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Pathogenesis of Pain in Peripheral Diabetic Neuropathy

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Recent advances in understanding the pain associated with diabetic neuropathy are likely to provide significant mechanistic insights and offer better therapies. In clinical research, new tools for measuring neuropathic pain and validation of histologic and other biomarkers will provide the foundation for research advances, and new clinical trial designs will allow better discrimination of beneficial treatments and may reveal underlying pathogenic mechanisms. Ongoing refinement of relevant animal models and assays to more accurately reflect the clinical condition will improve evaluation of novel pharmacologic approaches while dissecting peripheral versus central effects of diabetes on pain pathways will provide a more complete picture of the pathophysiologic mechanisms. Such multidisciplinary work may soon allow physicians to offer improved therapeutic options to patients suffering this distressing condition.

Introduction

Pain in peripheral diabetic neuropathy (PDN) is relatively infrequent, occurring in 15% to 30% of patients who suffer from PDN, whereas negative phenomena, such as numbness, predominate in diabetic patients [1]. The pathogenesis of pain in PDN is not well understood despite significant advances in understanding other forms of neuropathic pain [2]; this is because these advances in basic science have not been translated into clinical research. When it comes to information that is likely to contribute to better understanding of pain in PDN, there have been some interesting recent developments at both the clinical and basic science levels. In this update, we will first present recent developments in clinical research that are likely to contribute to elucidation of pathophysiologic mechanisms of pain in PDN and then address recent advances made in the basic sciences that may reveal new mechanisms and potential therapeutic targets.

Advances in Clinical Research

Descriptive tools

The concept that clinical symptoms and signs are a reflection of specific underlying mechanisms has been considered for some time [3,4]. Clinical research has been relatively slow to advance, primarily because of a lack of appropriate clinical investigation tools that would lead to confirmation of the underlying mechanisms of neuropathic pain. One positive recent development has been publication of normative data sets for quantitative sensory testing, which could be applied to the study of pain mechanisms in PDN [5•,6]. These newer data sets provide a framework to interpret positive sensory phenomena using methods of modern psychophysics and will complement the previously published normative data sets for diagnosis of sensory deficits [7–9]. In addition, publication of neuropathic pain symptom tools should contribute to the utility of those symptoms in further elucidating neuropathic pain mechanisms [10•]. These new tools can be used for differentiation of clinical presentation of patients as neuropathic versus non-neuropathic [11–14] and for quantitative measurement of symptoms and longitudinal monitoring [14–16]. Taken together, symptoms and signs are both a starting point and cornerstone in the process of elucidating underlying mechanisms because they provide temporal and special characteristics of the pathophysiologic abnormalities underlying pain in PDN, whereas the qualities of neuropathic pain in PDN provide additional information about specific mechanisms participating in the pathophysiologic processes.

Biomarkers

The results from neuropathic pain symptom tools and quantitative sensory tests, which provide physiologic data, can now be complemented with histologic information by quantification of intraepidermal nerve fiber (IENF) density [17,18]. At this time, the primary information obtained from IENF studies is a quantitative analysis of unmyelinated epidermal C fibers and is probably more important for diagnosis of degenerative small fiber neuropathy and sensory loss. However, recent work suggests that some

features of epidermal nerve fibers, such as microneuromas and end branching, may be associated with neuropathic pain [19]. Further research in this area will require that quantitative histologic information is combined with psychophysical information and with specific characterization of the receptors on surviving nerve endings. This complementary and comprehensive approach will allow investigators to achieve a more complete picture of the mechanisms of pain in PDN. Analysis of immune markers, such as tumor necrosis factor-α, interleukin (IL)-2, IL-4, and IL-10, as performed in other painful neuropathies [20], may provide additional perspectives on the pathophysiologic pain mechanism in PDN.

Although skin biopsies represent a mildly invasive means of visualizing nerves during diabetes relative to sural nerve biopsies, the development of surrogate biomarkers that can discriminate between painful and painless diabetic neuropathy without tissue removal is also emerging as a potentially useful approach to evaluating painful neuropathy in patients that may reveal aspects of the underlying pathogenic mechanism. Recent studies have shown that C fiber–mediated microvascular reactivity in the skin is different in diabetic patients with or without painful neuropathy [21], whereas using confocal microscopy to visualize sensory nerves in the cornea of diabetic patients [22] has the potential to further extend the biomarkers available for clinical studies of diabetic neuropathy and pain mechanisms. At present the place of corneal sensory nerve damage within the diaspora of progressive diabetic neuropathy is still under evaluation, but there is evidence that some aspects of the changes seen in corneal sensory nerves can be used to discriminate between painful and painless diabetic neuropathy [23••]. If this potential is confirmed, using corneal confocal microscopy as a noninvasive technique that monitors a surrogate for diabetic peripheral neuropathy and allows repeated evaluations may have significant benefits for clinical studies aimed both at understanding mechanisms and testing efficacy of therapeutics.

Mechanisms Implied by Successful Clinical Trials

Statistically significant and clinical meaningful responses to pharmacologic agents with specific modes of action represent another line of evidence that may point to the underlying mechanisms of painful diabetic neuropathy. In recent years, a number of large clinical trials have shown success in relieving pain in patients suffering from PDN, leading to the US Food and Drug Administration approval of duloxetine [24,25] and pregabalin [26,27]. These results suggest that descending modulation of sensory processing by serotonin and norepinephrine plays a significant role in the pain state experienced by diabetic patients who respond to duloxetine, whereas N-type calcium channels may play an important role in the maintenance of pain in diabetic patients who respond to pregabalin. The realization that a diverse range of mechanisms underlie pain in diabetic patients raises the possibility that PDN could be treated by applying principles of rational multidrug therapy [28], which calls for combining pharmacologic agents with different mechanisms of action for an improved analgesic effect [29].

Recent Advances in Preclinical Research

Animal models

Rodents with type 1 diabetes induced by the pancreatic β-cell toxin streptozotocin (STZ) remain the most commonly used model of diabetic neuropathy. STZ-diabetic mice rapidly progress to a degenerative neuropathy phenotype with loss of epidermal C fibers and are generally reported to show loss of sensation rather than indices of painful neuropathy [30,31]. In contrast, the relative progression toward degenerative neuropathy is delayed in STZ-diabetic rats and they, at least transiently, show indices of allodynia and hyperalgesia that make them a viable model for studying aspects of painful diabetic neuropathy. Similar features are reported in spontaneously diabetic rats [32–34]. There is also an emerging interest in rodent models of type 2 diabetes; both rat and mouse models appear to develop indices of allodynia and hyperalgesia that may make them useful for mechanistic studies and evaluation of new potential therapies [32,35–37].

Assays

Assessing the nature and intensity of pain perceived by animals is inherently fraught with interpretative pitfalls and investigators have been largely confined to using physiologic and behavioral responses as end points. Spontaneous pain, a not infrequent occurrence in diabetic patients, remains the most difficult to assess and diabetic rodents do not show autotomy or unusual vocalization patterns, both commonly cited manifestations of pain. Measures of ultrasonic vocalizations in rats indicate that while vocalization patterns change in certain nerve injury models of neuropathic pain, they are not altered by diabetes [38,39]. Consequently, most recent studies have largely retained the long-established approach of measuring behavioral responses to non-noxious or noxious stimuli as surrogates for allodynia and hyperalgesia, although one interesting histologic study used spinal Fos protein expression in response to noxious stimuli as a surrogate marker of input to the spinal cord [40]. Limb withdrawal from noxious heat or cold and from light touch can be equated to similar quantitative sensory tests in human subjects and are particularly attractive for screening therapeutics because they allow the multiple measurements needed to produce time course and dose:effect profiles. Application of pressure in the order of 100 to 300 g also remains in widespread use to demonstrate mechanical hyperalgesia in diabetic rats and could be argued to model the pressure pain described during standing and walking in some dia-

Table 1. Therapies that acutely and transiently alleviate allodynia or hyperalgesia in diabetic rats

Study	Treatment	Mechanism of action	Behavioral test
Beyreuther et al. [43]	Lacosamide	Various possibilities	Thermal allodynia/hyperalgesia, mechanical hyperalgesia
Jolivalt et al. [44]	Prosaptide TX14(A)	Unknown	Tactile allodynia
Jolivalt et al. [45]	Asimadoline	κ-Opioid receptor agonist	Tactile allodynia, formalin hyperalgesia
Joseph and Levine [46•]	Assorted agents	Inhibition of electron transport and ATP	Mechanical hyperalgesia
Sanchez-Ramirez et al. [47]	Benfotiamine	Various possibilities	Tactile allodynia, formalin hyperalgesia
Aubel et al. [48]	Cizolirtine	Various possibilities	Mechanical hyperalgesia
Khroyan et al. [49]	Syn 1020	NOP receptor antagonist	Tactile allodynia
Matsunaga et al. [50], Ramos et al. [51•]	SC58125	COX-2 inhibitor	Mechanical hyperalgesia, formalin hyperalgesia
Torres-Lopez et al. [52]	Proglumide	CCK receptor antagonist	Formalin hyperalgesia

ATP—adenosine triphosphate; CCK—cholecystokinin; COX-2—cyclooxygenase-2; NOP—nociceptin/orphanin FQ (N/OFQ) peptide.

betic patients [41], although concerns remain about the influence of manual restraint and paw muscle wasting on the assay. Finally, although the paw formalin test has no direct clinical correlate, it provides information regarding spinal sensory processing that is not readily available from the other, strictly nociceptive, tests.

Therapeutics

In the absence of a clear understanding of the mechanisms promoting pain in either diabetic patients or animals, a broad array of potential therapies that may alleviate pain by disrupting sensory processing mechanisms have been explored. Typically, these studies involve systemic or spinal delivery of drugs as a single bolus and then follow behavioral responses to sensory stimuli. Some recent additions to the list of agents that transiently alleviate allodynia or hyperalgesia in STZ-diabetic rats [42] are listed in Table 1 [43–50,51•,52].

These studies may also provide some insight into mechanisms that promote neuropathic pain in diabetic rats, particularly where no effect on the behavioral responses of normal rats can be demonstrated. However, such intervention studies are unlikely to reveal the underlying pathogenic cascade that leads from insulin deficiency and hyperglycemia to hyperalgesia. There have been a number of recent studies that have measured sensory responses in diabetic rats after a prolonged period of treatment in either prevention or reversal paradigms and that may plausibly begin to address mechanisms of induction of painful diabetic neuropathy. These include a range of agents whose mechanism of action is clouded by concurrent effects in lowering blood glucose. Aside from these, some of the agents recently studied after protracted treatment are listed in Table 2 [34,36,51•,53–57].

Unfortunately, the majority of these prolonged treatment studies do not include assessment of the effects of acute treatment on indices of painful neuropathy so that it is not clear that antihyperalgesic actions are not related to lingering effects of the last treatment rather than any cumulative prevention or reversal of the underlying mechanism.

Mechanisms

The behavioral tests described earlier address different sensory modalities. It should not be assumed that all of the manifestations of sensory dysfunction equated with painful diabetic neuropathy share a common etiologic mechanism. For example, although hyperalgesia in the formalin and thermal tests is prevented by aldose reductase inhibitor (ARI) treatment, indicating a pathogenesis related to hyperglycemia and glucose metabolism by aldose reductase, tactile allodynia is not prevented by ARIs [51•,58]. There is emerging evidence that tactile allodynia and mechanical hyperalgesia in STZ-diabetic rats may not be a consequence of hyperglycemia at all, but rather of insulin deficiency. Mechanical hyperalgesia is detected in rats treated with STZ that showed incomplete β-cell ablation so that insulin levels were reduced but not by enough to induce hyperglycemia [59]. Further, low-dose insulin treatment regimens can alleviate tactile allodynia and mechanical hyperalgesia in STZ-diabetic rats without lowering blood sugar levels and also in STZ-injected but normoglycemic rats [59,60]. Because insulin has growth factor–like properties in sensory neurons [61] and can protect mitochondrial function during hyperglycemia [62], insulin deficiency may contribute to differing patterns of neuropathy, including allodynia and hyperalgesia, seen in animal models of type 1 and type 2 diabetes [32].

There is a widely held assumption that increased primary afferent sensitivity or activity is a major drive of many neuropathic pain states, including diabetes, and the ability of drugs acting adjacent to peripheral nerve terminals to rapidly alleviate mechanical hyperalgesia and tactile allodynia supports this concept [45,46•]. Quantification of

Table 2. Therapies that prevent or reverse allodynia or hyperalgesia in diabetic rats

Study	Treatment	Mechanism of action	Behavioral test
Daulhac et al. [53]	U0126	MAPK inhibitor	Mechanical hyperalgesia
Daulhac et al. [53]	SB203580	p38 MAPK inhibitor	Mechanical hyperalgesia
Daulhac et al. [53]	SP600125	JNK inhibitor	Mechanical hyperalgesia
Ilnytska et al. [54]	1,5-isoquinolinediol	PARP inhibitor	Tactile allodynia, thermal hyperalgesia, mechanical hyperalgesia, formalin hyperalgesia
Li et al. [36]	Taurine	Antioxidant	Thermal hyperalgesia, mechanical hyperalgesia
Zhang et al. [34]	GCPII	NAALADase inhibitor	Thermal hyperalgesia
Inkster et al. [55]	Allopurinol	Antioxidant	Tactile allodynia, thermal hyperalgesia, mechanical hyperalgesia
Kumar et al. [56]	Resveratrol	Antioxidant	Thermal hyperalgesia
Ramos et al. [51•]	ICI222155	Aldose reductase inhibitor	Thermal hyperalgesia, formalin hyperalgesia
Stevens et al. [57]	Nicotinamide	Various possibilities	Thermal hyperalgesia, mechanical hyperalgesia

GCPII—glutamate carboxypeptidase II; JNK—c-Jun N-terminal kinase; MAPK—mitogen-activated protein kinase; NAALADase—N-acetylated α-linked acidic dipeptidase; PARP—poly(ADP-ribose)polymerase.

Fos-immunoreactive neurons in the dorsal horn of the spinal cord has recently demonstrated increased basal expression in STZ-diabetic rats, which can be interpreted as a marker of increased spontaneous activity of nociceptive primary afferents, assuming that diabetes does not inherently alter local factors that modulate expression of the protein [40]. However, contradictory reports regarding altered spontaneous and evoked activity of primary afferents in STZ-diabetic rats have not entirely resolved this issue. Although electrophysiologic recordings in spinal cord slices from STZ-diabetic rats indicate an increased frequency of stimulus-evoked glutamatergic excitatory postsynaptic currents in dorsal horn neurons [63], the release of glutamate in the spinal cord of conscious free-moving rats following paw formalin injection was decreased rather than increased [64].

There is accumulating evidence that direct effects of diabetes on the spinal cord can modify sensory processing and contribute to behavioral indices of neuropathic pain. Prior reports of altered expression of a variety of neurotransmitter receptors [42] are now being augmented by functional studies suggesting a decrease of some of the intrinsic glycinergic and GABAergic inhibitory systems [63,64,65•] that could have the effect of amplifying sensory processing pathways. Further, it has become apparent that the efficacy of ARIs to prevent formalin-evoked hyperalgesia in diabetic rats is contingent on blocking activity of the enzyme in the spinal cord and not in the peripheral nerve [51•]. ARIs do not have acute antihyperalgesic effects when delivered to the spinal cord [66]. Their ability to prevent formalin-evoked hyperalgesia in diabetic rats is associated with prevention of increased cyclooxygenase-2 (COX-2) protein and activity levels within the spinal cord. Prostaglandin release in the spinal cord is involved in the spinal sensitization associated with many neuropathic pain states and is prolonged in diabetic rats after paw formalin injection [67]. Thus, it appears that local hyperglycemia in the spinal cord can promote spinal sensitization via increased flux through aldose reductase and subsequent induction of COX-2 and prostaglandin release.

Although the precise mechanisms involved in this pathogenic cascade remain to be resolved, it is interesting to note that aldose reductase is restricted to oligodendrocytes in the spinal cord, making them the likely site of the primary, hyperglycemia-induced, lesion [51•,68]. While the primary focus of research on neuropathic pain in diabetes to date has been guided by descriptions of the site of pain perception by patients, and therefore focused on the peripheral nerves, the direct involvement of oligodendrocytes suggests that the spinal cord and higher central nervous system may also be generator or amplifier sites for what is subsequently perceived as being located elsewhere. This is not entirely without precedent, as cases of phantom limb pain after amputation demonstrate [69,70].

Conclusions

Advances in clinical and basic research directed at neuropathic pain, and specifically the pain associated with diabetic neuropathy, have been slow in coming. However, recent developments are likely to promote significant new insights into pathogenic mechanisms and to offer patients better therapies.

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