Carbonic anhydrase activity in sleep apnea – a potential therapeutic mechanism for intervention

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hjärtats aula, Blå stråket 5, Sahlgrenska Universitetssjukhuset, den 19 december, klockan 09.00

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Avhandlingen baseras på följande delarbeten:

I. Eskandari D, Zou D, Grote L, Schneider H, Penzel T, Hedner J. **Independent associations between arterial bicarbonate, apnea severity , and hypertension in a sleep apnea cohort**.
Submitted

II. Wang T, Eskandari D, Zou D, Grote L, Hedner J. **Increased Carbonic Anhydrase Activity is Associated with Sleep Apnea Severity and Related Hypoxemia**. SLEEP 2015; 38(7): 1067-1073

III. Eskandari D, Zou D, Karimi M, Stenlöf K, Grote L, Hedner J. **Zonisamide reduced obstructive sleep apnoea: a randomised placebo- controlled study**. European Respiratory Journal 2014; 44(1): 140-149

IV. Eskandari D, Zou D, Grote L, Hoff E, Hedner J. **Acetazolamide reduces blood pressure and sleep disordered breathing in hypertensive OSA patients**. Submitted

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Abstract

There is no pharmacological treatment for obstructive sleep apnea (OSA) in clinical practice. The overall aim of this thesis was to investigate the effect of carbonic anhydrase (CA) enzyme activity on sleep apnea severity and blood pressure (BP) regulation in OSA. We explored the association between arterial standard bicarbonate ($StHCO_3^-$), a proxy for CA activity, and apnea severity as well as hypertension status in a retrospective cohort of OSA patients (n=830, paper I). In a cross-sectional sleep clinic cohort (n=70), we explored the association between whole blood CA enzyme activity and OSA severity (paper II). Furthermore, we designed a randomized, placebo-controlled study to investigate the effect of pharmacological CA inhibition after zonisamide (ZNS) on sleep disordered breathing in overweight/obese OSA patients (n=42, paper III). Finally, the effect of CA inhibitor acetazolamide (AZT), continuous positive airway pressure (CPAP) or the combination thereof on sleep apnea and BP was investigated in a three-way cross-over study in 13 male hypertensive OSA patients (paper IV). Sleep disordered breathing was quantified by polysomnographic/polygraphic recording. Office systolic/diastolic BP (SBP/DBP) and vascular stiffness were assessed. Arterial/venous $StHCO_3^-$ was collected. In paper I, we found that arterial $StHCO_3^-$ was independently associated with apnea-hypopnea index (AHI) as the measure of OSA severity ($p<0.001$). In addition, arterial $StHCO_3^-$ was positively associated with both a hypertension diagnosis and DBP ($p=0.007$ and 0.048, respectively). In paper II, CA activity was associated with AHI, nocturnal hypoxemia as well as DBP ($p=0.007$, 0.011 and 0.046, respectively). In paper III and IV, therapeutic intervention using ZNS and AZT, significantly reduced AHI by 33(39) % (placebo-adjusted) and 42(27) % ($p=0.02$ and 0.001, respectively). AZT reduced office BP in parallel with improvement of vascular stiffness compared to CPAP. In conclusion, our studies suggest an independent association between CA activity and OSA. High CA activity may represent a novel mechanism for development of hypertension in OSA. Drugs with CA inhibitory properties may provide a promising target for disease modifying treatment in OSA and its related comorbidities.

Keywords: bicarbonate, blood pressure, carbonic anhydrase, hypertension, obesity, obstructive sleep apnea, vascular function

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