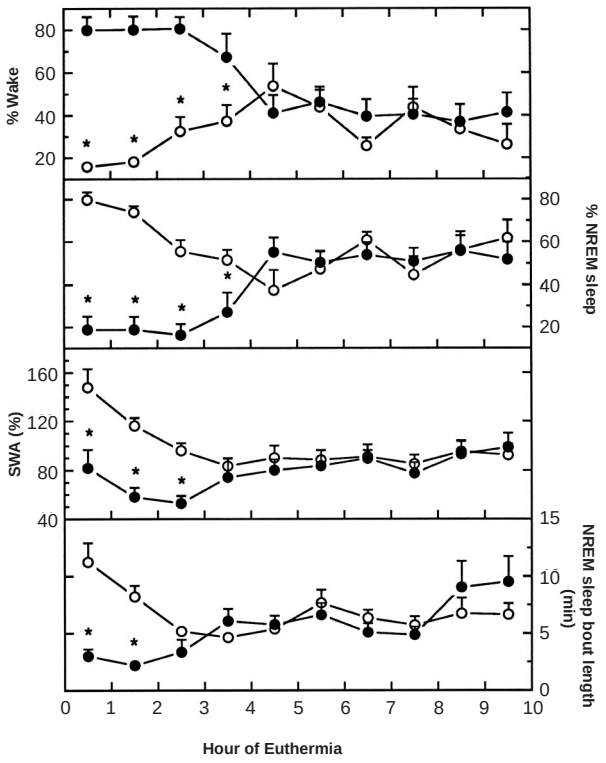

Figure 2. Effects of 3 to 4 h manual sleep deprivation on % wake, % NREM sleep, SWA, and NREM sleep bout length during the first 10 h of euthermia. Open circles designate baseline undisturbed euthermic interval control, and closed circles designate sleep deprivation (SD) euthermic interval (N = 10). Asterisk indicates significant difference ($p < .05$) between SD and C at that time point.

incursions of slow waves and sleep spindles, animals were gently touched with a small artist's brush to awaken them. Animals were given fresh cotton nesting material during the last 15 minutes of the SD and were not disturbed once the deprivation was terminated. The durations of the SD interval and the subsequent hibernation bout were measured and compared to undisturbed durations. Sleep parameters (hourly values of SWA, % NREM sleep, % wake, % REM sleep, NREM sleep bout length, nBA, and T_{br}) were compared between the baseline and the SD intervals by repeated measures ANOVA.

Sleep homeostasis during the middle of interbout euthermic intervals was also investigated. Recording conditions were the same as in the hibernation SD experiments described above, except that T_a was maintained at 20°C to extend the interbout euthermic intervals. Baseline interbout euthermic intervals (N = 5) were recorded to determine the relationship between duration of voluntary wakenings and SWA in NREM sleep prior to and following these intervals of wakefulness (N = 38). The absolute % change in SWA (calculated in 20-minute intervals) was determined by subtracting the SWA prior to the interval of wakefulness from the SWA following wake. Two animals were also subjected to manual SD (3 h) in mid-euthermia by gentle handling, and their sleep was analyzed during the subsequent 12 h following the SD to investigate whether SWA was elevated following SD in mid-euthermia.

RESULTS

During the hibernation season, the sleep and SWA profiles for the undisturbed interbout euthermic intervals were similar to previously reported undisturbed sleep at low T_as in this species (Fig. 1). When the animals were undisturbed, the interbout euthermic intervals lasted 13.5 ± 1.7 hours, and the hibernation bouts averaged 106.8 ± 9.5 hours. Squirrels spent the majority (70%) of the euthermic intervals asleep. SWA and incidence of NREM sleep were maximal during the first three hours of the euthermic intervals. SWA and NREM sleep bout length were highest during the first hour of euthermia and fell monotonically during the next several hours (Fig. 2).

SD during the first three to four hours of the euthermic interval was effective in preventing the animals from obtaining consolidated sleep. Wake during the sleep deprivation differed from spontaneous wakefulness in that there were periodic incursions of spindles and SWA during aborted attempts to enter NREM sleep during the sleep deprivation. During SD, animals spent 80% of their time awake and about 20% in NREM sleep (Fig. 2). The fact that the animals were repeatedly trying to enter sleep during the SD protocol indicated they were not stressed by the procedure. The NREM sleep which did occur during SD had significantly lower SWA (67.5 ± 15.3% versus 108.7 ± 5.6%), shorter NREM sleep bout length (4.5 ± 0.6 min versus 7.0 ± 0.5 min), and a greater number of brief arousals (1.12 ± 0.09 nBA/minute of NREM sleep versus 0.69 ± 0.04) than baseline sleep at the same time in euthermia, indicating that sleep deprivation resulted in more fragmented sleep. T_{br} was significantly elevated above baseline only during the hours three and four of the SD. SD during the first four hours of the euthermic interval awake or in intense NREM sleep had no apparent effect on any of the measured sleep parameters during the remainder of the euthermic period. Neither SWA nor % NREM sleep were elevated following termination of the SD (Figs. 1 and 2). Instead, hourly values for SWA, % NREM, % wake, and NREM sleep bout length following the termination of the SD were not significantly different from the baseline data at those same time points (Fig. 2). SD also resulted in significantly longer euthermic intervals, 14.2 h longer than controls (one-sample *t*-test, $p < 0.005$), and shorter subsequent hibernation bouts (31.5 h shorter than controls [one-sample *t*-test, $p < 0.005$]).

Sleep following the sleep deprivation did not resemble intense recovery sleep, with high SWA, minimal waking, and long NREM sleep bouts as did sleep immediately following arousal from hibernation. When sleep during the first two hours of recovery following the SD was compared to sleep during the first two hours of undisturbed baseline euthermic intervals, the recovery sleep had significantly lower SWA and shorter NREM sleep bout lengths, as well as lower incidence of NREM sleep and higher incidence of wake (ANOVA $p < 0.05$).

After the initial five hours of euthermia, sleep during the remainder of the interbout euthermic interval appeared to be homeostatically regulated and to reflect the immediately preceding duration of wakefulness. During interbout euthermia there were prolonged episodes of wakefulness (15 minutes to 3

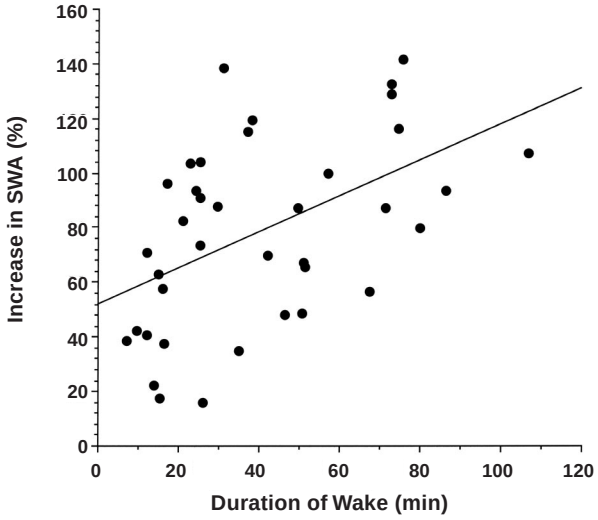

Figure 3. Relationship of the duration of spontaneous intervals of wake at T_a of 20°C and change in SWA (SWA following wake-SWA prior to wake). Longer periods of wake were followed by higher SWA, and hence greater changes in SWA (least squares regression, $p < 0.005$, R = 0.496, N = 38).

hours) followed by sleep bouts. SWA was heightened at the onset of these sleep bouts in comparison to SWA prior to the episode of wakefulness, and the magnitude of the increase of SWA was related to the duration of wake (Fig. 3). While the SWA prior to a period of wake was not significantly related to the duration of wakefulness (regression, $p = 0.22$), SWA level following wake was significantly related to the duration of wakefulness (regression, $p = 0.005$). SWA prior to wake averaged 62.5 ± 2.9%, while peak SWA at sleep onset following wake averaged 140.8 ± 4.9%, following periods of wake averaging 40.3 ± 4.2 minutes. The response of squirrels (N = 2) to 3 h SD's in mideuthermia (at least 5 hours from the time of arousal) also showed typical SWA rebounds following the termination of SD that are indicative of sleep homeostasis. During the SD the animals averaged 94% wakefulness, and in the subsequent NREM sleep SWA rapidly rose to an average of 193% above control values and steadily declined as sleep progressed.

DISCUSSION

EEG studies of several species have revealed a high incidence of NREM sleep with exceptionally high levels of SWA immediately following a return to euthermia from a bout of torpor or hibernation. This post-torpor peak of SWA undergoes a monotonic decline as sleep progresses (Daan et al., 1991; Deboer and Tobler, 1994; Larkin and Heller, 1996; Trachsel et al., 1991). Since this profile of SWA is identical to what is observed following prolonged wakefulness, it has been suggested in the studies referenced above that the bout of torpor or hibernation may represent a period of sleep deprivation. Clearly the adaptive significance of torpor and hibernation is energy conservation, and it is reasonable to speculate that torpor and hibernation evolved as extensions of NREM sleep (Krilowicz et al., 1988; Walker et al., 1977; Walker et al., 1981). Therefore, it was proposed that the low brain temperatures of torpor and hibernation were incompatible with the biochemistry of sleep restorative processes (Daan et al., 1991; Trachsel et al., 1991). The fact that the level of SWA following bouts of hibernation was inversely proportional to the brain temperature during hibernation supported this argument (Larkin and Heller, 1996). We therefore expected that if we sleep deprived animals immediately following their return to euthermia, we would displace and augment the SWA that characterized the recovery sleep. Instead, much to our surprise, when animals were sleep deprived for four hours following their return to euthermia and then permitted to sleep, the anticipated peak in SWA did not occur. We must therefore conclude that the SWA following a bout of hibernation is not a reflection of the homeostatic regulation of NREM sleep. Results similar to those we report here have been produced by Strijkstra and Daan working on the European ground squirrel (personal communication).

It is possible that the lack of a rebound in SWA following the termination of the SD was because the animals were stressed and overstimulated by the SD protocol and were unable to sleep. If animals were overstimulated by the SD protocol, then there should have been increased amounts of wake above normal levels, lower incidence of NREM sleep, and more fragmented NREM sleep, measured by higher nBA, during the recovery period. However, this does not seem to be the case since measurement of % wake, % NREM sleep, NREM sleep bout duration, and nBA all indicate that the animals were able to enter sleep soon after the termination of the sleep deprivation. The lengthening of the experimental SD euthermic interval and the shortening of the subsequent hibernation bout may be effects of SD on sleep homeostasis or they may be disturbance artifacts of the SD protocol.

An obvious question to ask is whether hibernators in general or this species in particular shows the homeostatic relationship between SWA and prior wakefulness which has been demonstrated in many non-hibernating species. Our results show that with the exception of a period of time immediately following arousal from hibernation, the golden-mantled ground squirrel responds to prolonged wakefulness with the expected increase in SWA. During mid-interbout euthermia the animals have spontaneous periods of prolonged wakefulness which are followed by episodes of NREM sleep with initial high SWA that declines monotonically. Similarly, SD by gentle handling during mid-interbout euthermia or in summer squirrels that are not hibernating (unpublished data) results in an increase in SWA in recovery sleep. Except for the hours immediately following arousal from a bout of hibernation, homeostatic regulation of SWA during NREM sleep seems to be normal in this species. Therefore, the fact that the SWA normally seen immediately following arousal from hibernation is completely eliminated by SD during the first 4 hours of euthermia indicates that this post-arousal peak in SWA does not reflect sleep homeostasis.

One possible interpretation of these data is that the SWA peak following arousal from hibernation reflects some

neurological process associated with recovery from the low temperatures of hibernation rather than the neurological processes normally associated with recovery from prior wakefulness. Heightened SWA is associated with hypoglycemia (Amiel et al., 1991; Bendtson et al., 1991; Lewis et al., 1974; Pramming et al., 1988). High SWA has also been correlated with periods of intense synaptogenesis. During postnatal development in rats and humans, the developmental courses of SWA levels, synaptic density, and cortical metabolic rate are strikingly similar (Feinberg et al., 1990; Frank and Heller, 1997; Gramsbergen, 1976). All three factors increase following birth, peak at the same developmental age, and then decrease to adult levels. It is possible that these or some other neurological process may be responsible for the SWA peak observed following arousal from hibernation.

The relationship between hypoglycemia and SWA is interesting to pursue. The arousal from hibernation involves an enormous metabolic effort, and recent work on the regulation of SWA has resulted in the hypothesis that depletion of cerebral energy reserves during waking leads to increased release of adenosine by neurons. Increased extracellular adenosine acting through the A1 receptor hyperpolarizes thalamic and cortical cells and thereby increases SWA (Benington and Heller, 1995). At present, however, there is no evidence of hypoglycemia following arousal from hibernation. In *S. lateralis*, glucose levels remain steady throughout the hibernation bout (Andrews and Taylor, 1988; Twente and Twente, 1967). Measurements of plasma glucose, brain glucose, and brain glycogen during arousal from hibernation have given no indication of hypoglycemia during arousal (Galster and Morrison, 1975; Galster and Morrison, 1970; Lust et al., 1989; Nestler, 1990). Rather, plasma and brain glucose levels increased during the arousal. Analyses of plasma glucose during the course of the euthermic interval also indicated no hypoglycemia in the hours following arousal which could coincide with the SWA peak (Galster and Morrison, 1975; Galster and Morrison, 1970; Lust et al., 1989; Nestler, 1990; Nizielski et al., 1989). These measurements, however, may not tell the whole story. Neurons require a constant supply of glucose, and that is a function both of blood glucose levels and cerebral circulation. Brain electrical activity increases early in the arousal process. It is possible that regional shortages of glucose occur due to lack of perfusion even if blood glucose levels are normal. Relations between brain energy metabolism, arousal from hibernation, and SWA require more investigation.

Possible relationships between high SWA and neural structural recovery following hibernation at low temperature also warrants attention. The SWA peak following arousal from hibernation corresponds to the time during which there is massive dendritic regrowth and synaptogenesis. Studies of dendritic morphology and synaptic contacts in the hippocampus of hibernating squirrels have shown that there is a substantial loss of synapses and of dendritic branching during hibernation and rapid regeneration of dendrites and synapses following the initiation of arousal from hibernation (Popov and Bocharova, 1992; Popov et al., 1992). The authors suggested that the loss of synapses and dendritic branching may be related to the decreased brain electrical activity during hibernation and that these losses may be even greater in the cortex than in the hippocampus.

Popov's suggestion that the decrease in electrical activity in the brain may determine the amount of loss of dendrites and synapses provides interesting possible insights into the SWA patterns we have observed. The SWA peak following arousal from hibernation is negatively correlated to T_{br} and EEG cortical activity during hibernation. Hibernation at lower T_as is characterized by lower levels of cortical activity and higher subsequent peak SWA. In fact, when animals hibernate at a brain temperature above 25°C, they display fairly normal sleep EEG patterns during hibernation and no elevation of SWA following arousal (Larkin and Heller, 1996). Thus, it is possible that the elevated SWA immediately following arousal from hibernation at low temperatures may represent temperature-dependence of dendritic and synaptic loss during hibernation and recovery during arousal. It may be that growth factors involved in this structural recovery process promote SWA, but their release is not sleep dependent and the recovery processes they control are not sleep dependent. This will be a fruitful area for future investigations.

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