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Age-related changes in the hamster's circadian system partially reversed by treatment with Sulbutiamine, a vit b-1 related compound

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SHORT REPORT

Age-related Changes in the Hamster's Circadian System Partially Reversed by Treatment with Sulbutiamine, a Vit B-1 Related Compound

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Abstracting keywords: aging, circadian rhythms, phase shift, activity-rest cycle, Sulbutiamine.

Numerous mental and physical disorders (e.g. some forms of depression and insomnia, Alzheimer's disease) have been associated with abnormal timing in the circadian system which regulates the 24-h pattern of many behavioral, endocrine, biochemical and neural events in humans. In addition, aging in mammals, including humans, is associated with various abnormalities in circadian rhythms: loss of cohesion, dampened amplitude, changes in the free running period and changes in the phase-angle of entrainment (Brock, 1991). Our recent findings in old hamsters indicate that there are also age-related changes in the response of old animals to the phase shifting effects of both photic and non photic stimuli (benzodiazepines, dark pulses) (Van Reeth and Turek, 1989, 1991, Rosenberg et al. 1991). Indeed, in old hamsters, there appears to be a total loss of responsiveness to the feed back effects of the activity-rest state of the animals on the circadian clock. This latter finding suggests that disorders of time-keeping frequently found in elderly people might be due in part to a weakening of the interactions between the activity-rest cycle and the circadian clock.

Restoration of the response of old hamsters to the phase shifting effects of activity-inducing stimuli is observed after transplantation of fetal grafts containing the suprachiasmatic nuclei (SCN) in the region of the SCN of old hamsters (Van Reeth et al., 1994). This observation suggests that some age-related changes in the circadian system might be reversible, and led us to use pharmacological tools to possibly reverse some of these changes. Sulbutiamine, an anti-fatigue drug commonly used in human patients, was thought to be a likely candidate for reversing the effects of aging on the circadian clock, since chronic treatment with

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this drug can improve the level of vigilance, modify sleep architecture, as well as improve behavioral and cognitive performance in old animals. Moreover, the effects of Sulbutiamine on the central nervous system are thought to be mediated through serotoninergic and/or cholinergic pathways, making this drug a particularly attractive candidate for being a chronobiotic agent: the mammalian circadian clock, located in the SCN of the hypothalamus, receives an very dense projection of serotoninergic fibers from the midbrain raphe nuclei, and cholinergic agonists can dramatically alter the functioning of the circadian clock.

To test the possible effectiveness of Sulbutiamine in reversing age-related changes in the circadian system, various parameters of the circadian rhythm of locomotor activity were compared between old hamsters (18-19 months old) fed either with a control or Sulbutiamine-enriched diet for 50 days. Visual inspection of activity profiles in animals of both groups indicates that chronic treatment with Sulbutiamine improved cohesiveness in the circadian rhythm of locomotor activity of old hamsters, and increased the amplitude of the activity-rest cycle. Treatment with Sulbutiamine induced significant changes in the phase-angle between the onset of locomotor activity and the light-dark cycle: while phase-angles of entrainment were similar in the two groups of old hamsters before treatment, the mean phase-angle of entrainment of old hamsters under Sulbu-

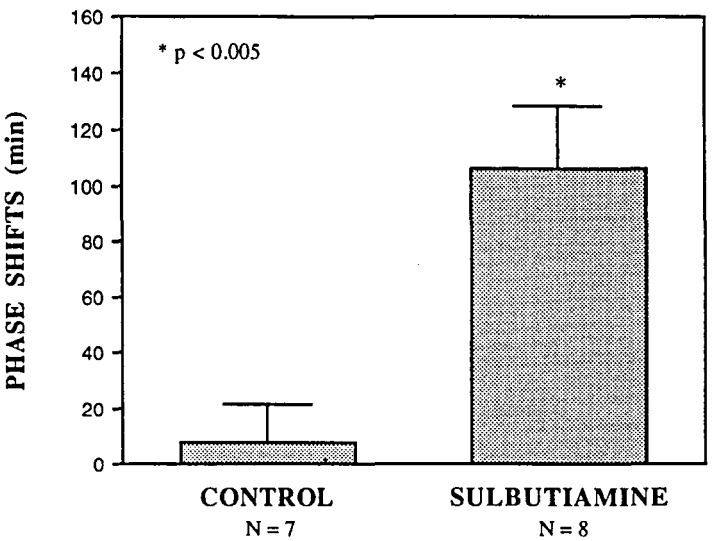

Fig. 1. Mean (± S.E.M.) phase shifts in the activity rhythm of hamsters that were injected with 5 mg/kg triazolam at circadian time 6 in constant darkness. Control hamsters are on the left, and Sulbutiamine-treated hamsters are on the right. A value above the solid line indicates a mean advance in the onset of locomotor activity. Numbers at the bottom of each bar indicate the numbers of animals injected with triazolam in each group.

tiamine treatment was significantly delayed. As expected from results of our previous experiments, old hamsters (fed with control diet) showed very small phase shifts in response to an activity-inducing stimulus (i.e. an injection of 5 mg/kg triazolam i.p.) at circadian time 6 in constant darkness. In contrast, old hamsters fed with Sulbutiamine dramatically increased their response showing large phase shifts after the triazolam injection (Fig. 1).

These results demonstrate that chronic treatment with Sulbutiamine can reverse at least some of the effects of aging on the circadian clock of old hamsters, and suggest that appropriate neuropharmacological interventions might be able to reverse changes in the circadian system that occurs spontaneously in aging. Further development of drugs acting as circadian organizers might thus be useful for normalyzing disturbed circadian rhythms in elderly patients.

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