Increased CaMKII-dependent pro-arrhythmic activity in a novel mouse model of obstructive sleep apnoea

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Background: Obstructive sleep apnoea (OSA) is frequently associated with atrial arrhythmias, but detailed mechanisms remain elusive. Most recently, we found an increased CaMKII-dependent pro-arrhythmic activity in patients with sleep apnoea. Since patients suffer from various confounding comorbidities, we have developed a novel mouse model of OSA by tongue enlargement.

Purpose: We tested if mice with OSA exhibit increased atrial CaMKII-dependent pro-arrhythmic activity.

Methods: Polytetrafluorethylene (PTFE) was injected into the tongue of 12 wild-type (WT) and 10 CaMKII knock-out (CKO) mice. 9 WT and 9 CKO mice were used as control without PTFE injection. Inspiratory flow limitations and apnoeas were monitored during murine sleep phases by whole-body plethysmography (Buxco). After eight weeks, isolated atrial cardiomyocytes were incubated with the Ca-sensitive dye FURA-2 AM for 15 min. Regular Ca transients were elicited by electrical field stimulation (1 Hz, 20 V for 4 ms) using epifluorescence microscopy. Pro-arrhythmic non-stimulated events were defined as deviations from diastolic Ca baseline between two stimulated Ca transients.

Results: Sonographic measurements revealed a significant increase in mean tongue diameter from (in mm) 3.7±0.1 to 5.1±0.1 after PTFE injection (n=23, $p<0.0001$). There was a significant correlation between magnitude of tongue diameter and frequency of apnoeas in OSA mice (p=0.046, r^2=0.19, Fig. 1A). Interestingly, we observed a significantly increased frequency of pro-arrhythmic events of (in s^{-1}) 0.06±0.01 in WT OSA mice compared to 0.02±0.01 in WT control mice (p=0.047, Fig. 1B). Similar results were observed at higher stimulation frequencies (2 and 4 Hz). There was a significant correlation of pro-arrhythmic events with inspiratory flow limitations (p=0.03, r^2=0.24, Fig. 1C) and with the frequency of apnoeas by strong trend (p=0.06, r^2=0.18). In contrast, no increase in atrial pro-arrhythmic events was observed in CKO mice after PTFE injection (for CKO mice after PTFE vs. CKO mice without PTFE, 0.03±0.01 s^{-1} vs. 0.03±0.01 s^{-1}, p=0.89, Fig. 1B). Accordingly, the correlations between pro-arrhythmic events and both inspiratory flow limitations (p=0.36, r^2=0.05, Fig. 1C) and apnoeas (p=0.82, r^2=0.004) were completely abolished in CKO mice.

Conclusion: In a novel mouse model of obstructive sleep apnoea, atrial pro-arrhythmic activity was increased in a CaMKII-dependent fashion, which may have therapeutic implications.

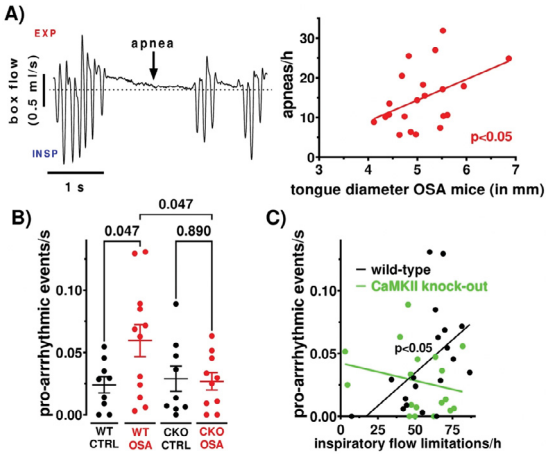

Figure 1