ICV Orexin-A Ameliorates the Lasting Effects of Early Postnatal Dysfunction of Brain Muscarinic Cholinergic System on Sleep-Wakefulness Cycle in Adult Rats

Neli Maglakelidze,
Olga Mchedlidze, Mariam Babilodze, Eka Chkhartishvili, Eter Chijavadze, Nargiz Nachkebia

Laboratory Neurobiology of Sleep-Wakefulness Cycle at Ivane Beritashvili Center of Experimental Biomedicine, Tbilisi, Georgia

Introduction

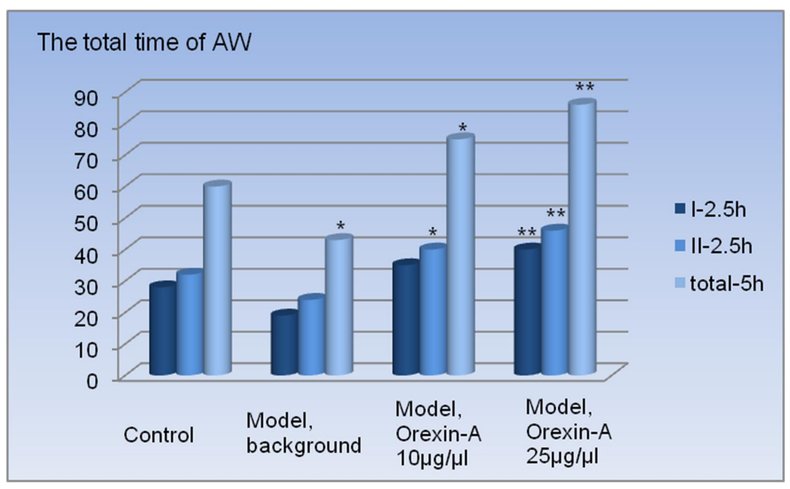
Orexin/Hypocretin-producing neurons are believed as involved in the strengthening of arousal and wakefulness state that becomes unstable if Orexins are deficient in the brain. On the other hand, suppression of wakefulness can be one of the main reasons for the development of sleep disorders and depression. Therefore, it is believed that the hypothalamic Orexinergic system may also be involved in the pathophysiology of depression. The aim of the present investigation was to study the effects of intra-cerebro-ventricular (ICV) administration of Orexin-A on sleep disturbances produced by early postnatal exposure of rat pups to the dysfunction of muscarinic cholinergic system (MChS).

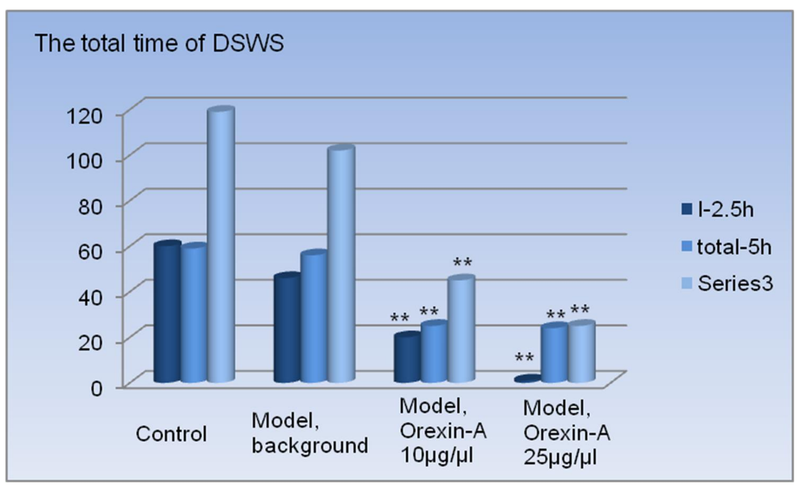
Methods

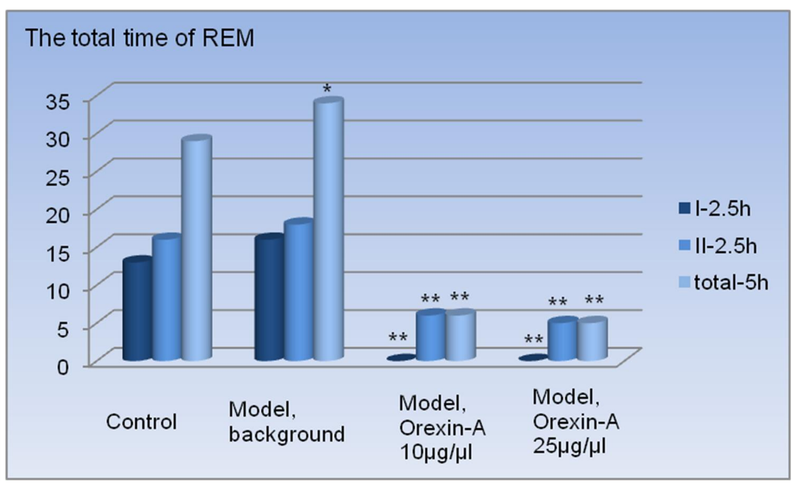
Dysfunction of MChS was produced by subcutaneous injection of scopolamine (30 mg/kg) in rat pups (n=10), twice daily, from postnatal days 7 to 28. Control rat pups (n=5) received the same volume of saline. Experiments were started 2–3 months after discontinuation of the drug administration. Implantation of stainless steel screws, for epidural EEG registration, and microinjection cannulas (Plastics Ones) were made under general anesthesia. Two doses of Orexin-A (10 µg/µl and/or 25µg/µl) were microinjected in the lateral ventricle. Experiments were started after the post-surgery recovery period. EEG registration of the sleep-wakefulness cycle have been started immediately after ICV microinjection of Orexin-A and/or saline, and lasted continuously for 6 hours daily (10.00 a.m. - 16.00 p.m.) for three consecutive days on each animal. Statistical treatment was made by the Students' test.

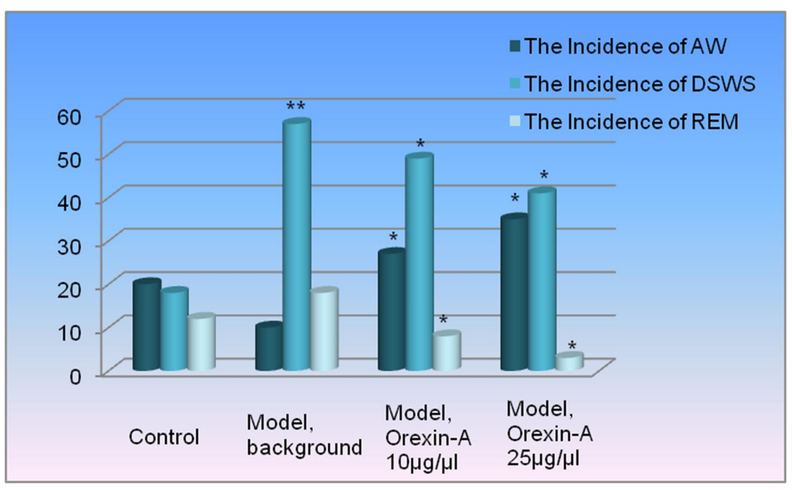
Results

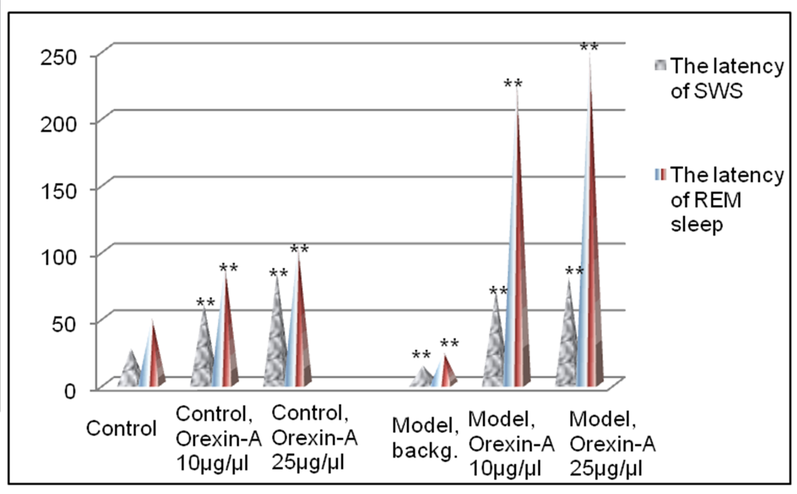
It was found that animals exposed to the early postnatal dysfunction of MChS were characterized in adult age by significant sleep disturbances that were similar to sleep disorders, characteristic of major depressive disorder. ICV microinjection of Orexin-A dose-dependently ameliorated sleep disturbances, which was manifested in the enhancement and stabilization of wakefulness, in an increase of the latency of REM sleep, which was reduced in these animals, and a decrease in the incidence of REM sleep that has the tendency to develop more frequently as during major depressive disorder.

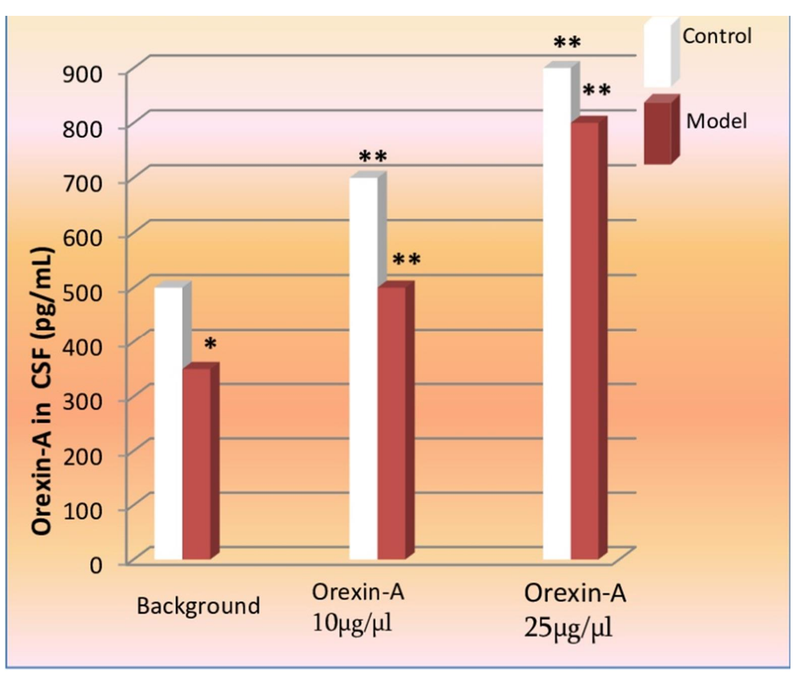












Conclusion

Elevation of the level of Orexin-A in CSF significantly ameliorates sleep disturbances in adult animals, subjected in early ontogenesis to the dysfunction of MChS.

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