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Review

Aβ-fiber nociceptive primary afferent neurons: a review of incidence and properties in relation to other afferent A-fiber neurons in mammals

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Abstract

The existence of nociceptors with Aβ-fibers has often been overlooked, and many textbooks endorse the view that all nociceptors have either C- or Aδ-fibers. Here we review evidence starting from the earliest descriptions of A-fiber nociceptors, which clearly indicates that a substantial proportion of cutaneous/somatic afferent A-fiber nociceptors conduct in the Aβ conduction velocity (CV) range in all species in which CV was carefully examined, including mouse, rat, guinea pig, cat and monkey. Reported proportions of A-fiber nociceptors with Aβ-fibers vary from 18% to 65% in different species, usually >50% in rodents. In rat, about 20% of all somatic afferent neurons with Aα/β-fibers were nociceptive. Distributions of CVs of A-fiber nociceptors usually appear unimodal, with a median/peak in the upper Aδ or lower Aβ CV range. We find no evidence to suggest discontinuous differences in electrophysiological or cytochemical properties of Aδ and Aβ nociceptors, rather there are gradual changes in relation to CV. However, some functional differences have been reported. In cat, A-fiber nociceptors with lower mechanical thresholds (moderate pressure receptors) tend to have faster CVs [P.R. Burgess, D. Petit, R.M. Warren. Receptor types in cat hairy skin supplied by myelinated fibers. J. Neurophysiol. 31 (1968) 833–848]. In primate (monkey) A-fiber nociceptors that responded to heat were divided into type I A mechano-heat (AMH) units (Aδ and Aβ CVs) with lower mechanical and higher heat thresholds and may include moderate pressure receptors, and type II AMH units (Aδ CVs) with higher mechanical/lower heat thresholds. It is important that the existence of Aβ nociceptors is recognised, because assumptions that fast conducting, large diameter afferents are always low threshold mechanoreceptors might lead/have led to misinterpretations of data.

Theme: Sensory systems
Topic: Pain modulation: anatomy and physiology

Keywords: Action potential; Conduction velocity; Aβ-nociceptors; Nociception; DRG; Pain

Contents

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1. Introduction

Nociceptors are distinguished by their relatively high thresholds for activation, i.e. they can be activated by intense stimuli that are damaging (noxious) or potentially damaging to the tissues, but not by innocuous stimuli, such as warming or touch; their adequate stimulus is noxious [59]. Thus nociceptive primary afferent neurons have been defined as having receptive endings that have a high stimulus threshold and that respond preferentially to noxious (tissue-threatening, subjectively painful) stimuli [8] or more simply as units that uniquely signal stimuli intense enough to cause damage to the tissue [42]. Despite the fact that the earliest descriptions of A-fiber nociceptive neurons included units conducting in the Aβ conduction velocity (CV) range, there is a widespread belief, endorsed by many or most modern textbooks even including certain chapters in the Textbook of Pain, e.g. Ref. [18], that nociceptors have only C- or Aδ-fibers and that all Aα/β-fiber afferents are low threshold mechanoreceptors (LTMs). Here, we review the evidence, and provide further evidence, that a substantial proportion of A-fiber nociceptors conduct in the Aβ CV range. The issue of the presence and role of Aβ nociceptors has not previously been reviewed in any detail, although aspects of their electrophysiological properties have been addressed recently in a brief review (see Ref. [36]). We also compare the electrophysiological, cytochemical and sensory receptive properties of Aβ and Aδ nociceptors and of Aβ nociceptors with Aα/β-fiber LTM neurones.

1.1. Conduction velocity classes

Primary afferent dorsal root ganglion (DRG) neurons are usually divided on the basis of their CVs into C-, Aδ- and Aα/β-fibers (cutaneous afferents) or into group IV, III, II and I fibers (muscle afferents) [42]. Such classes were originally derived from compound action potentials, with the fastest Aα/β/group I wave being carried by large myelinated fibers, the slowest being the C/group IV wave carried by unmyelinated fibers, and the wave carried by small myelinated afferent fibers being the Aδ/group III wave (see Ref. [52]). For references and compound action potential recording methods, see Ref. [14].

1.2. How is Aβ conduction velocity determined?

Extracellular recordings of compound action potential usually reveal three distinct groups of waves, Aα/β, Aδ and C waves, that can be distinguished on the basis of their electrical thresholds and CVs. The compound action potential shape is dependent on proportions of fiber types in different nerves. In purely afferent nerves such as dorsal roots, the Aα/β wave is dominated by LTMs, since these are more numerous than Aα/β nociceptors, although it is less clear whether D hair (Aδ LTM) units (see later for definition) or Aδ nociceptors dominate the Aδ wave. The contribution from each would depend on (a) their relative frequencies and (b) the stimulus strength used to generate the CAP, since nociceptors may have higher thresholds than D hair units. The relative frequencies of fiber types can vary

according to species and nerve type. For example, 80% of Aδ units are D hair units in adult cat posterior femoral cutaneous nerve [4] but we find this value to be only 16% in both guinea pig and rat lumbosacral DRGs.

For comparison between species of CV ranges of Aδ and Aβ-fiber nociceptors, we have plotted in Fig. 1, CV distributions of A-fiber nociceptors and some types of A-fiber LTM units recorded in the same nerves or ganglia. Fig. 1A, B and C are replotted from published papers, and D, E and F are from this laboratory. In A–E the vertical dotted line indicates the upper end of the main body of the D hair range excluding occasional outliers with faster CVs. In A and B this was 30 m/s and was used as the upper end of the Aδ CV range [4]. In rat and guinea pig (Fig. 1D and E) this line is coincident with the mean value for upper end of the Aδ wave of the dorsal root compound action potential in adult rat (6.4 m/s, n=4 ([19]) and young adult guinea pig (4.2 m/s, n=10 ([16]), an example of compound action potential recording is shown in Fig. 1F. This confirms that the upper border of the main part of the D hair CV range can indeed provide a good indication of the upper end of the Aδ CV range as originally suggested by the cat studies [4]. Following this approach, the upper value for the Aδ range in the mouse study would be 7 m/s, although 10 m/s was chosen [33]. However, using the fastest D hair (nearly 10 m/s) to define the border in that study in which a wide range of ages was used (5–32 weeks), is likely to overestimate the Aδ/Aβ border for all but the oldest animals. The lower values for guinea pig (and slightly lower for rat) than for mouse reflect the younger ages (see Table 1), and that these were dorsal root recordings made at 30 °C. Further details of Aδ upper borderlines defined in papers that examine A-fiber nociceptive CVs are provided in Table 1 with information on species, nerve, temperature and age/weight of the animals where available.

1.3. Factors that influence conduction velocity and its calculation

Many factors may influence CVs including species, age/size, the nerve type, the temperature of the preparation, and whether or not utilisation time (see below) is excluded. To amplify these points, examples of the effects of species are shown in Table 1, and Fig. 1. CVs of myelinated afferent fibers increase substantially with age up to 300 days [3,57] and CV and body weight increase simultaneously during the rapid growth of young animals [3]. The velocity of conduction along afferent A fibers may slow towards the periphery [26]. The CV of the rat sciatic nerve (peak CV of A-fibers) varied about 1.2 m/s per degree centigrade over the range of 20–40 °C [3]. A Q_{10} of approximately 1.6 in the temperature range of 27–37 °C was reported for mammalian myelinated nerves (see Ref. [69]). Fibers of the same neurons conduct more slowly in the dorsal root than the peripheral nerve [68]. The utilisation time is the time taken for an AP to be generated after application of an electrical stimulus and unless excluded it causes a reduction in the calculated CV, creating a proportionately greater error when the latency is short [68]. Thus failure to exclude utilisation time causes an error (underestimate) of CV that is likely to be greater for faster conducting fibers especially in smaller animals with short conduction distances. All these factors mean that the borderlines between the CV ranges need to be directly determined, e.g. by compound action potential recordings or D hair CV range in animals of the same age and species, on the same segment of nerve, at the same temperature, and using the same stimulus methods. Inappropriate classifications do commonly occur, however. For instance, the upper limits of 30 m/s for Aδ-fibers appropriate for adult cat peripheral nerve (Fig. 1 [42] are sometimes erroneously applied to rat studies).

1.4. Conduction velocities of A-fiber nociceptors

CVs of A-fiber nociceptors have been reported as extending up to 65 m/s in cat [4,5] and up to 70 m/s in monkey [65], clearly including units with Aβ-fibers since in both species the Aδ range was only up to 30 m/s (see Fig. 1). Thus the presence of A-fiber nociceptive units with CVs in the Aβ range is apparent in the earliest studies of A-fiber nociceptors [4,5] (data replotted in Fig. 1A and B) and is also a consistent finding in other species including guinea pig, rat and mouse (Fig. 1 and Table 1). As can be seen in Table 1 and Fig. 1, the proportion of recorded nociceptive A-fiber units conducting in the Aβ CV range is consistently relatively high (ranging from 18% to 65%) in different species.

The lack of clear peaks of Aδ and Aβ CVs in the CV frequency distribution of A-fiber nociceptors leads to the appearance of a single unimodal distribution across the A-fiber CV range (Fig. 1). This might be one of the reasons for Aβ-fiber nociceptors having been largely ignored, and raises the question of whether they are functionally distinct from Aδ nociceptors. The shape of the CV distribution of all A-fiber nociceptors is skewed with a peak towards the upper end of the Aδ (D hair) range or at the Aδ/Aβ border (e.g. guinea pig and rat, Fig. 1D,E) and with a long tail projecting into the CV range of the faster conducting cutaneous LTM units, usually reaching about half way along the extent of Aαβ range or even further in some species (e.g. Fig. 1D, rat). Thus it is clear, in a variety of species, that there are nociceptive A-fiber neurons that conduct in a range defined as Aβ either by compound action potential measurements or by comparison with Aδ (D hair) LTM units. Because few of these fibers have CVs in the upper Aαβ CV range, we and others call them Aβ-fiber nociceptors, while the fast conducting LTMs are said to have Aα/β-fibers.

2. Soma size in relation to sensory properties

It is frequently stated that small DRG neurons are slowly conducting C-fiber nociceptors and large neurons are LTMs

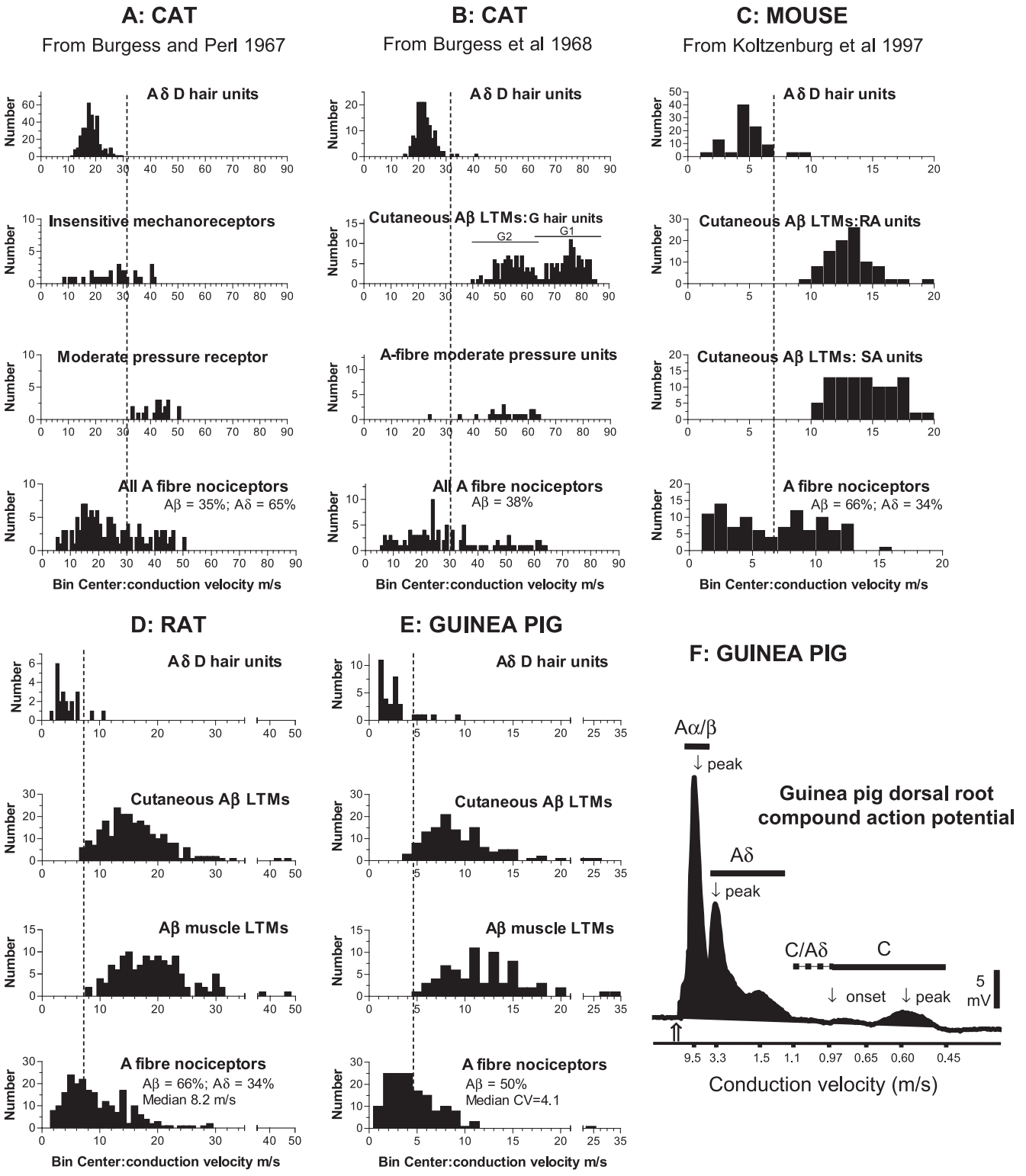


Fig. 1. Examples of distributions of CVs of individual identified A-fiber nociceptive units compared with D hair (Aδ LTMs) and with groups of cutaneous and/or muscle Aα/β LTM units. CVs were measured along peripheral nerve recorded extracellularly (A–C) or along dorsal roots recorded intracellularly from DRG neurons D, E. For comparison with E, a compound action potential is shown in F from the same type of nerve (S2 dorsal root) in the same age and sex guinea pig, recorded at the same temperature (30 °C), as those used in the experiments that yielded the data in E. A, B and C are replotted from published papers [4,5,33], while D and E are from data accumulated over several years in this laboratory. In the cat, rat and guinea pig the CV distributions of A-fiber nociceptive units peak in the upper end of the Aδ D hair CV range. The vertical dotted line indicates the upper end of the Aδ CV range determined from the Aδ D hair units distribution in A, B and C, and from compound action potential measurements along similar nerves in the same aged animals for D and E; in D and E this line coincides with the upper end of the main population of D hair units. In all species a substantial proportion (from 18% to 65%) of A-fiber nociceptors have CVs that extend above the dotted line into the Aβ CV range. The cat papers were the first to describe properties of A-fiber nociceptors, and clearly include Aβ nociceptive fibers. Temperatures at which recordings were made and ages of animals are given in Table 1.

Table 1
Comparison of the reported incidence of Aβ nociceptors in a variety of species

Species	Age	Temperature (core or nerve)	Aδ/Aαβ border used (m/s)	Main D hair upper CV (m/s)	Aβ HTM/A-nociceptive (%)	Peripheral nerve (PN) or dorsal root (DR); cell/fiber	Aδ/Aαβ borderline based on	Reference
Monkey	Young 5–7 kg	Core 38 °C	30		18	PN fiber	Distribution of CVs	Treede et al. [65]
Cat	Young	Nerve 36.5 °C	30	30	38	PN fiber	D hair CVs	Burgess et al. [5]
Cat	Young 2–3 kg	Nerve 36.5 °C	30	30	30	PN fiber	D hair CV CAP	Burgess and Perl [4]
Cat	Not stated	?	36	34	22	PN cell	Not stated	Koerber et al. [31]
Rat	5–8 w 120–180 g F	37 °C	8–14	–	No sensory properties	PN soma	Distribution of CVs	Harper and Lawson [26]*
Rat	Adult 200–400 g	Core 36–37 °C	15?	<15	~48	PN fiber	D hair CVs	Lynn and Carpenter [44]
Rat	Young 5 w	Core temp "physiological"	14	~14	~65	PN cell	Referred to papers	Ritter and Mendell [55]
Rat	7 w, 150–180 g, F	Nerve 30 °C	6.5	6.5	64	DR cell	CAPs	Fang et al. [19]
Guinea pig	Young 1–2 w 130–220 g, F	Nerve 30 °C	4	4	48	DR cell	CAPs, D hair CVs	Lawson et al. [38]
Guinea pig	Young 1–3 w 150–300 g, F	Nerve 30 °C	4.2	4.2	50	DR cell	CAPs, D hair CVs	Djouhri et al. [15]
Mouse	Adult 5–32 w	32 °C	10	7	25%>10 m/s, 50%>7 m/s	PN fiber	D Hair CV CAPs	Koltzenburg et al. [33]

Data from published papers (last column) in studies in which the borderline between Aδ and Aα/β CVs has been measured or considered. Methods used to determine this borderline (given in column 4) are in column 8. CAP means that compound action potential measurements were used to determine the CVs of Aδ and Aαβ waves; D hair CVs means that from CV distribution histograms, the top CVs in the main part of the Aδ LTM D hair distribution was used, distribution of CVs means that although sensory properties were not determined, the borderline was inferred from CV distribution histograms referred to papers: here the borderline used was obtained from Lynn and Carpenter [44] and Harper and Lawson [26]. Available information on age, weight and sex of animals is shown in column 2, and data about animal core temperature or nerve temperature (of the pool in which the nerve conducted) are in column 3. Where both are available, the nerve temperature is used instead of animal core temperature. Note that the Aδ/Aαβ border used (column 4) is close to the "main D hair upper CV" (column 5) except for the mouse, where the fastest D hair CV (10 m/s) was used in the paper, but the top of the main D hair distribution was 7 m/s (Fig. 1). Column 6 gives the percentage of all A-fiber nociceptors that conducted in the Aβ range.

with Aα/β-fibers. Although slowly conducting neurons tend to be small, there is considerable overlap in cell size among DRG neurons with C-, Aδ- and Aα/β-fibers [26]. A higher proportion of C- than Aδ- and of Aδ- than of Aα/β-fiber DRG neurons are nociceptive, with the result that a higher proportion of small than of large neurons is nociceptive. Thus, while small size indicates a higher probability of nociceptive function, some large neurons are also nociceptive.

The assumption that an immunochemical marker of small to medium sized neurons is necessarily expressed selectively on nociceptive neurons may not always be correct. For instance Nav1.7-LI (like immunoreactivity) is expressed more in small and medium sized neurons, but its expression is related more closely to slower CV and to broader action potentials than to nociceptive properties [17]. This and the fact that some nociceptive neurons with Aβ-fibers have large somata (unpublished observations), show that cell size alone as an indicator of nociceptive function may be misleading. Primary afferent (DRG) neurons can be more accurately classified on the basis of their response properties. Since such functional classification was covered in depth in several previous reviews (e.g. Refs. [42,52]) only a brief account of the functional classes of A-fiber DRG neurons will be given here.

3. Nociceptive neurons

Many nociceptive neurons respond to more than one of the following stimulus modalities: noxious mechanical, noxious thermal and noxious chemical (e.g. Refs. [2,4]). However, many studies on receptive properties of primary afferent neurons, including the early studies [2,4], use only heat and mechanical stimuli. The nociceptive units that respond to both these types of stimulus are called mechano-heat (MH) sensitive units. Consequently the terms CMH and AMH are often used to refer to C-fiber and A-fiber mechano-heat-sensitive units, respectively. However, these often respond also to noxious chemical stimuli, and thus the term 'polymodal nociceptor' was coined to describe this subset of cutaneous C-fiber afferents [2], see review [52].

3.1. Aδ- and Aβ-fiber nociceptive neurons

Some A-fiber nociceptive units have non-specialized peripheral terminals in the dermal–epidermal border [34]. They have been defined, on the basis of their responses to mechanical stimuli only, as mechanical nociceptors, insensitive mechanoreceptors and moderate pressure units [4]

(see later). In later studies, A-fiber nociceptors have been divided, on the basis of their responses to mechanical and thermal stimuli, into three groups: (i) high threshold mechanoreceptive (AHTM) units responding only to noxious mechanical stimuli, (ii) mechano-heat (AMH) units that respond to noxious mechanical stimuli and also promptly to a single application of noxious heat and (iii) mechano-cold (AMC) units responding to both noxious mechanical and noxious cold stimuli.

Most (86%) of A-fiber nociceptors in primate (monkey) responded to noxious heat, and were thus AMH units. These have been subclassified into type I AMH and type II AMH units according to their responsiveness to noxious heat stimuli [65,66]; see also Ref. [53]. Type I units (in glabrous and hairy skin) have a higher heat threshold and a lower mechanical threshold than type II units. However, although their heat threshold is high (typically >53 °C) to short (1 s) heat stimuli, it is lower (40–50 °C) to long (30 s) stimuli [65]. They respond to such prolonged heat stimulus with a long lasting discharge with an increasing firing frequency that has a delayed onset (5 s) and a late peak (16 s) [65]. In the monkey, the mean CV of Type I AMH units was 25 m/s with a maximum of 70 m/s [65]. The maximum CV of the Aδ range in this species was 30 m/s; two-thirds of type I units were Aδ and a third were Aβ units. Because type I units usually responded to chemical stimuli as well, they have also been referred to as A-fiber polymodal nociceptors [11]. The high heat threshold of type I units to short stimuli, and the fact that long heat stimuli are rarely used, has probably resulted in them being classified as HTM units in our and many other studies [4,5], while their lower mechanical threshold may have placed them in the moderate pressure category (see below) in some studies. Type I units have been described in cat [56], rabbit [21] and rat [60] and they have been suggested to mediate the first pain to noxious mechanical stimuli (see Ref. [53]).

In the monkey, type II units were only found in hairy skin and all had Aδ fibers (<30 m/s). They had a lower heat threshold to short stimuli (median 46 °C) [65] with a prompt, short lasting heat response. Their high mechanical threshold might have led to some of them being classed, in some studies, as very high threshold nociceptors or unresponsive (silent) units. It was suggested (see below) that the first pain sensation to heat may be served by the type II (Aδ-fiber) units (see Ref. [53]). Note that if A-fiber units in rat have similar heat responses to those of type I and II MH described in monkey, the Aδ nociceptive units activated by fast heat ramps in the study of Yeomans and Proudfit [73] may have been the slower conducting (Aδ) type II AMH units.

3.2. Percentages of A-fiber nociceptors with Aβ-fibers

In the earliest studies of properties of cutaneous nociceptive A-fibers in cat [4,5] that showed units conducting in the Aβ range, some of these Aβ-units were insensitive mechanoreceptors or moderate pressure receptors, but since both types fired more enthusiastically to noxious (such as pin prick or squeezing with forceps) than to non-noxious stimuli, their adequate stimulus was clearly in the noxious range and they were, therefore, classed as nociceptors. In the cat, 18–38% of nociceptive A-fibers had Aβ CVs (>30 m/s) and within the subdivisions of A-fiber nociceptors, 8% of high threshold nociceptors, 35% of insensitive mechanoreceptors and 100% of moderate pressure receptors had Aβ CVs [4,5]. In rat about 50% of A-fiber nociceptive afferents (HTMs) had Aβ CVs [44] (Table 1). That some A-fiber nociceptive afferents conduct in the Aβ CV range has been confirmed in more recent *in* vivo studies of extracellular recordings (teased fiber technique) in several species including monkey [65,66], rat [60] and mouse [33] (see Table 1). In the monkey, using an Aδ/Aβ borderline of 30 m/s, 18% of A-fiber nociceptive afferents conducted in the Aβ CV [65]. However, the borderline was selected from a frequency distribution of all A-fiber CVs but could have been anywhere from 20 to 30 m/s, and therefore this 18% might be an underestimate. Similarly in the mouse, 20% had Aβ-fibers with an Aδ/Aβ borderline of 10 m/s [33], but if 7 m/s was used (see earlier, and Fig. 1) the percentage would be 50%. In one rat study, all A-fiber nociceptive units [60] were classified as having Aδ-fibers, but this was a result of choosing (without any direct determination of CV ranges) a borderline of 30 m/s for Aδ-fiber units which is inappropriate for the at (Fig. 1, Table 1). These examples serve to illustrate the importance of determining the Aδ/Aβ borderline with some accuracy.

Many in vivo studies using intracellular recordings in DRG neurons have confirmed the presence of Aβ nociceptors and show that substantial proportions of A-fiber nociceptive neurons conduct in the Aβ-fiber CV group in cat [31], rat [55] and guinea pig [15] (see Table 1). In a recent study in the rat (Djouhri et al., unpublished data), the proportion of A-fiber nociceptive neurons that had Aβ-fibers was 64%, very similar to that (65%) reported previously also in rat [55]. However, these percentages might be overestimates because with intracellular recording method there is an inevitable sampling bias towards neurons with larger somata.

In order to determine percentages of all Aαβ fiber neurones that are nociceptive, we carried out six experiments in which we accepted all neurons penetrated at random (because of our interest in nociceptive neurons, we normally reject many Aα/β fiber LTM neurons, although all other neuronal types are accepted). In these six experiments, about 19% of the Aα/β-fiber units sampled (n=125) were nociceptive (Djouhri et al. unpublished observations).

The presence of nociceptive neurons conducting in both Aδ- and Aβ-fiber CV ranges raises the question of whether these two groups differ in properties other than in their CVs. We have found no obvious differences between sensory receptive properties of Aδ- and Aβ-fiber

nociceptive neurons in vivo in either guinea pig or rat. Indeed, we classed most Aδ- and Aβ-fiber nociceptive neurons as HTMs, and only small proportions (about 2% in each group) as AMH units, responding to noxious mechanical stimuli as well as to noxious heat (hot water >50 °C). However, with such heat stimuli, we could not divide A-fiber nociceptive into the type I and type II units seen in the monkey. Also, in common with most other in vivo studies of the receptive properties of A-fiber DRG neurons, our studies did not test responses to chemical stimuli such as ATP, bradykinin, low pH and capsaicin. Thus we have no data on chemical responsiveness of Aδ- and Aβ-fiber nociceptive neurons in rat and guinea pig. However, others have reported that all type II AMHs showed a strong response to capsaicin, whereas most, but not all, A HTMs and type I AMHs were capsaicin insensitive [54]. Furthermore, some A-fiber nociceptors responded more vigorously to intradermal injection of a cocktail of inflammatory mediators than did C-fiber nociceptors [11] indicating that these may be considered as A-fiber cutaneous chemoreceptors.

3.3. Why have Aβ nociceptors often been ignored?

In spite of the strong evidence for the existence of myelinated nociceptive afferents fibers with CVs in the Aβ range in different species (Fig. 1), Aβ-fiber nociceptive neurons are often ignored in the literature, and textbooks often promote the view that nociceptors conduct only in the C- and Aδ-fiber range. This misleading view is perhaps due to: (i) the fact that the CVs of A-fiber nociceptors tend to peak in the Aδ-range, albeit at the upper end of the range [4,5] (see Fig. 1), (ii) the inappropriate use of Aδ-fiber upper CV limits that are too high; for instance an upper limit for Aδ-fibers of 30 m/s is sometimes somewhat arbitrarily, and incorrectly, applied to rat studies (e.g [60]), (iii) the proportion of fast Aαβ fibers that are nociceptive is fairly small (about 20% in rat), and (iv) CVs measured towards the periphery conduct more slowly than the same fibers measured more centrally, and thus the Aδ/Aβ CV border is accordingly lower, a factor that is not often taken into account.

3.4. Importance of distinguishing between Aβ nociceptive and other A-fiber neurons

It is important to distinguish between Aβ and Aδ nociceptive neurons, not least because of the need to differentiate between the contributions of Aα/β-fiber LTMs and Aβ-fiber nociceptive neurons to hyperalgesia and allodynia associated with inflammation and following nerve injury. It has been suggested that tactile allodynia following peripheral nerve injury is due to impulses carried to the CNS along residual (intact) Aβ-fibers in the presence of central sensitization (see Ref. [12]), and it is often assumed that these Aβ-fibers must be LTMs. However, the possibility has not generally been considered that Aβ nociceptors might contribute to, account for, the abnormal pain. For instance, a slight decrease in their mechanical thresholds, especially in the moderate pressure receptors, might render them responsive to innocuous stimuli. Furthermore, greater firing in moderate pressure receptors once threshold is reached could contribute to allodynia.

4. Non-nociceptive A-fiber neurons

Broadly speaking, non-nociceptive neurons can be divided into low threshold thermoreceptive (cool and warm receptive) and low threshold mechanoreceptive (LTM) neurons. However, most non-nociceptive afferent DRG neurons projecting to skin and skeletal muscle are LTMs. Cutaneous LTMs conduct in all CV ranges (Aα/β-, Aδ- and C-fiber CV), and muscle afferent LTMs conduct in group I and group II ranges. Experimentally, LTMs are identified in vivo by their responses to non-noxious mechanical stimuli such as light brushing of the limb fur, light pressure with blunt objects, and pressure with calibrated von Frey hairs. Fibers of cutaneous and muscle LTMs make up a large proportion of fast conducting myelinated fibers (Aα/β/types I and II), but smaller proportions of more slowly conducting fiber groups (see Ref. [52]).

4.1. Aδ-fiber LTMs

These units are found in hairy skin and called “D hair” units after the very fine Down hairs. D hair units are extremely sensitive to slow movement of hair, but also respond to both stretch and frequently to cooling of the skin [42]. Although the detailed morphological structure of the receptive terminals of D hair units is not known, they may be associated with hair follicles [42].

4.2. Aα/β-fiber LTM units

Aα/β-fiber LTM units can be divided according to their responses to sustained mechanical stimuli (sustained pressure) into rapidly adapting (RA) and slowly adapting (SA) units. SA units fire with a static or phasic firing pattern to a sustained mechanical stimulus and are important in signalling steady displacement of the skin. RA units tend to fire only during the initial application or removal of a constant mechanical stimulus and are important in the detection of mechanical stimuli of changing intensity and movement. RA units are found in both glabrous and hairy skin and are divided into several subtypes (see Refs. [28,42]). A group of rapidly conducting Aα/β-fiber units that responds to muscle manipulation is the proprioceptive afferents including group I and group II muscle spindle afferents and Golgi tendon organ afferents.

5. Electrophysiological membrane properties of A-fiber DRG neurons

The membrane properties of DRG neurons are often examined with intracellular recordings from their somata not only because such recordings are difficult to make from the terminals, but also because there are some similarities between the properties of the cell bodies (soma) and their terminals [25]. Electrophysiological recordings show that DRG neurons are heterogeneous in their afferent CVs, receptive properties and their somatic AP configuration. Some neurons exhibit APs with inflections on the descending phase with a tendency for APs with such inflections to be broader (longer duration) than those without inflections [74]. Although inflected APs tend to occur primarily in the C- and Aδ-fiber groups (see Ref. [32]), a population of Aβ-fiber neurons also exhibit APs with such inflections [27,31,40].

5.1. A-fiber nociceptive neurons versus A-fiber LTMs

In both cat [31] and rat [55], A-fiber nociceptive neurones exhibit longer AP and afterhyperpolarization (AHP) durations than A-fiber LTMs in both the Aδ and Aα/β-fiber CV ranges (see review [32]). We have confirmed these findings in guinea pig [13,15] and rat (Djouhri et al. unpublished data). Fig. 2 illustrates the patterns in guinea pig and clearly shows that both Aδ- and Aβ-fiber nociceptive neurons have significantly longer mean AP and AHP durations and larger AP overshoots than LTM neurons in the same CV range. The difference between AP and AHP durations is more apparent in the slower CV range, with a merging in AP durations between fast conducting Aβ nociceptors and Aβ LTM units (Fig. 2D and E). We find similar patterns in rat (paper in preparation). For details see Refs. [15,13] and for review see Ref. [36]. Thus in cat, rat and guinea pig, Aβ nociceptors have longer AP and AHP durations than Aα/β LTM units.

Another issue is whether Aβ-nociceptors have higher electrical thresholds than Aβ-LTMs. Comparing our voltage stimulation thresholds (using a 0.03 ms duration stimulus), we find that, for evoking an intracellular spike, the dorsal root fibers of Aβ nociceptors have mean voltage thresholds that are approximately twice that of cutaneous Aαβ LTMs and three times that of the muscle spindle Aαβ LTMs (unpublished observations). This is an inexact method, as it depends on factors other than fiber membrane properties, such as the amount of fluid that may accumulate on the stimulating electrodes that are immersed in the liquid paraffin, and on how close the fiber in question is to the electrode. Nonetheless, since these errors are random, the difference we see is indicative of a real difference in electrical threshold.

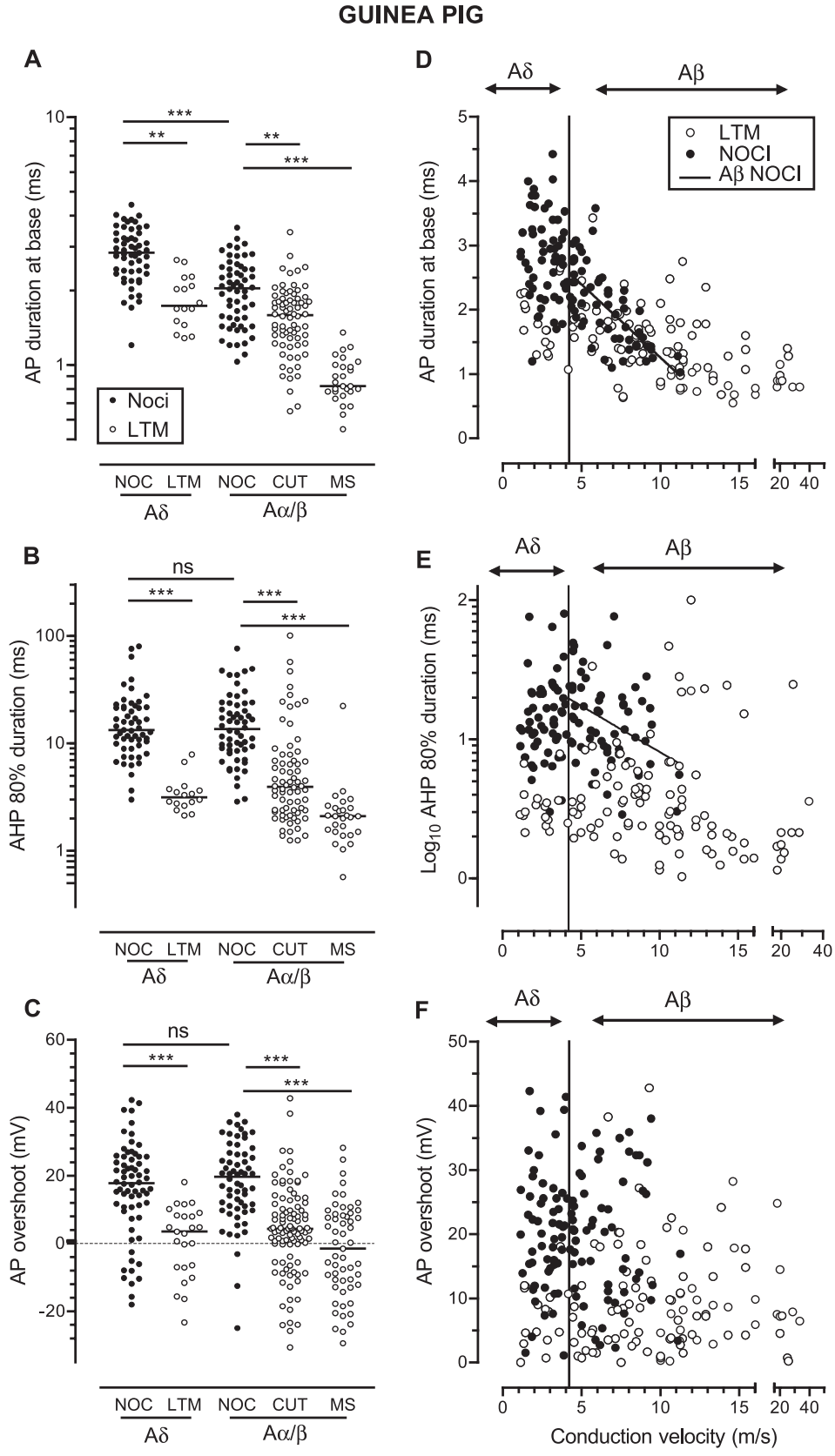
5.2. Aβ-fiber nociceptive versus Aδ-fiber nociceptive neurons

There is very little, if any, data in the literature to aid comparison between the electrophysiological properties of the Aδ- and Aβ-fiber nociceptive neurons. However, the clearest difference we found between the two groups was that Aδ-fiber nociceptive neurons exhibited broader APs than Aβ-fiber nociceptive neurons in guinea pig (Fig. 2, see Ref. [36]) and rat (in preparation). Interestingly, the AP duration showed an inverse linear correlation with CV in Aβ nociceptors ($P<0.0001$, $r^2=0.48$), but not in Aδ nociceptors (Fig. 2D). Furthermore, although there was no difference in median AHP duration between these two groups, a weak linear correlation with CV was seen only for Aβ nociceptors ($P<0.05$, $r^2=0.15$) (Fig. 2E). There was no correlation between AP overshoot and CV for either group (Fig. 2F). Thus within the Aβ nociceptors, those with faster CVs tended to have narrower APs and shorter AHPs with the AP durations in the fastest conducting units becoming indistinguishable from those of Aβ LTMs.

6. Cytochemical properties of A-fiber DRG neurons

Although immunocytochemical studies carried out on unidentified DRG neurons have provided valuable information on differential expression of several molecules (e.g. peptides, proteins, enzymes, receptors) in different subgroups (different sizes) of DRG neurons, there have been only few studies, mostly from this laboratory, relating specific molecular expression to particular sensory properties in identified neurons. Such studies involves intracellular recording in DRG neurons in vivo and determination of

Fig. 2. On the left, scatterplots in A, B and C of distributions of action potential variables in relation to nociceptive and LTM properties as well as to CV range in guinea pig. Each symbol represents a single physiologically identified neuron (for methods, see Refs. [13,15]). Units were included in these graphs only if they had a stable membrane potential (Em) more negative than −40 mV, and an AHP as reported previously [13,15]. In A,B,D and E, only units with overshooting APs were included; but in C and F, units that did not overshoot but had AP heights of at least 20mV were also included. In A, B and C, five groups are plotted: Aδ nociceptors, Aδ D hair LTMs, Aβ nociceptors and Aα/β LTMs that are cutaneous (CUT) or probable proprioceptive afferents (MS, muscle spindle and Golgi tendon organ afferents). NOC=nociceptors, LTM=low threshold mechanoreceptive unit, CUT=cutaneous, AHP 80% duration means duration of AHP to 80% recovery from its greatest depth back to Em. Kruskall–Wallis (non-parametric equivalent of one way ANOVA) was carried out on all groups with Dunn's post test on selected groups, namely Aδ-nociceptors versus D hair units, Aδ-nociceptors versus Aβ-nociceptors, Aβ-nociceptors versus cutaneous LTMs and Aβ-nociceptors versus Aα/β cutaneous and proprioceptive LTM units. * indicates $P<0.05$, ** $P<0.01$, *** $P<0.001$, ns=not significant ($P>0.05$). On the right, in D, E and F, the same data are plotted against dorsal root CV. The vertical line shows the Aδ/Aαβ border of 4.2m/s. Linear regression analysis was carried out on Aδ nociceptors, Aβ nociceptors, Aδ LTMs and Aβ LTMs. The only correlations were for Aβ-nociceptors, for both AP duration at base, and AHP duration. Data replotted, with additional data from Refs. [13,15].


GUINEA PIG
A
B
C
D
E
F
AP duration at base (ms)
AHP 80% duration (ms)
AP overshoot (mV)
Log10 AHP 80% duration (ms)
Noci
LTM
NOCI
Aβ NOCI
NOC LTM NOC CUT MS
Aδ
Aα/β
ns
Conduction velocity (m/s)

sensory receptive properties followed by intracellular dye injection to enable subsequent immunocytochemistry. This section summarizes the results of such studies particularly those relevant to A-fiber DRG neurons. The section also provides a brief overview of some of the receptors/ion channel proteins that may be implicated in transduction of mechanical, thermal and chemical stimuli in A-fiber neurons or large sized DRG neurons most of which have A-fibers as already mentioned. For a much more detailed review of cytochemical properties of DRG neurons (see Ref. [37]).

6.1. Neuropeptides

In guinea pig, the neuropeptide substance P (SP) was expressed in half the cutaneous nociceptive neurones examined, mainly those with C-fibers, but also some with Aδ- and a few with Aα/β-fibers in Ref. [38], see Fig. 3, while CGRP was mainly in nociceptive neurons with C-, Aδ and Aα/β fibers, although a few Aβ-fiber LTM neurons were also weakly positive [39]. For both peptides, the proportion of immunoreactive nociceptive neurons and the relative intensity of the staining, declined with increasing CV, such that positive Aβ nociceptors were very few and only weakly positive (for substance P see Fig. 3A). It is generally assumed that central and peripheral SP and CGRP release is from slowly conducting nociceptive neurons, but the presence of these peptides in some Aδ- and Aβ-fiber nociceptors (Fig. 3) suggests that such neurons might also contribute to their release.

6.2. Ion channels and currents

Because voltage-gated Na^+ channels play an important role in regulating neuronal excitability and in the initiation and propagation of APs, they are obvious candidates for mediating the electrophysiological differences between A-fiber nociceptive and LTMs. We have therefore, examined expression of Na^+ channel subtypes Nav1.7, Nav1.8 and Nav1.9 in physiologically identified DRG neurons. Nav1.9 was found to be expressed exclusively in nociceptive C-, Aδ- and Aβ-fiber neurons [19], Nav1.8 was strongly expressed only in nociceptive neurones and weakly in some LTMs of all CV groups [16] and Nav1.7 was expressed in both nociceptive and LTM neurons, with a slightly higher mean intensity in nociceptive neurons [17]. The results for A-fiber neurons are summarised in Fig. 3 which shows that Nav1.9 was expressed only in nociceptive neurons and that overall, a higher proportion of nociceptive than of LTMs showed Nav1.7- and Nav1.8-LI. For all these channel subunits, the level of expression was greater in Aδ- than Aβ-fiber nociceptors. Negative linear correlations between CV and relative intensity of Nav1.7 and Nav1.8 in A-fiber nociceptors (Fig. 3) show that there tends to be lower intensity of immunoreactivity for both channels in the faster conducting A-fiber neurons. Nav1.8 is correlated with AP duration in A-fiber DRG neurons [16]; thus shorter AP durations in faster conducting nociceptors are related to a lower expression of Nav1.8 in such neurons.

Another ion channel that may contribute to the differences in AHP durations between A-fiber nociceptive and LTM neurons is the hyperpolarization activated non-specific cation current (Ih), which is thought to reduce AHP duration, increase firing frequency and decrease adaptation [50]. Although Ih current is prominent in most or all large DRG neurones and is in fewer small neurones [10,58], there is no published information about the sensory receptive properties of the DRG neurons that express Ih or other ion channels such as K channels that must also contribute to electrophysiological differences between A-fiber nociceptive and LTM neurons.

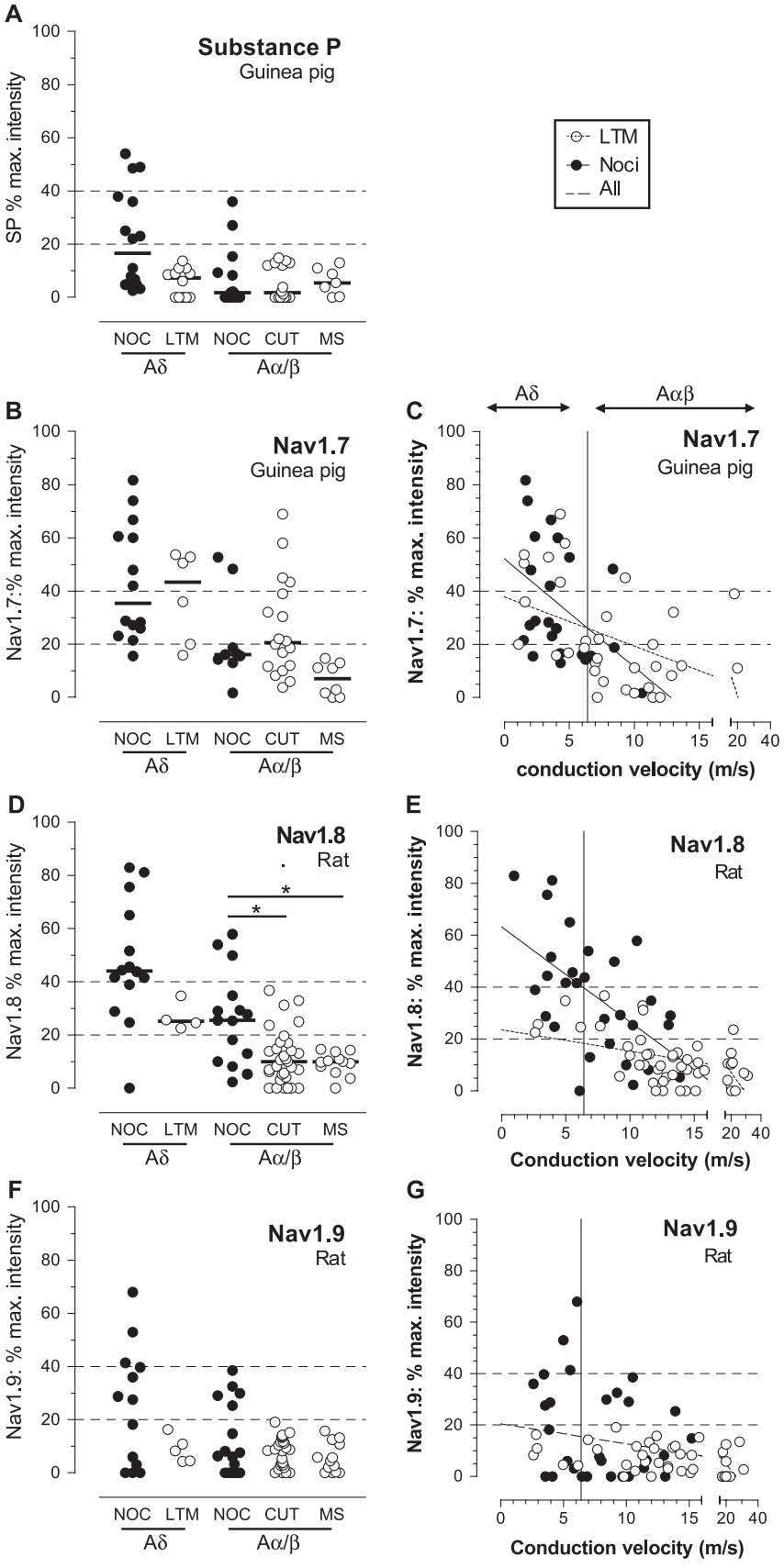
6.3. Neurotrophic receptors and nociceptive markers

Expression of tyrosine kinase A (trkA), the high affinity receptor for nerve growth factor (NGF) [1] and IB4 (isolectin B4) binding are often said to be in separate subpopulations of nociceptive DRG neurons. In direct studies on individual neurons in rat in vivo, one study showed IB4 binding on C- and a small proportion of A-fiber nociceptive DRG neurons in rat [24], but another larger study showed no labelling of A-fiber nociceptive neurons with IB4 [20]. All neurons with identified sensory receptive properties that were intensely labelled with trkA were nociceptors conducting in C-, Aδ- or Aα/β-fiber ranges [20]. Thus most A-fiber nociceptive neurons expressed trkA but did not show IB4 binding. For a recent overview of the expression of other neurotrophic receptors in DRG neurons, see Ref. [37].

6.4. Molecular transducers of noxious and innocuous stimuli

Several candidate molecules or receptors/ion channels have been implicated in detection of different thermal, mechanical and chemical stimuli (see reviews [29,37]).

Fig. 3. Distribution of immunocytochemical properties of Aβ and Aδ nociceptors and LTM units. Scatterplots are shown on the left, and on the right are plots to show the relationship of relative intensity of the immunoreactivity to dorsal root CV in the same neuron. Linear regression lines are shown only where $P<0.05$. For symbols and regression line formats for all graphs see top right. The Y axis (% max. intensity) shows immunocytochemical staining intensity as a percentage of maximum neuronal cytoplasmic staining in the same DRG section. For all graphs, each point is from a single DRG neuron, from which intracellular recordings were made in a deeply anaesthetised rat or guinea pig, whose sensory properties were identified, and into which fluorescent dye was injected, to enable subsequent immunocytochemical examination, using ABC immunocytochemistry (Vector Laboratories). For details of antibodies, see Ref. [39] for Substance P, Ref. [17] for Nav1.7, Ref. [16] for Nav1.8, and Ref. [19] for Nav1.9. These papers are the sources of the data replotted here, and provide the experimental details.


A
Substance P
Guinea pig
SP % max. intensity
LTM
Noci
All
NOC LTM NOC CUT MS
Aδ
Aα/β
B
Nav1.7
Guinea pig
Nav1.7:% max. intensity
C
Aδ
Aαβ
Nav1.7
Guinea pig
Nav1.7: % max. intensity
conduction velocity (m/s)
D
Nav1.8
Rat
Nav1.8 % max. intensity
*
*
E
Nav1.8
Rat
Nav1.8: % max. intensity
Conduction velocity (m/s)
F
Nav1.9
Rat
Nav1.9: % max. intensity
G
Nav1.9
Rat
Nav1.9: % max. intensity
Conduction velocity (m/s)

One possible candidate that may be related to A-fiber nociceptive function is TRPV2 (VRL-1) receptor, a member of the TRP (transient receptor potential) protein family. It has been suggested that this may play a role in thermotransduction in A-fiber nociceptive neurons, because it is present in a subpopulation of medium and large neurones and responds to temperatures >52 °C. This high heat threshold is similar to that (typically >53%) of type I A-fiber mechano-heat nociceptors [9] (see Ref. [65]). The molecular transduction mechanisms of mechanical nociceptors are not well understood although a number of candidates have been identified (for review, see Refs. [29,37]. TRPV4 may be involved because TRPV4 knockout mice show impairment of responses to noxious mechanical stimuli [64].

7. Central projections

In addition to electrophysiological differences between nociceptive and LTM neurons, these two groups have distinct central projections. They show generally non-overlapping termination in the dorsal horn of adult spinal cord, with Aδ-nociceptive neurons projecting to both superficial (lamina I and IIo (outer lamina II) and deeper laminae (lamina V), whereas A-fiber LTMs terminate deep in superficial laminae (IIi-V) (for review, see Ref. [22]). Recent studies have shown that neonatal LTMs project to the same regions of the dorsal horn as their adult counterparts [70]. Some Aβ-fiber (CV>30 m/s) nociceptive neurons were shown to terminate in the superficial dorsal horn lamina II [41] in the cat and monkey, with similar termination patterns to Aδ-nociceptive fibers [41]. Studies on neonatal and 3-week-old mice appear to confirm this, with two central arborisation patterns of units classed as A-fiber nociceptors, one projecting to lamina I and II outer, and one showing diffuse projections throughout laminae I–V [70]. The latter group may include moderate pressure receptors [70]. Furthermore, there is evidence that trkA-expressing DRG neurons project most heavily to lamina I and IIo, whereas IB4-binding and Ret-expressing DRG neurons project most heavily to the inner lamina II (IIi) (see Ref. [62]). This is consistent with functional/anatomical differences between these two groups of afferent neurons, that are not yet fully understood but which might partly be explained by IB4 binding on C-fiber nociceptive neurons, and by trkA expression in C- and A-fiber nociceptors (see earlier).

8. A-fiber neurons and pain

Activation of nociceptors usually results in pain once the nociceptive information reaches the appropriate centres of the brain in a conscious animal.

8.1. A-fiber nociceptive neurons and physiological 'normal' pain

In contrast to C-fiber nociceptors which mediate burning or second pain, A-fiber nociceptors are thought to evoke sharp pricking or first pain because the latency of withdrawal response to this pain is too short to be carried by slowly conducting C-fibers [6]. These rapidly conducting A-fibers that signal very precisely the localization of the noxious stimulus (unlike C-fiber nociceptors) are likely to be important in triggering rapid precise reflex withdrawal responses. Interestingly, A-fiber nociceptors respond to noxious mechanical stimuli with higher discharge frequencies than C-fiber nociceptors [23] and are thought to provide more information to the CNS about the intensity of noxious mechanical stimuli than C-fiber nociceptors because they encode such stimuli in the noxious range [23,61]. It has also been suggested that A-fiber nociceptive afferents may be important for discrimination of the quality of a noxious stimulus on the basis that they distinguish probe size and encode stimulus intensity better than C-fiber nociceptors [23]. There is evidence that probable type I AMH afferents (mechanosensitive A-fiber nociceptors with relatively low mechanical thresholds) give rise to sharpness perception in response to punctate stimuli [23,45] and that probable type II AMH units (A-fiber nociceptors with higher mechanical thresholds) may mediate mechanically evoked cutaneous pain [23].

First pain to heat, as noted earlier, is thought to be mediated by type II A-fiber nociceptors (Aδ-fibers) on the basis of their thermal threshold being near that for first heat pain (see Ref. [53]). Consistent with this role is the absence in primate glabrous skin, of these units (monkey hand) and of an A-fiber latency first pain sensation (human hand) [7]. Such a role of A-fiber nociceptors is supported by their greater response to rapid skin heating (high heating rates) than that of C-fiber nociceptors (see Ref. [73]). Sustained heat pain due to longer lasting noxious heat stimuli may have a contribution from type I AMH fibers which give a vigorous (late) response to such stimuli applied to the glabrous skin of the human hand (see Ref. [53]).

The sensation of cold pain may have various qualities including cold-related aching, burning or pricking. The afferent fibers that mediate these different qualities are not understood, although A-fiber nociceptors may play a role in signaling cold pain sensation, through AMC fibers. In addition, all A-fiber nociceptors were shown to respond to extreme cold stimuli below 0 °C in rat [60].

Although chemogenic pain is often considered to be the province of C-fiber nociceptors, A-fiber nociceptors, in particular type II AMH fibers, may also contribute since they can respond to various chemical stimuli including serotonin, histamine, bradykinin and capsaicin [11,54] and since some A-fiber nociceptors were found, as noted earlier, to give a response to intradermal injection of a cocktail of

inflammatory mediators that was more vigorous than that of C-fiber nociceptors.

8.2. A-fiber nociceptive neurons and abnormal pain

There is evidence to suggest that the primary heat hyperalgesia that develops at the site of burn injury is mediated by peripheral sensitisation of nociceptors (e.g. Refs. [35,47]). Type I AMH units (with Aδ or Aβ CVs) are thought to mediate this primary hyperalgesia in monkey [47] because in the glabrous skin of monkey hand they showed a marked sensitisation after a burn, in contrast to CMHs which were desensitized by this injury. Although the pain and hyperalgesia that develop in the presence of an A-fiber block are thought to be attributable to activation of C-fiber nociceptors [75], a role for A-fiber nociceptors cannot be ruled out, because many A-fiber nociceptors have long unmyelinated branches that may extend beyond a radial nerve compression block [51]. Also, the results of capsaicin desensitization and nerve block experiments suggest that capsaicin-insensitive A-fiber nociceptors not only play a role in pain resulting from punctate mechanical stimuli (see above), but also play a role in punctate secondary hyperalgesia [45].

8.3. A-fiber LTM neurons and abnormal pain

Pain induced by activation of nociceptive neurons with mechanical stimuli is inhibited in the CNS by the concurrent activation of LTMs [67]. This together with evidence that tissue injury decreases the responsiveness of A-fiber LTMs has led to the suggestion that Aβ-fiber LTMs are implicated in mechanical hyperalgesia (increased pain to normally painful stimuli) via a central disinhibition mechanism (see Ref. [53]). Furthermore, it was hypothesized that tactile allodynia following peripheral nerve injury might be due, at least in part, to impulses carried to the CNS along residual (intact) Aβ-fiber LTMs combined with the effects of central sensitization, a state of increased excitability of spinal cord neurons (see Ref. [12]). It is thought that central sensitization may amplify the sensory input from intact afferents contributing to neuropathic pain behaviours in animals after nerve injury (see Ref. [12]). Additionally, behavioural signs of tactile allodynia in rat after spinal nerve injury were unaffected by elimination or desensitization of C-fiber nociceptors with capsaicin [49] supporting the importance of A-fiber afferent neurons. However, as noted earlier, the possibility has not generally been considered that Aβ nociceptors might contribute to, account for, the abnormal pain. Indeed, the possibility has not been excluded that a slight lowering of threshold and/or increase in firing frequency in moderate pressure receptors may play a role in mechanical allodynia.

There is also evidence that SP and brain derived neurotrophic factor (BDNF) are up-regulated in axotomized large-sized DRG neurons [30,48], but whether these were LTM or nociceptive prior to axotomy has not been determined. If these neurons are among those that show spontaneous activity after nerve injury (e.g. Ref. [43]), then such activity may lead to release of these neuromodulators (SP and BDNF) in the dorsal horn of the spinal cord and thus contribute to central sensitization via phosphorylation of the NMDA receptors on spinal neurons [46]. Although there is a view that central sensitization can only be induced by afferent activity in C-fibers (e.g. Ref. [71]), it has recently been suggest that central sensitization can be triggered by input from A-fiber afferent neurons on the basis that axotomized A-fibers but not C-fibers show spontaneous activity following peripheral nerve injury [43,63]. It has been suggested that ectopic spontaneous activity seen in A-fiber afferent neurons after nerve injury may render them capable of triggering and maintaining central sensitisation [43,63]. However, amongst intact DRG neurons that run with axotomised neurons, C-fiber neurons become spontaneously active [72]. It is therefore not yet clear whether the spontaneous activity of axotomised A-fiber neurons, or of adjacent intact C-fiber neurons, is most important either for central sensitisation or the generation of spontaneous pain.

9. Conclusions

In this review we present clear evidence for the existence in a number of species of nociceptive primary afferent neurons conducting in the Aβ CV range. Indeed, the percentage of A-fiber nociceptors that conduct in the Aβ range is about 50% in rodents, and in rat the percentage of Aαβ-fiber neurons that is nociceptive is about 20%. Thus Aβ nociceptors are a substantial population that should no longer be ignored. Aβ nociceptors differ from Aδ nociceptors in showing a less extreme form of various properties typical of nociceptive neurons such as longer APs, and expression of SP, CGRP and of the Na^+ channel subunits Nav1.8 and Nav1.9. These differences between Aδ and Aβ nociceptors appear to be one of degree with a gradual decline in nociceptive phenotype with increasing CV in Aβ nociceptors. The narrower AP in Aβ- than Aδ-fiber nociceptive neurons may reflect the lower expression of Nav1.8 in the faster conducting neurons. Interestingly, in the larger species some of the faster conducting Aβ nociceptors (moderate pressure receptors) have lower mechanical threshold than the more slowly conducting ones, although in all other respects they appear similar. These may include the units with the less extreme nociceptive phenotype at the top of the Aβ CV range. Although we have not found obvious differences in the receptive properties between Aδ and Aβ nociceptors in either guinea pig or rat, evidence from studies in the monkey suggests that the type II AMH (Aδ-fiber) nociceptive neurons may mediate first pain sensation to heat, whereas first pain to noxious mechanical stimuli may be served by type I AMH (Aδ and Aβ-fibers)

nociceptive neurons [65]. Aα/β-fiber neurons have been implicated in tactile allodynia following tissue and nerve injury, and it has usually been assumed that these are LTMs. However, the possibility that Aβ-nociceptive fibers may contribute to this abnormal sensation has not been excluded, or even perhaps considered. Although direct evidence of Aβ-fiber nociceptor sensitization is lacking, it might require only a modest decrease in threshold in moderate pressure receptors for gentle touch to activate nociceptive pathways.

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