Skin incision-induced receptive field responses of mecanosensitive peripheral neurons are developmentally regulated in the rat

M. Danilo Boada, Silvia Gutierrez, Kelly Giffear, James C. Eisenach, and Douglas G. Ririe
Department of Anesthesiology, Wake Forest School of Medicine, Winston-Salem, North Carolina

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Boada MD, Gutierrez S, Giffear K, Eisenach JC, Ririe DG. Skin incision-induced receptive field responses of mecanosensitive peripheral neurons are developmentally regulated in the rat. J Neurophysiol 108: 1122–1129, 2012. First published June 6, 2012; doi:10.1152/jn.00399.2012.—Maturation of the nervous system results in changes in both central and peripheral processing. To better understand responses to injury in the young, developmental differences in the acute response to incision were investigated in both tactile and nociceptive myelinated peripheral mecanosensitive afferent neurons in vivo. Neuronal intrasomal recordings were performed in juvenile and infant rats in 34 L5 dorsal root ganglia, and each neuron was phenotypically defined. Neurons had a mecanosensitive receptive field in the glabrous skin on the plantar surface of the hind paw, which was characterized at baseline and for up to 45 min after incision. Fundamental maturational differences in the effect of incision were clear: in high-threshold nociceptive mechanoreceptors, the mechanical threshold decreased immediately and the receptive field size increased rapidly in juvenile rats but not in infant rats. Additionally, a divergence in changes in the instantaneous response frequency of tactile afferents occurred between the two ages. These differences may help explain maturational differences in responses to peripheral injury and suggest that differences in central nervous system responses may be partially mitigated by spatially confined and frequency-dependent differences resulting from tactile and nociceptive mecanosensitive input.

development; dorsal root ganglia; intracellular electrophysiology; maturation; peripheral nerve

Skin injury produces considerable changes in afferent signaling and processing that leads to a hyperexcitability state (Treede et al. 1992; Brennan et al. 2005). These changes in excitability occur in both young and old alike. Both peripheral (primary sensory neuron) and central (secondary order neuron) changes are present, and a broad spectrum of sensory fibers are affected (Treede et al. 1992; Dougherty 2003; Nagakura et al. 2008; Ririe et al. 2008; Duarte et al. 2005; Obata et al. 2006; Zahn et al. 2005). Primary sensory neurons encode peripheral damage, but they also may play a role in maintaining an abnormal responsiveness state to protect the injured area and prevent further damage. One key component of this injury-induced sustained response is that it is driven by slow conducting nociceptive receptors (mecanosensitive, thermosensitive, and silent units) a few hours after the damage occurs (Kang and Brennan 2009; Pospisilova and Palecek 2006; Pogatzki-Zahn et al. 2005; Kissin et al. 2005; Woo et al. 2004). However, it is less clear how the acute and hyperacute responses (early and initial responses to damage) in neuronal subtype specific fibers modulate or contribute to nociception and processing immediately after surgical tissue trauma. In particular, the speed with which changes occur in neuronal responses and processing of information within the receptive field (RF) and the contribution of fast nociceptors [Aδ-range high-threshold mechanoreceptors (AHTMRs)] or tactile units [low-threshold mechanoreceptors (LTMRs)] to this process and differences during development have not been fully elucidated.

Surgical treatment of diseases occurs throughout growth and development. As part of surgical treatment, incision is associated with tissue trauma and injury to distal nerve endings resulting in increased nociceptive input into the developing central nervous system. This may have significant effects on neural connections and the establishment of neural circuits, including establishing unintended connections or failure to establish normal pathways through synaptic strengthening and pruning (Katz and Shatz 1996; Beggs et al. 2002; Hua and Smith 2004). Although it is well accepted that providing analgesia to infants improves survival from surgical procedures, the knowledge of the short- and long-term consequences of differences in noxious input during development are poorly understood (Anand and Hickey 1987, 1992). Noxious stimuli early in development can result in exaggerated responses and increased vulnerability to stress disorders and anxiety in later life (Taddio et al. 1995; Anand et al. 1999; Ruda et al. 2000; Torsney and Fitzgerald 2003; Peters et al. 2005; Schmelze-Lubiecki et al. 2007). Furthermore, long-term sensory processing changes from early childhood surgery may be a marker for a primed system vulnerable to resulting abnormalities in processing of sensory information from surgery in later life (Peters et al. 2005; Schmelze-Lubiecki et al. 2007; Beggs et al. 2012).

Peripheral receptive field characteristics under normal development have been established. Withdrawal thresholds increase as a function of age in both rats and humans (Reynolds and Fitzgerald 1995, Fitzgerald et al. 1988, Andrews and Fitzgerald 1994). This reduction in sensitivity occurs during the normal course of development. Additionally, the RF is larger and decreases with increasing age, resulting in a more focal response with a greater character of input (Fitzgerald et al. 1994). With injury, the RF size increases even to a greater extent in the very young, further decreasing the focal precision and spatial discrimination (Torsney and Fitzgerald 2002; Ririe et al. 2008). Consistent with these localized effects, behavioral manifestations of pain are age dependent, with more specific pain behaviors increasing with age and nonspecific pain behaviors decreasing (Guy and Abbott 1992; Teng and Abbott 1998). However, the underlying neurobiology important to these developmental changes have not been fully elucidated. Few studies have addressed the peripheral responses to surgical
injury during development, but rather focus on changes in the spinal cord dorsal horn (Ririe et al. 2006, 2008). Afferent activity early in development seems to be important for establishing future responses (Walker et al. 2009), but it is unknown if developmental differences in the responses of subsets of primary sensory neurons immediately after surgical injury play a role (Ririe et al. 2003). We hypothesized that peripheral neuronal responses to incision are developmentally discrete and may alter input to the dorsal root ganglion (DRG) and dorsal horn. These developmentally different inputs may result in altered integration of peripheral mechanical stimuli with consequences for development of normal and nociceptive circuits in the brain and spinal cord both short and long term. To improve understanding of the impact of surgical injury early in development, in the present study, we focused on the role of peripheral fast-conducting mechano-sensitive afferents (both nociceptive and non-nociceptive) in developmental differences in qualitative processing of peripheral receptive field information and fiber subtype electrical signature changes before and after surgical skin tissue trauma (incision) in both infant and juvenile rats.

METHODS

After approval of the protocol by the Institutional Animal Care and Use Committee, male Sprague-Dawley rats at either 1 wk (infant) or 4 wk (juvenile) of age were anesthetized with isoflurane, and electrophysiological experiments were performed as previously described (Boada et al. 2010, 2011). Briefly, the trachea was intubated, and animals were ventilated with humidified oxygen. The ECG was monitored, and animals were immobilized with pancuronium bromide. Isoflurane was maintained at 2% throughout the study (Tevan Pharmaceuticals). As shown in Fig. 1, the DRG at L5 and the adjacent spinal cord were exposed by laminectomy, and the spinal cord was continuously perfused with oxygenated artificial cerebrospinal fluid [aCSF contained (in mM) 127.0 NaCl, 1.9 KCl, 1.2 KH2PO4, 1.3 MgSO4, 2.4 CaCl2, 26.0 NaHCO3, and 10.0 d-glucose]. The spinal column was secured using custom clamps in a preheated (32–34°C) recording chamber, where the perfusate was maintained at 37°C (MPRE8, Cell MicroControls, Norfolk, VA). The pool temperature adjacent to the DRG was monitored with a small thermocouple (IT-23, Physitemp, Clifton, NJ). Rectal temperature (RET-3, Physitemp) was maintained at 34 ± 1°C with radiant heat. DRG somata were impaled with borosilicate microelectrodes (80–250 MΩ) containing 1 M potassium acetate [in some cases, 20% Neurobiotin was also used (Vector Laboratories, Burlingame, CA)]. Intracellular penetrations with a resting membrane potential of less than or equal to −35 mV were characterized further. Direct current output from an Axoclamp 2B (Axon Instruments/Molecular Devices, Sunnyvale, CA) was digitized and analyzed offline using Spike2 (CED, Cambridge, UK). The sampling rate for intracellular recordings was 21 kHz throughout (MicroPower1401, CED).

After stable impalement of a neuron, the plantar surface of the foot was searched with a fine sable hair brush to locate the peripheral RF. For afferents requiring higher intensities, subsequent searches used increasingly stiffer probes and finally sharp-tipped forceps. Afferents with cutaneous RFs were distinguished from those with deep RFs by displacing the skin to ensure that RFs tracked rather than remained stationary. Mechanical thresholds (MTs) were characterized with calibrated von Frey filaments (Stoelting, Wood Dale, IL), and areas (spots) were defined where a response could be elicited by threshold mechanical force [high-sensitivity area (HSA)]. The adaptation rate was evaluated using micromanipulator-based probes; responses to skin stretch and vibratory stimuli were also tested. In all cases, RFs were characterized and measured with the aid of a zoom stereomicroscope. To protect the skin health before incision (particularly important in neonates), if for any reason (e.g., unsuccessful stable impalements) the skin was exposed to overstimulation as consequence of our RF search, the experiments were aborted. This study includes only cells with a naïve (untouched) RF collected within 30 min of every experiment (<10 min for neonates). No further attempts were made to collect more cells on the same preparation after the first record (and RF activation, 1 cell/animal).

Once a cell had been identified, a small (3 ± 1 mm) and superficial (0.5 mm) incision was performed beginning at 1 ± 0.5 mm from the cellular RF center (the most sensitive area) parallel to the foot midline. After this procedure, the cellular RF was tested {MT, RF size, and response dynamics [number of action potentials (APs) per stimuli]} every 2.5 min (on the first 10 min/4 trials) to detect any change or deviation from the initial state. The initial 10 min, the cellular RF was tested every 5 min and terminated after 30 min (4 more trials). After the desired record had been obtained, no further cells were collected, and the experiments were terminated (1 cell/animal).

Active membrane properties of all identified sensory neurons were analyzed, including the amplitude and duration of the AP and the afterhyperpolarization (AHP) along with the maximum rates of spike depolarization and repolarization; durations were measured at half-amplitude rather than baseline to minimize hyperpolarization-related artifacts (D50 and AHP50). Passive properties were analyzed, including membrane resting potential, input resistance, time constant, inward rectification, and, where possible, rheobase; all but the latter were determined by the injection of incremental hyperpolarizing current pulses (±0.1 nA, 500 ms) through balanced electrodes. Conduction velocity (CV), MTs, and vibratory responses (VRs) were also measured. These comprised the 12 measurements of the fibers used in the analysis. Because intact lumbar DRGs serve multiple nerves, spike latency was obtained by stimulating the RF at the skin surface using a bipolar electrode (0.5 Hz); this was performed after all natural stimulation to prevent potential alterations in RF properties. Because we were interested in latency from terminals, all measurements were obtained using the absolute minimum intensity required to excite neurons consistently without jitter; significantly shorter latencies, seen at traditional (i.e., 2- to 3-fold threshold) intensities and presumably reflecting spread to more proximal sites along axons. Stimuli ranged in duration from 50 to 100 μs; utilization time was not taken into account. Conduction distances were measured for each afferent on the termination of the experiment by inserting a pin through the RF

Fig. 1. A: schematic diagram of the in vivo rat L5 preparation (lateral view). Colored areas delineate approximate dermatome boundaries where skin sensory neuron receptive fields (RF) were located. B: paw diagram (left) and photograph (right) showing the foot position.
(marked with ink at the time of recording) and carefully measuring the distance to the DRG along the closest nerve. This was used to determine CV.

Based on responses to mechanical stimuli, CV, and the adaptation rate, mechanosensitive afferents were classified to follow standard definitions (Boada et al. 2010). Active and passive membrane properties were related to this classification. All included cells satisfied the following requirements: resting membrane potential more negative than −30 mV, AP amplitude ≥30 mV, and the presence of spike AHP.

Data are presented as means ± SD except for MTs, which are presented as medians and ranges. Statistical analysis was performed with one-way ANOVA with Bonferroni correction where appropriate except for MTs, where a Wilcoxon signed rank was used for statistical analysis due to the nonparametric nature of the MT being discrete fiber force on a logarithmic scale. Significance was P < 0.05.

RESULTS

A total of 34 physiologically identified and well-characterized naïve (untouched) L5 DRG sensory neurons were recorded intrasomally in vivo in juvenile and infant rat spinal preparations. On the plantar surface of the paw, 19 neurons were recorded in postnatal day 28 (P28) animals (8 tactile neurons and 11 nociceptors) and 15 neurons in postnatal day 7 (P7) animals (7 tactile neurons and 8 nociceptors) from a total of 34 male rats. DRG temperature was tightly controlled around normal core temperature (37 ± 0.5°C). Intracellular recordings ranged from 25 to 45 min with a stable resting membrane potential throughout.

Initial Steady State

Somatic electrical properties and CV. Afferent nerve fiber identities were related to their CV and AP duration (D50) at both ages. In infant animals, both types of afferents clustered below the Aβ cutoff (CV mean: 3.1 ± 0.6 m/s) on glabrous skin (Fig. 2). As expected at this age, tactile neurons had a faster CV than nociceptors (4.6 ± 1.1 vs. 2.01 ± 0.4 m/s, P < 0.01) with a shorter AP duration (0.8 ± 0.07 vs. 1.4 ± 0.1 ms).

In juvenile animals, both afferents had increased CV compared with afferents in younger animals (CV mean: 14.2 ± 1.2 m/s, P < 0.001). Fast nociceptors (AHTMRs) remained slower than tactile afferents (LTMRs, 10.9 ± 0.9 vs. 18.6 ± 1.5 m/s, P < 0.05) but with significantly shorter AP durations than in similar fibers in infants (0.9 ± 0.1 ms, P < 0.05). AP duration of the tactile group was similar between juveniles and infants (0.7 ± 0.05 ms).

RF properties. Before incision, the RF of different subtypes of primary sensory neurons were analyzed by MT, RF size, and number of HSAs per cellular RF. Infant (P7) RF responses of nociceptors (high-threshold mechanoceptors) were different from juveniles (P28), with P7 animals having a lower MT: 1 mN (range: 0.16–10 mN) vs. 58.8 mN (range: 1.4–98 mN; Fig. 3), larger absolute RF size (6.1 ± 0.5 vs 2.1 ± 0.2 mm²; Fig. 4), and a multi-HSA configuration (1–3 HSAs/cellular RF vs. 1 HSA/cellular RF; Fig. 5). On the other hand, naïve neonatal tactile afferents (LTMRs) showed a lower MT [0.04 mN (range: 0.02–0.07 mN)] and smaller absolute RF size (5.5 ± 0.9 mm²) than similar afferents observed in juveniles [MT: 0.07 mN (range: 0.04–0.16 mN) and RF size: 23.6 ± 10.4 mm²]. No difference in multi-HSA configuration was present between the two ages for LTMR neurons (2–3 HSAs/cellular RF).

Incision-Induced Changes in Peripheral Mechanosensitive Afferents

After skin incision, AHTMRs in juvenile animals had a rapid (<2.5 min) and dramatic reduction in MT (94.3%, P < 0.001). The maximal reduction in MT over the time course of the recording was reached 10 min after incision. The MT of tactile afferents remained unaffected across the same time period in juvenile animals. At P7, the MT of AHTMRs did not change after incision. Overall, LTMRs in P7 animals showed no significant change in MT (Fig. 3). However, three of the tactile afferents demonstrated a seemingly paradoxical increase in MT accounting for the large range.

The RF size of juvenile AHTMRs increased from 2.1 ± 0.2 to 33.6 ± 5.6 mm², reaching a maximal extension 20 min after the incision (Fig. 4). There was no change in the RF size of LTMRs in response to incision in juvenile animals. Interestingly, there was no change in AHTMR RF size in response to incision in P7 animals. However, there was an increase in the LTMR RF size in P7 animals. The increase in RF size in the juvenile paw after incision was preceded by the appearance of more HSAs (median: 3). These emerging sensitivity spots were tested further only when the areas in between them failed to elicit any response when threshold mechanical force was applied (Fig. 5A). This appearance of a “new” HSA within the cellular RF did not appear to occur in a random fashion, and their development occurred with time. In all of the juvenile nociceptors analyzed, the secondary HSA appeared around the wounded area, often reaching a lower MT that the initial HSA after 20 min (Fig. 5B). There was no increase in HSA per RF in P7 animals. In all cases, responses of nociceptive afferents to incision (number of APs per stimuli) were greatly increased when tested at the original threshold force (before the incision; Fig. 5C).
The instantaneous response frequency (IRF) was lower at threshold for P7 animals compared with P28 animals for both nociceptive and tactile neurons (Fig. 6). The IRF was increased in both LTMRs and AHTMRs in P7 animals. However, in P28 animals, the IRF was increased in AHTMRs and reduced in LTMRs in response to incision. No somatic electrical property was changed by incision, and CV was unaffected in all neurons at both ages.

DISCUSSION

This study provides novel data about the direct effects of skin incision on phenotypically defined mechanosensitive afferents during development. While developmental differences in RF size in response to incision have been reported, the role and contribution of the peripheral nerve itself have not been directly addressed (Boada et al. 2011; Ririe et al. 2008). Changes in peripheral nerve responses have been thought to occur through local changes in the spinal cord dorsal horn or through differences in descending inputs (Jones et al. 2007; Vandermeulen et al. 2000). Our study demonstrates that the peripheral nerve cannot only alter tuning of spatial input directly through altering the RF size in response to injury but may play a larger role in facilitating the interpretation of tactile information through frequency changes in signaling occurring through different fast-conducting mechanosensitive populations in a developmentally regulated manner (see Table 1). This may contribute to developmentally confined alterations in mechanosensitive nociceptive processing in the central nervous system.

In juvenile rats, nociceptive AHTMR afferent neurons are greatly altered from incision. The RF change in these fibers is
consistent with the development of primary hyperalgesia by a direct effect on the nerve terminals themselves from the injury or from inflammatory mediators over the terminals in close proximity to the wounded area (Pogatzki et al. 2001, 2002; Liang et al. 2010). This is expected and consistent with injury-induced pain. However, the speed of this sensitization process, the magnitude of the RF size changes, and the emergence of additional HSA (spots) are surprising. The juvenile mechanosensitive low threshold (Aβ) fiber lack of response and high threshold (Aδ) fiber response to incision are similar to that seen in adult animals after incision (Hamalainen et al. 2002). Background activity was found to be present in adult animals in A fibers, but was not altered by incision. In our study, no background or spontaneous activity was found in either age at baseline or after injury in any neuron in our study. This could be related to the differences in methodology, whereby fiber teasing was used in previous studies and intact neurons were evaluated in the present study. It is interesting that fast-conducting fibers in the infant do not change the RF size. This would suggest that there is less effect of the injury with respect to inflammatory process in the periphery. It also suggest that the immediate change in RF when measured at second-order wide dynamic range neurons in the infant animal.

Fig. 5. A: schematic diagram of temporal RF changes after injury on two nociceptors (a and b) recorded in the glabrous skin (paw) of a juvenile rat. The straight line shows the extent and location of the incision. The numbers beside a or b represent the order in which high-sensibility areas (HSAs) emerged (0, initial RF; gray) and their relative areas of sensibility (1, 2, or 3 RFs, white), with the center noted with a dot where the threshold was established. Also, the final RF size after 20 min is shown (the entire large circular area). B: absolute values of each HSA mechanical threshold measure every 5 min after the incision. Note that the b2 value was lower than the value reached at b0. C: electrical response elicited by the application of suprathreshold mechanical force on the initial cellular RF 10 min after the incision. Scale bars = 2 s, 40 mV.

Fig. 6. Instantaneous response frequency (IRF) of tactile and nociceptive neurons to threshold mechanical force in juvenile (A) and infant (B) animals. The IRF for both tactile (LTMR) and nociceptive (AHTMR) neurons was not different between ages. However, whereas there was a significant increase in IRF for AHTMR neurons at both ages, there was a significant increase in IRF for infant animals and a significant decrease in IRF for juvenile animals. △, tactile neurons (LTMRs); ⋄, nociceptors (AHTMRs).
is solely dependent on local and descending modulation and not the peripheral nerve itself (Ririe et al. 2008). The emergence of spots may in part explain the responses of “mechanically insensitive neurons” that become sensitive after incision in adult animals, suggesting that their sensitization from incision may in part be from local factors contributing to the enhanced mechanical responsiveness of normally silent terminals (Hamalainen et al. 2002). In our study, the neurons were not “insensitive,” but rather spots expanded and sensitivity increased simultaneously. The emergence of these highly sensitive spots in juvenile animals in our study is consistent with the peripheral nerves contributing to the generation of hyperalgesia (Treede 1992). The emergence of these spots may contribute to the summation of input that is partially generated peripherally and not just centrally mediated (Price et al. 1989). It is of great interest that the emergence of spots does not occur with the injury in the infant animal. In stark contrast to the responses to incision in older animals, the effects of incision on nociceptive AHTMR neurons in the infant rat is notably absent with respect to MT, HSA, and size of the RF. However, the instantaneous frequency of AHTMR neurons in young animals had a similar response as AHTMR neurons in older animals, with an increase in instantaneous frequency. This highlights the lack of robustness of the response to injury in the periphery in the young, with the peripheral neuron having less dimensionality to the nociceptive input from peripheral injury. Whether this translates into increase in pain per se in the older animal or less pain in the younger animal is unclear. The low-fidelity signal in the young may be amplified centrally and produce effects that are out of proportion to the apparent peripheral neuronal responses. Another mechanism for the summation of the peripheral input may be present in the young. It is plausible that the increase in IRF in the young animal in the LTMNr neuron (opposite the direction of IRF change in the juvenile) may be critical for the summation and interpretation of the input as pain in the infant. Whether these relationships remain over time after the injury is not known, and whether this IRF contributes to coding information in the dorsal horn may be important in understanding developmental response to injury.

Tactile afferents in older animals have a limited response to incision, and this is somewhat surprising. Moreover, instead of tactile LTMNr neurons increasing activity input to the spinal cord in response to incision, the instantaneous frequency suggests that the input from tactile afferents is actually reduced from incision. In contrast, the instantaneous frequency response of LTMNr neurons in infant animals had a similar response as AHTMR neurons: increasing instantaneous frequency. This would seem to be a manner for the more immature somatosensory system to enhance or code nociceptive input from the periphery to gain information. In the older animal, the increased instantaneous frequency from AHTMRs is not needed or used since fidelity of the system is gained through different dimensional changes of input (threshold, RF size, and spot development), whereas dimensionality and information fidelity is coding is enhanced by using the instantaneous frequency response of tactile LTMNr neurons in the younger animal. This may further be the case with the LTMNr activating more superficial lamina in younger animals (Fitzgerald et al. 1994). This peripheral response of LTMNr in the young may contribute to and partially explain the response to light stimuli being coded as pain in the young and may contribute to resulting long-term responses to injury in later life (Walker et al. 2007, 2009; Fitzgerald et al. 1994; Torsney et al. 2000).

Future studies will need to focus on C-fiber-mediated differences in peripheral responses to tissue trauma since developmental differences in dorsal horn responses to C-fiber activation occur (Walker et al. 2007). Since differences in the dorsal horn in response to incisional injury may also be affected by myelinated mechanosensitive fibers, we focused on fast-conducting myelinated fibers in this study. It will be important to better define the peripheral nerve C-fiber responses to incision as well. While some C-fibers are mechanosensitive, defining the subsets of C-fibers and their responses require determining heat responses as well. This will be the focus of future studies to understand peripheral neuronal responses to surgical tissue injury.

Decreased effects on the immune response to peripheral injury may be at least partially attributable to differences in input from the periphery (Beggs et al. 2012; Ririe et al. 2006; Li et al. 2009). The fact that block of peripheral input with local anesthetic has a differential effect on both subacute responses and long-term responses suggests that the peripheral input is critical. The contribution of differential coding of peripheral input in these phenomena is unclear, but future studies will need to be directed at determining the maturational effects of the altered inputs on dorsal horn and higher center connectivity in the young. In addition, the ability of the brain to discriminate between touch and pain may be dependent on the coding of the peripheral input through maturational input characteristics of the afferent nerve fibers, including temporal differences in the arrival of input as well as the quality, strength, and overall character of the peripheral input (Fabrizi et al. 2011).

The present study addressed fundamental questions with regard to the primary mechanical hyperalgesia from skin injury during development. It is clear that the injury-induced re-

### Table 1. Summary of neuronal changes with incision

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<th>Mechanical Threshold</th>
<th>Receptive Field Size</th>
<th>Spot Configuration</th>
<th>Instantaneous Response Frequency</th>
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<td>P28 animals</td>
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<td>LTMNRs</td>
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Increases (↑) or decreases (↓) of magnitude are shown, with magnitude expressed as the number of arrows. P7, postnatal day 7; P28, postnatal day 28; HTMNRs, high-threshold mechanoceptors; LTMNRs, low-threshold mechanoceptors.
sponses of both kinds of fast-conducting afferents (nociceptive and non-nociceptive) are quite different. In addition, development further affects the peripheral responses from mechanosensory activation. This likely reflects fundamental maturational differences in peripheral input to the central system. This suggests that while the general notion of “nociceptive” cells transducing painful stimuli across a single information channel appears correct in adults and juveniles, this is likely a simplified notion of a larger and more complex coding mechanism of fast-conducting peripheral mechanosensitive neurons in early development.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.D.B., J.C.E., and D.G.R. conceived and designed the research; M.D.B., S.G., K.G., J.C.E., and D.G.R. performed experiments; M.D.B., J.C.E., and D.G.R. analyzed the data; M.D.B., S.G., K.G., J.C.E., and D.G.R. interpreted the results of experiments; M.D.B. and revised manuscript; M.D.B., S.G., and D.G.R. approved final version of manuscript.

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