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(312) Stimulation of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor evokes mixed responses in nociceptive fibers of mouse glabrous skin

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This study examined the contribution of AMPA receptors to peripheral nociception using teased plantar nerve attached to glabrous skin of male C57B/6 mice. Identified receptive fields were isolated using a plastic well. After measuring mechanical (MECH), heat and cold responses, serial 10X dilutions of AMPA ranging from 1 pM to 1 mM were pipetted into the well. Firing activity was collected over 2 min for each dilution. After a 2 min wash-out, MECH, heat, and cold responses were re-measured. A 50% increase or decrease in threshold or firing rate was considered significant. Sixteen of 40 fibers responded directly to AMPA. Five fibers displayed gradual increases in background firing over the total dose range (EC50 26.6 nM). Eleven fibers displayed bimodal distributions (EC50 11.3 pM and 3.0μM). AMPA effects on heat, cold and MECH responses were mixed. Before and after profiles measured in 34 fibers showed these changes: HEAT: 7 fibers more sensitive threshold; 5 less sensitive 7 fibers increased firing rate; 13 decreased COLD: 3 fibers more sensitive threshold; 8 less sensitive 12 fibers increased firing rate; 10 decreased MECH: 9 fibers more sensitive threshold; 4 less sensitive 13 fibers increased firing rate; 12 decreased Changes in the three modalities were independent, i.e., a change in one modality was not predictive of or correlated with changes in other modalities. All 34 fibers showed changes in at least one parameter. AMPA responsive nociceptive fibers represent mixed populations. The GluA2 subunit is a candidate for conferring differing response properties since this subunit blocks calcium permeability. Trafficking of GluA2 subunits changes the calcium permeability of the AMPA receptor and may change the responsiveness of AMPA-containing nociceptive fibers to heat, cold or mechanical stimulations. Future research using antagonists directed at GluA2-containing and GluA2-lacking AMPA receptors can elucidate these mechanics in nociceptive function.

(313) Opening of KCNQ/Kv7 channels blocks both spontaneous activity in small DRG neurons and signs of chronic pain after spinal cord injury

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Spinal cord injury (SCI) often causes chronic, intractable pain. Increased spontaneous activity (SA) has been found months after contusive SCI in a large fraction of nociceptors. SA recorded in small dissociated DRG neurons is significantly correlated with hypersensitivity of withdrawal reflexes tested prior to dissociation. The association of nociceptor SA with depolarization and increased membrane resistance suggests that SA involves a decrease in open K+ channels. Conversely, opening background K+ channels that remain after SCI might be a useful strategy to reduce nociceptor SA and ameliorate chronic pain. KCNQ/Kv7 channels are expressed in presumptive nociceptors, and are important for controlling resting membrane potential and excitability. Whole-cell patch clamp recording and dorsal root filament recording were performed in this study. KCNQ/Kv7 currents were unchanged after SCI compared to controls, suggesting that alterations of other K+ channels are responsible for the chronic depolarization and increased membrane resistance observed after SCI. A specific KCNQ channel blocker (XE991,10 μM) caused similar depolarization and repetitive firing in previously silent neurons dissociated from naïve, sham and SCI rats. Importantly, retigabine (10 μM), an FDA-approved opener of KCNQ channels, hyperpolarized DRG neurons and reversibly reduced SA and repetitive firing in vitro and in vivo. Furthermore, hypersensitivity of hindlimb and forelimb withdrawal reflexes to mechanical and thermal stimuli 1 month after SCI was reversed by retigabine (10 mg/kg i.p.). Preliminary results indicate that retigabine also reduces an operant measure of pain. Thus, KCNQ channel openers that potently reduce nociceptor activity may be a useful treatment for chronic pain after SCI. (Bedi, J Neurosci, 2010; Carlton, Pain, 2009; Passmore J Neurosci, 2003.) Supported by the Paralyzed Veterans of America and Craig H. Neilsen Foundations.

(314) Nociceptor activity is altered in Group II mGluR knock-out rats

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Previous studies from our laboratory demonstrate that Group II metabotropic glutamate receptors (mGluRs) are expressed by peripheral nociceptors and their activation inhibits pain behaviors and nociceptor activity in the inflamed state. We obtained Group II mGluR2 KO and WT rats from Transposagen to further elucidate the role of these receptors in pain transmission. We recorded from identified nociceptors using our in vitro skin-nerve preparation. The glabrous skin of the hindpaw is dissected free keeping the plantar nerves intact. The nerves are teased apart to isolate single units for recording. The receptive field of each unit is defined and responses to heat, mechanical and mustard oil (1μm, TRPA1 agonist) are determined. The data shows that the background discharge rate in KO rats (0.35±0.08 imp/s, n=13) is significantly increased compared to WT (0.11±0.04 imp/s, n=10). Furthermore, application of 1 μM mustard oil induces a significant increase in discharge rate in KO (1.19±0.26 imp/s, n=13) compared to WT rats (0.68±0.12 imp/s, n=10). However, the responses to heat and mechanical simulation are not significantly different in KO vs. WT (no change in threshold or discharge rate). We have previously shown that Group II mGluR2s do not maintain a tonic inhibitory control over nociceptors thus the increase in background activity in the absence of the receptors is unexpected. Our behavioral data demonstrate the KO rats have an increase in nocifensive behaviors in response to MO applied to the hindpaw and this data confirms these findings at the single fiber level. The data suggest that Group II receptors negatively modulate TRPA1 in the naïve state and loss of this control produces enhanced responses to a TRPA1 agonist.

E23 Psychophysics/Hyperalgesia

(315) Temporal summation in chronic pain patients: the impact of catastrophizing, distraction analgesia and opioid use

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Catastrophizing has been shown to be greatly elevated in individuals with chronic pain. Previous studies have indicated that high catastrophizers have higher temporal summation of pain, and that this is likely due to supraspinal rather than spinal mechanisms. Similarly, distraction analgesia involves activation of a supraspinal centers. The ability of distraction to inhibit pain has been studied in healthy volunteers, revealing that high catastrophizers have a delayed analgesic response to distraction. In this study, we investigated the interaction of catastrophizing with distraction analgesia in chronic pain patients (n=149). Pain patients had a mean pain score of 5±2.4 out of 10, and half were chronically taking opioids to manage their pain. Patients underwent quantitative sensory testing (QST), including a pinprick train paradigm to measure temporal summation, both in the presence and absence of a distracting handgrip algometer task. Pain patients with high catastrophizing scores did not differ from low catastrophizers on most QST measures, but had significantly greater temporal summation. Interestingly, in the presence of a distraction task, the extent of temporal summation in high catastrophizers was reduced to the level of low catastrophizers. Moreover, distraction's inhibitory effect on temporal summation in high catastrophizers was not altered by controlling for current pain scores or depression. When controlling for opioid use, however, chronic opioid users did not have the beneficial effect of distraction on temporal summation, while non-opioid users did. These data reconfirm previous findings that catastrophizing is associated with a greater tendency toward temporal summation, and that this may be attributable to increased attention to pain, as distraction is able to partially inhibit this. Furthermore, these data suggest that the inhibitory effect of distraction on pain may be altered by chronic opioid use.