IMPAIRED SLEEP CONTINUITY AFTER INTRACEREBROVENTRICULARLY ADMINISTERED NESFATIN-1 IN RATS

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Purpose of the study

The recently discovered molecule nesfatin-1, the N-terminal fragment of the neurelinb 2 protein (NUCB2) is expressed in several hypothalamic nuclei. Immunohistochemical studies showed that the largest population of nesfatin-1/NUCB2-immunoreactive (IR) neurons is in the lateral hypothalamus (LH) of the rat brain. The LH is part of the lateral hypothalamic area (T HA) which plays an important role in the regulation of sleep. A double immunofluorescent study of the THA revealed that approximately 80% of the nesfatin-1/NUCB2-containing neurons co-express melanin concentrating hormone (MCH), and all MCH-containing neurons are nesfatin-1/NUCB2 IR.

Therefore we studied the effect of intracerebroventricularely (icv) administered nesfatin-1 on certain vigilance stages and sleep continuity of rat.

Methods

- Male Wistar rats weighing 350-350 g were equipped with electroencephalographic (EEG) and electromyographic (EMG) electrodes, and a plastic cannula was implanted into the right lateral ventricle of the rats.
- On the day of the experiment 25 pmol/5 µl of nesfatin-1 (n=6) or 5 µl physiological saline (n=6) was injected icv at light onset and EEG, EMG and motility were recorded.
- Due to the stress caused by the icv procedure sleep data of the 2nd-6th hours of passive phase were evaluated by Sleep Sign® software followed by visual supervision. The sleep data were summarized.
- The number of non rapid eye movement (NREM) sleep episodes shows the number of NREM sleep stage episodes, with 16 sec minimal stage length, preceded and followed by at least 16 sec of non-NREM. The episodes must consist at least 80% of NREM.
- Statistical analysis was performed by One Way ANOVA using STATISTICA 7.0 software. Data are presented as mean ± standard error of mean (SEM).

Results

During the five investigated hours of passive phase, the icv administered nesfatin-1 significantly increased the number of awakenings after a various sleep stage (F(1,10)=5.10; p<0.05, Fig. 1) compared to the control group. Parallel with this we also found a significant elevation in the number of NREM sleep episodes (F(1,10)=5.81; p<0.05, Fig. 2). Consequently, sleep became more fragmented. The ratio of total sleep (TS) to total wake (TW) showed a significant decrease (F(1,10)=5.83; p<0.05, Fig. 3).

Conclusion

Our data show that icv administered nesfatin-1 has a disrupting effect on sleep architecture.

Icv administered nesfatin-1 has been shown to induce Fos activation in the serotonergic dorsal raphe nucleus (DRN) and noradrenergic locus coeruleus (LC). The early gene product Fos is a widely used indirect indicator of ongoing neuronal activity. Considering that the DRN and LC are important parts of the ascending arousal system, we can hypothesize that an elevated serotonergic or noradrenergic tone, due to icv administered nesfatin-1 may contribute to the impaired sleep continuity. As elevated nesfatin-1 level is typical in depressed patients, and it can penetrate the blood-brain barrier, we suggest that an altered central nesfatin-1/NUCB2 expression may be responsible, at least in part, for the sleep abnormalities in depression. However, the nesfatin-1’s precise mechanism of action in the regulation of sleep architecture needs to be clarified in the future.

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References