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Pharmacological therapy in obstructive sleep apnea – Methodology and interventional aspects of carbonic anhydrase modulation

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Kammaren, Huvudentrén, Blå stråket 5, Sahlgrenska sjukhuset, den 8 december, klockan 13.00.

av Erik Stenkilsson Hoff

Fakultetsopponent:

Professor T. Douglas Bradley

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Avhandlingen baseras på följande delarbeten

I. Erik Hoff, Ding Zou, Sophia Schiza, Yeliz Demir, Ludger Grote, Izolde Bouloukaki, Sükrü Beydemir, Davoud Eskandari, Kaj Stenlöf, Jan Hedner. **Carbonic anhydrase, obstructive sleep apnea and hypertension: Effects of intervention.** Journal of Sleep Research 2019; 29: e12956

II. Erik Hoff, Christian Strassberger, Ding Zou, Ludger Grote, Kaj Stenlöf, Jan Hedner. **Modification of endotypic traits in obstructive sleep apnea by the carbonic anhydrase inhibitor.** Chest 2023, *in press*

III. Erik Hoff, Saliha Musovic, Ali M. Komai, Ding Zou, Christian Strassberger, Kaj Stenlöf, Ludger Grote, Jan Hedner. **The effect of sulthiame on potential biomarkers in moderate to severe obstructive sleep apnea.** 2023, *submitted*

IV. Erik Hoff, Ding Zou, Ludger Grote, Kaj Stenlöf, Jan Hedner. **The placebo effect in pharmacological treatment of obstructive sleep apnea, a systematic review and meta-analysis**. Sleep Medicine 2023; 106: 1-7

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Pharmacological therapy in obstructive sleep apnea – Methodology and interventional aspects of carbonic anhydrase modulation

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Abstract

Background: Obstructive sleep apnea (OSA) is a common disease with consequences such as daytime sleepiness and cardiovascular disease. Recurrent total or partial collapse of the upper airway during sleep, leads to sleep fragmentation and intermittent hypoxia/hypercapnia. The underlying mechanisms include a collapsible upper airway, unstable ventilation, low arousal threshold and insufficient muscle compensation in the pharynx region. The main treatments, positive airway pressure (PAP) and mandibular advancement devices, address anatomical causes. In many patients, these treatments are not tolerated or efficacious. Improved understanding of the pathophysiology has paved the way for new treatment targets. In this thesis, carbonic anhydrase (CA) activity as an OSA biomarker is investigated together with studies on CA inhibition as an OSA therapy, in addition to a systematic evaluation of placebo effects in OSA pharmacotherapy.
Methods and Results: In paper I, we studied 33 PAP-treated subjects with OSA plus 9 OSA patients treated with PAP and/or the CA inhibitor acetazolamide (ACT). CA activity was higher in hypertensive participants and PAP treatment per se did not reduce CA activity. The activity was numerically reduced by ACT. In paper II we investigated the sulthiame (STM) effect on pathomechanisms in 58 subjects from a randomised controlled trial. STM reduced ventilatory instability and the upper airway was stabilised. In paper III, we showed that both CA activity and HIF-1α concentration were reduced by STM up to two weeks after last drug intake. In paper IV the placebo effect of drug treatment in OSA was analysed in a systematic review. Objective OSA measures were not systematically affected by placebo whereas effects in subjective symptoms, like daytime sleepiness, need to be accounted for.

Conclusion: The CA system plays an important role in OSA pathophysiology and appears to be a promising target for drug treatment. Further studies are needed to define a potential role for CA activity as a diagnostic biomarker in OSA. STM stabilised ventilation and an increased the upper airway stability. Future drug studies in OSA need to be placebo controlled and appropriately sized to enable characterisation the complex mechanisms underlying this disease.

Keywords: obstructive sleep apnea, carbonic anhydrase, endotype, drug therapy, hypoxia, hypoxia inducible factor 1α, placebo

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