VOLTAGE-GATE SODIUM CHANNELS AS POTENTIAL TARGETS TO SUPPRESS PATHOLOGICAL COUGH

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Introduction Pathological cough as chronic non-productive, postviral or excessive cough in COPD is regarded to be secondary to inappropriate activation of vagal sensory nerves. Respiratory nodose Aδ-fibres and jugular C-fibres participate in regulation of cough. Current advances in understanding of voltage-gate sodium channels (NaVs) lead to the rational hypothesis that drugs capable of selective blockade of NaVs subtypes may be an effective and save strategy for the treatment of pathological cough in comparison of centrally acting antitussives. Recent electrophysiological studies revealed that NaV1.7 is essential for action potential conduction in sensory nerves and NaV 1.8 plays a key role for action potential initiation in C-fibres.
Aim To evaluate the effect of locally applied (inhaled) selective NaV1.8 inhibitor (A-803467) on cough in guinea pigs tussive challenge model.
Methods We used a standard TRPV1 receptor activator capsaicin (25μM) to evoke cough. An experimental group was pretreated with NaV1.8 inhibitor by inhalation of aerosol (A-803467, 3mM) for 10 min followed by inhalation of capsaicin aerosol for 5 min in the continuous presence of A-803467 (3mM). In control experiments the vehicle was used instead of A-803467.
Results In control experiments, we observed a reproducibility of cough response to inhalation of capsaicin (25μM) (5.73±0.6 vs. 5.8±0.35, n=15). Preinhalation and continuing inhalation of NaV1.8 inhibitor A-803467 (3mM) blocked capsaicin-induced cough (5±0.47 vs. 1.9±0.35 n=13, $P<0.01$). A similar response was observed in electrophysiological studies where the bradykinin-induced action potential discharge in jugular C-fibres was by 50% inhibited by NaV1.8 blocker.
Conclusion Our results support a concept that targeting NaV1.7 and NaV1.8 is a rational strategy forward for the effective treatment of pathological cough.

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