214

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ANAL SPHINCTER RESPONSE TO SACRAL NEUROMODULATION IN SHEEP

Hypothesis / aims of study

Sacral neuromodulation (SNM) at the third sacral (S3) foramen is an established treatment modality for fecal incontinence (FI). Clinically, stimulation of the S3 nerve can induce external anal sphincter (EAS) contractions which are of utility for establishing the accuracy of nerve targeting and titrating the stimulation intensity for therapy delivery. The goals of this study were to establish a chronic sheep model to measure EAS electromyography (EMG) function, and quantitatively compare and characterize the EMG response of the EAS to SNM.

Study design, materials and methods

A total of 5 adult Polypay sheep were used for this study. Of these 5 sheep, 3 were implanted bilaterally (n=6 nerve roots) at S3 with stimulation leads (4 contacts: 0 most distal, 1, 2 and 3 most proximal, Medtronic Model 3889) under fluoroscopic guidance. Electrode 3 was preferentially positioned ventral to the S3 foramina. The EAS was implanted with two sensing electrodes (Medtronic Model 4351) at both the 3 and 9 o'clock positions. All leads were tunnelled cranially and externalized dorsally for easy connection to external instrumentation. The animals were allowed to recover for one week prior to monitors. Weekly anesthetized and awake monitors were initiated, consisting of variable intensity stimulation (0-10V, 10 Hz, 210 µs pulse width) unilaterally delivered with a Biopac STM100C stimulator - one of the four contacts was assigned as the cathode (-) and another as the anode (+). EMG responses were collected using Biopac EMG100C bioamplifiers (gain=2000) from both the contralateral and ipsilateral EAS leads, and an anal plug. The remaining 2 sheep were implanted and instrumented in a similar fashion, but used exclusively while anesthetized to study EMG attenuation by both kilohertz SNM and succinylcholine (0.5 mg/kg) injection.

Results

SNM induced acute EMG responses of the EAS in both anesthetized and awake sheep. The sensed EMG signals exhibited constant latencies and uniform morphologies that increased in amplitude in response to graded stimulation. However, differences were noted in the sensed EMG responses depending on the selected stimulation electrodes (cathode). The order according to response threshold from low to high was 3 < 2 < 1< 0 (Figures 1 A and C). In addition, the electrode pairs with non-adjacent space (e.g. 1-/3+) tended to be more effective than that of non-spaced (e.g. 1-/0+) pairs, though such differences were not statistically significant. Two-way ANOVA analysis (Figures 1 B and D) demonstrates a statistically significant difference for the stimulus-response functions between 3-/0+ and 0-/1+.

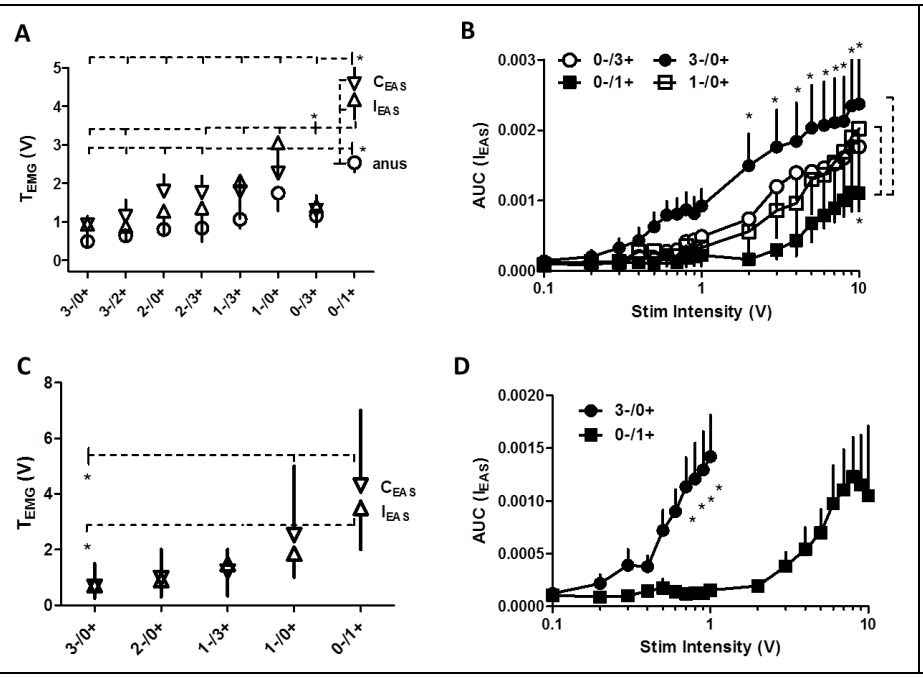

Figure 1. EMG from ipsilateral EAS (I_{EAS}), contralateral EAS (C_{EAS}) and/or anus to SNM during anesthetized (A, B) and awake (C, D) monitors. A and C. Comparison of threshold to trigger EMG signals (T_{EMG}) to SNM among different electrodes pairs. B and D. Summary data of stimulus-response functions of increased EMG activities (area under the curve, AUC) to graded intensity of the SNM. n=6, * p<0.05, ANOVA, Bonferroni post test.

The EMG signals from I_{EAS} and C_{EAS} may generally be separated into two components based on delays (1st: ~2 ms, 2nd: ~8 ms). The first I_{EAS} EMGs appeared significantly stronger than the first C_{EAS} and the second I_{EAS} EMGs were equally presented in anesthetized and conscious sheep (Figure 2). In the conscious condition, the second C_{EAS} EMG occurred earlier at a lower intensity of SNM with a higher response amplitude, which is distinct from the anesthetized condition in that the C_{EAS} EMG was evoked only to high intensity of SNM (>3 V).

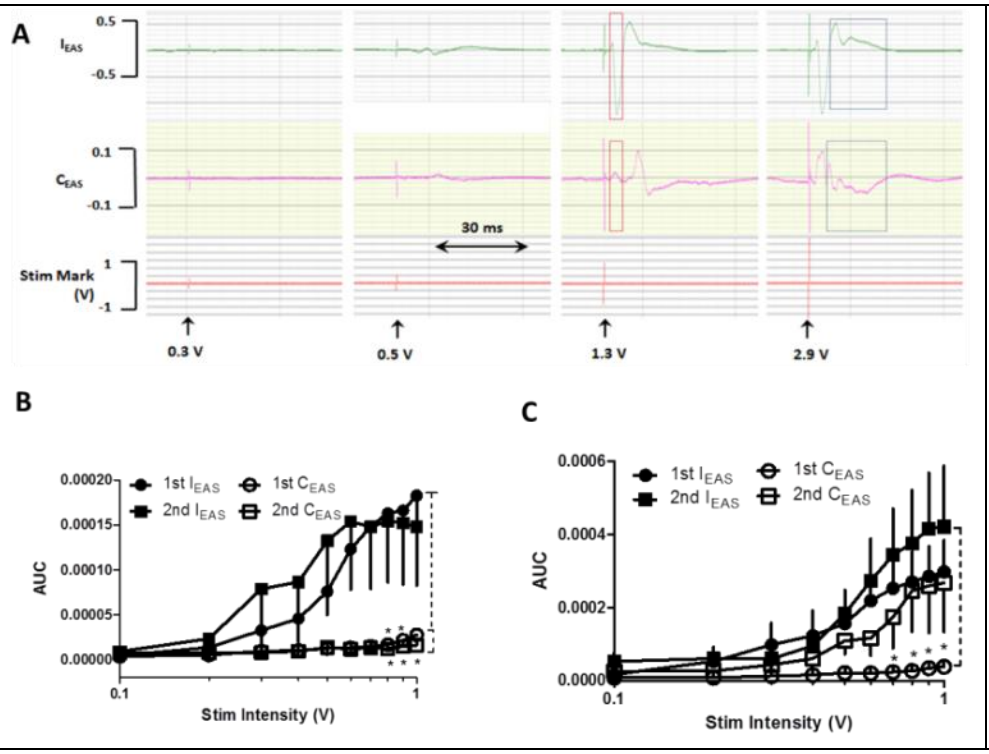

Figure 2. Two components of EMG responses to SNM (3-/0+). **A.** Raw traces of EMG (mV) from I_{EAS} and C_{EAS} to SNM in a conscious sheep. The SNM (Stim Mark) is shown at the bottom panel. **B and C.** Waveform analysis of two components of EMG activities to graded intensity of the SNM in anesthetized (B) and conscious condition (C). n=6, * p<0.05, ANOVA, Bonferroni post test.

Finally, we characterized the nature of the EMG response in two anesthetized sheep. The EAS contraction evoked by 10 Hz stimulation was blocked by pretreatment with 1 min, 1 kHz stimulation and the blockage was reversible after the offset of the pretreatment. The recovery of the evoked EMG activity from the inhibition was fitted with monoexponential regression against the recovery duration, resulting in a time constant of 24.5 s. Bolus injection of succinylcholine abolished the EMG response for 15 minutes post induction.

Interpretation of results

The nature of EMG signals to SNM is confirmed by the desensitization to kilohertz frequency stimulation and systemic administration of succinylcholine. The sensitivity of EMG responses (threshold or amplitude of response) varied among stimulation configurations regarding the cathode or the distance between cathode and anode. The general order of EMG thresholds (smallest to largest) was from proximal stimulation contacts relative to distal contacts and space factor such as nonadjacent pairs was favorable. Significantly lower voltage required to evoke EMG response to 3-/0+ stimulation compared to the 0-/1+ stimulation likely reflects that the electrode 3 could be placed directly adjacent to the nerve innervating to the EAS as contact 3 just passes through the open foreman. The short delay and equally stronger first I_{EAS} component and weaker first C_{EAS} in anesthetized and awake sheep suggest that this component is triggered by direct efferent activation and there is less overlap between ipsilateral and contralateral EAS innervation. The second EMG component from I_{EAS} may be due to excitatory recurrent collaterals between ipsilateral motoneurons. In awake sheep, however, the second component from C_{EAS} had a significantly stronger signal than that in anesthetized sheep. This sensitivity to anaesthesia may indicate a reflex phenomenon.

Concluding message

This is the first large animal model we are aware of for chronically characterizing and comparing EAS EMG responses and their sensitivities to SNM with different stimulation configurations. These data demonstrate the value of sheep with chronically implanted quadripolar stimulation leads and intramuscular EAS electrodes as a model for studying EAS function and the related EMG response following SNM. As the evoked EMG response is an important objective marker for evaluation of SNM on direct or reflex contraction of the EAS in clinical practice, this model could ultimately be used to study the effects of SNM for FI therapy. EMG responses to acute and chronic stimulation will be further investigated in this model for their potential contribution on long term therapeutic efficacy of SNM for FI.

Disclosures

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