Introduction

Animal Models of Peripheral Neuropathy: Modeling What We Feel, Understanding What They Feel

Joanna M. Brell

Almost everyone has experienced the severe discomfort associated with hitting the "funny bone," the pushing of the humerus distal medial epicondyle against the ulnar nerve. There is nothing amusing, however, about neuropathic pains and paresthesias that occur chronically, as with peripheral neuropathy. This issue of the *Journal* details the science of peripheral neuropathy as discovered through animal models. This introduction highlights the clinical description of peripheral neuropathy in order to center on the challenges of constructing animal models.

Peripheral neuropathy (PN) is a pervasive and complex condition affecting approximately 20 million people in the United States and more than 10% of persons aged 40 years or older (Gregg et al. 2004). PN encompasses a variety of etiologies and manifestations. The majority are acquired consequences of other conditions or processes. Table 1 summarizes some of the causes or contributors to PN. About one third of cases are considered to be idiopathic (Dyck et al. 1981). Many patients diagnosed with idiopathic PN have abnormal glucose tolerance tests or elevated fasting glucose levels and are considered to be prediabetic (Smith and Singleton 2013). Hypertriglyceridemia and obesity without diabetes also may be important etiologic or contributing factors in humans (Tesfaye et al. 2010) and rodents (Vincent et al. 2009). Diabetes mellitus is the most common identified cause of PN, and 60–70% of the current 26 million diabetics (Centers for Disease Control and Prevention 2011) have some degree of neuropathy. The increasing worldwide prevalence of metabolic syndrome and its associated conditions, including diabetes, suggest that PN will continue to be an important clinical subject. Mitochondrial abnormalities related to oxidative stress from hyperglycemia or hyperlipidemia are hypothesized to play an important role in diabetic PN (Picard and Turnball 2013; Sleigh et al. 2011). The use of pharmaceuticals (nucleoside/nucleotide reverse transcriptase inhibitors and cancer chemotherapy compounds) that target mitochondria is also associated with development or worsening of PN (Leung 2012; Xiao and Bennett 2012). Whether mitochondrial damage is a common mechanism in all PN remains to be determined. Without question, animal models will continue to be important in unraveling the pathobiology of PN.

The most common type of PN is distal symmetrical sensorimotor polyneuropathy, which occurs in diabetes, with diminished thermal and vibratory sensation leading to sensory loss and eventually involving pain and autonomic fibers (Tesfaye et al. 2010). With PN, clinical symptoms depend on the predilection of causative conditions to target particular peripheral fiber types (sensory, motor, autonomic, or different permutations of these three) and the type of stimulus that activates each nociceptor (e.g., thermal or mechanical). Assorted regions and functions of the peripheral neuron are affected, whether by direct injury or genetic predisposition, including dorsal root ganglion cation channel signaling (Staaf et al. 2009), axon transport (Holzbauer and Scherer 2011), and myelin sheath formation (Robinson et al. 2008). Clinically, a continuum of symptoms can occur, ranging from muscle weakness, spasticity, hyporeflexia, burning-type or aching pain, hyperalgesias, hypoalgesias, allodynia, dysesthesias, paresthesias, anesthesia in the hands and feet, poor proprioception, and hypotension to cardiac conduction abnormalities. Sensorimotor and sensory neuropathies occur more frequently than autonomic neuropathy, which may affect bowel function, bladder emptying, heart rate variation, and blood pressure controls. Human peripheral nervous system (PNS) perturbations lead to sensations that are episodic, paroxysmal, or constant, as well as evoked or spontaneous sensations, a spectrum of situations that render preclinical modeling problematic.

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Table 1 Example causes of and contributors to peripheral neuropathy

Metabolic
Diabetes mellitus (Juranek et al. 2013; O'Brien et al. 2013)
Hypothyroidism (Ørstavik et al. 2006)
Uremia/renal failure (Krishnan and Kiernan 2007)
Infectious
Human immunodeficiency virus (Brannagan et al. 1997; Mangus 2013)
Varicella zoster virus (Oaklander 2001; Steain et al. 2010)
Mycobacterium leprae (Truman et al. 2013; Visser et al. 2012)
Immune
Guillain-Barre syndrome (Kanda 2013; Soliven 2013)
Chronic inflammatory demyelinating polyneuropathy (Pollard 2002)
Toxic
Anticancer therapy (chemotherapy, radiation therapy) (Hausheer et al. 2006; Höke 2013)
Alcohol (Koike et al. 2003)
Arsenic (Vahidnia et al. 2007)
Nutrition
Deficiencies in vitamins B1, B12 (Ohnishi et al. 1980; Tefferi and Pruthi 1994)
Deficiencies in α-tocopherol (Sokol 1988)
Excessive doses of pyridoxine (B6) (Krinke et al. 1985; Rao and Sills 2013)
Traumatic
Extremity amputation (Flor et al. 2006)
Surgical (thoracotomy) (Wildgaard et al. 2009)
Inherited
Charcot-Marie-Tooth disease (Vavlitou et al. 2010)
Familial amyotrophic lateral sclerosis (Barret et al. 2011)
Acute porphyria (Lin et al. 2011)

Challenges in Modeling Neuropathic Pain

Although all symptoms are burdensome, neuropathic pain (NeP) clearly impacts patient function, even though symptoms of paresthesia and anesthesia may occur more frequently (Baron 2009; Xiao and Bennett 2012). Of the 116 million US adults with pain, approximately 18% have neuropathic-type pain (Toth et al. 2009). Poor quality sleep, depression, and anxiety are associated with chronic NeP (Turk et al. 2010). Neuropathic pain is related to high use of healthcare resources as well as decreased workplace productivity (Tölle et al. 2006). Molecular targets continue to be identified for pain manipulation, both centrally and peripherally; however, neuropathic pain has been notoriously difficult to control. NeP mechanisms are well reviewed in the pain literature (Von Hehn et al. 2012). The activation of nociceptors leads to the interruption of usual PNS signaling and includes events such as the ectopic firing of neurons, alterations in spinal cord circuits, and the subsequent changes in somatosensory cortex organization (Gustin et al. 2012). The cognitive aspects of human NeP allow for individual concepts of pain: the International Association for the Study of Pain makes this clear in their definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Loeser and Treede 2008). This differs from nociception, which is defined as "the neural processes of encoding and processing noxious stimuli" (Loeser and Treede 2008). Additionally, acute pain can evolve to chronic pain over time; however, the process is not as discernible as signs of acute pain, especially in animal systems (Farmer et al. 2012). Although PNS damage can be quantified in animal models and by clinical neurologic testing, more injury does not always equate with more pain or sensory symptoms (Baron 2009; Gilron et al. 2013), supporting the multifaceted dimensions of NeP.

Experienced human sensations are connected to external and environmental influences. For example, in chemotherapy-induced PN, many factors are weighed when considering whether the neuropathy is severe enough to warrant the discontinuation of potentially life-saving anticancer therapy. Figure 1 highlights the integration of pathophysiologic components of nerve damage and patient circumstances that influence symptom gravity and clinical decision-making. These oncology-related psychosocial issues include stage and prognosis of underlying condition, level of disability from the neuropathy, previous experience with pain, social support, economics, and employment status. In postamputation phantom limb pain, personal factors related to anxiety and stress influence patient pain scores (Ephraim et al. 2005). Thus, nerve damage is not the sole determing factor of the human neuropathic condition. This total patient experience informs preclinical research and suggests that animal models include some psychosocial aspects.

Higher cortical encoding of the transmitted peripheral nociceptive information is challenging to discern in animal models. Animal models are not as adept at recapitulation of human sensory conditions because animals do not have specific means to relay the quality of pain. Many models use nonspontaneous or evoked reflex reactions to simulate human pain; evoked and spontaneous pain may not use the same pathways (King et al. 2011). Because of animals' limited ability to discriminate allodynia and hyperalgesia, these human sensations have been considered by some researchers to lack animal correlates (Hansson 2003; King et al. 2011). Reflex testing models have not been reproducible and informative enough to lead to novel agents approved for neuropathic pain (Barrot 2012). Observable activities and behaviors in rodents, such as abnormal posture, changes in grooming, paw licking, aggressive behavior, and facial

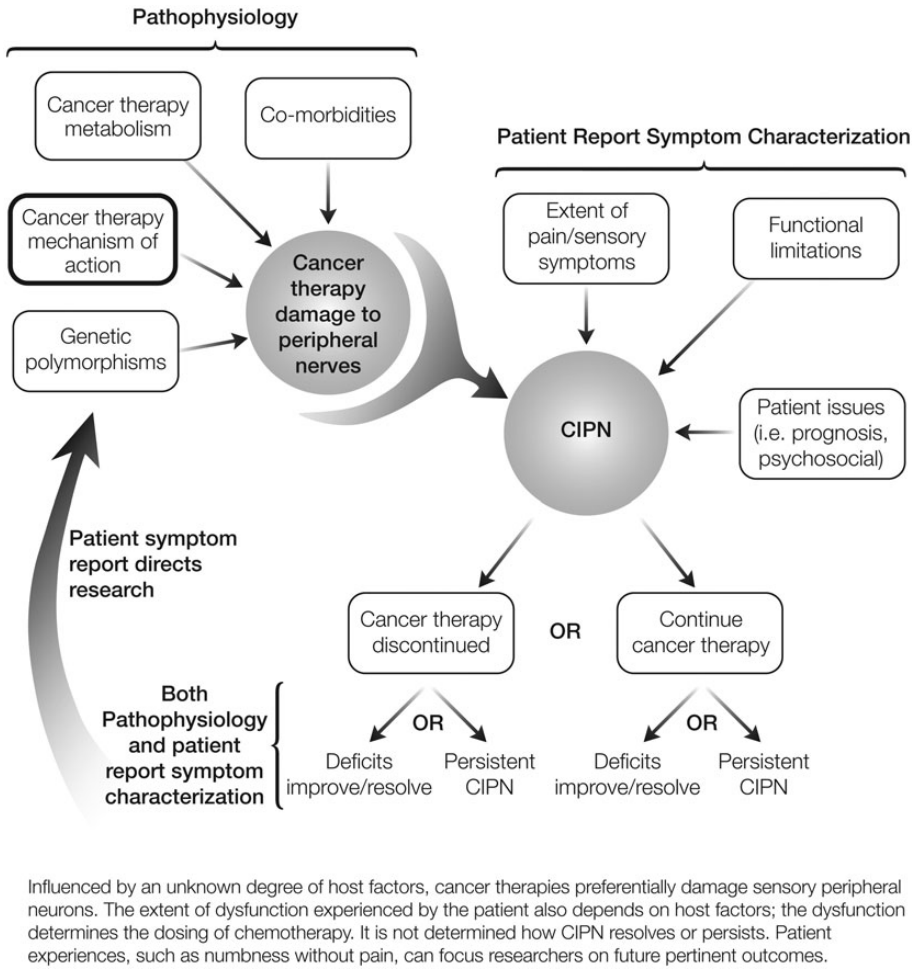

Figure 1 Components of chemotherapy-induced peripheral neuropathy (CIPN).

expressions, may reflect abnormal unevoked sensations and be usefully relevant to human PN. Correlation with specific human behaviors could be classified and validated for replication and interrogated for the concomitant molecular processes. Functional compromise, such as alterations in sleep cycles, social function, and cognition in response to neuropathy, should also be considered in future models (Barrot 2012). Experimental conditions could better emulate human clinical trial design with the goal of better informing human clinical studies. For example, although many studies have used one sex of animal, assessing both sexes may inform clinical sex differences in some NeP (Mogil and Chanda 2005; Monti et al. 2007). In addition, blinded assessments have been recommended for animal studies (Mogil 2009) as in human randomized controlled trials. The type of diet and the rodent strain have been shown to affect thermal hyperalgesia in partial sciatic ligation rats and heat sensitivity in the nonligated groups (Shir and Seltzer 2001). A neuropathic pain model is more than the inducement of nerve damage; optimal experimental design also includes the hypothesis-driven selection of species; animal age; husbandry; types of procedures tested; time after injury; and selection of measurements for spontaneous, operant, or complex behaviors (Mogil 2009).

Behavioral assessment would complement the sophisticated animal imaging, neurophysiologic tests, and assessment of exercise that are annotated in animals. Innovative behavior models, such as measurement of climbing activity in *Drosophila*, which has been shown to decrease with the addition of cisplatin and evidence of PN on histology examination, are being developed (Podratz et al. 2011). Confounding factors with models include the influences of stress, disease, or injury inflicted to create the PN model. The animals' usual functions, such as oral intake, can be interrupted as a consequence of the method of acquiring PN, impeding the actual neuropathy assessment. Beyond maintaining the health and comfort of laboratory animals, which is ethically imperative, it is also essential that animals are used only to conduct scientifically rigorous studies that will yield fundamental data. However, seemingly unfavorable consequences of model development could benefit the experiments if they mimic the comorbidities that occur in human neuropathy but do not incapacitate the animals. Some models of PN-associated diseases, such as leptin-deficient/obese mice (Drel et al. 2006; O'Brien et al. 2013) and 5T33MM multiple myeloma mice (Asosingh et al. 2000), are genetically and phenotypically relevant to the human conditions but have been challenging to

create and validate as NeP models. New assessment models that are validated to correlate with human spontaneous sensation will be breakthroughs in modeling human NeP (Barrot 2012).

Preclinical assessments of pharmacologic therapies for neuropathic pain and other facets of PN have rarely translated into United States Food and Drug Administration–approved beneficial drugs. The lack of approved agents for PN has fueled criticism about the validity of animal models for neuropathic pain. Neurokinin 1 receptor antagonists, which were eventually show to be inactive in human studies, are the most commonly cited example. Although analgesic activity with neurokinin 1 receptor blockade was highly supported in animal models, the primary hypothesis of substance P as the sole or primary neuropeptide for human pain transmission is confounded by the numerous other transmitters that seem to simultaneously regulate the sensation of pain (Hill 2000). Regardless, there currently are no substitutes for animals when assessing pain and other sensations, even though nonanimal models such as dorsal root ganglion and myelinated axon cultures and fabricated skin with sensors (Salowitz et al. 2013) have an important role in researching biology.

Although the predictive value of preclinical work in PN can be enhanced, the conduct of human trials could also be augmented. Suggested modifications of certain aspects of chronic pain clinical trial designs should improve confidence in analgesic clinical trial results, especially to insure that negative trials are truly negative (Dworkin et al. 2012). In some types of neuropathy, methods to obtain objective and generalizable human subject data by the use of patient-reported outcomes (PROs) have not been standardized. PROs are the patients' self-report of how they feel and function in the context of a medical condition or therapy for a condition, without any external interpretation. The majority of PRO instruments are questionnaires; PRO tools for neuropathic symptoms and pain have been used to describe responses to interventions as the primary outcome measures. However, not all of these are validated or provide complete information for either neuropathic pain or other neurosensory endpoints. Their inconsistent use across studies does not allow for cross-trial comparisons, hampering comparisons and data interpretation and illustrating the advantage of requisite agreement on some common measures. More objective and standardized definitions will tighten eligibility criteria to improve the reliability of clinical trial results. In chemotherapy-induced PN, efforts at clarifying the most informative measures and standardization are ongoing (Cavaletti et al. 2013).

Regarding NeP, the National Institutes of Health (NIH) Pain Consortium is a trans-NIH effort to encourage and advance all forms of pain research, including neuropathic pain, and to encourage partnerships between academia, industry, and government entities (http://painconsortium.nih.gov/). The Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public–private partnership with the US Food and Drug Administration promotes research and activities related to pain/NeP to ultimately develop efficacious analgesics that are safe and available to all patient populations (www.acttion.org/). Peripheral nerve symptom severity and chronicity have spawned patient advocacy groups such as the Neuropathy Association. This nonprofit organization provides patient support and education; another aspect of their mission is advancement of PN research (www.neuropathy.org). These groups ensure that the clinical burden of PN remains in the public forefront and is a research community priority.

Topics in This Issue

Accomplished animal researchers have depicted the best use of their models for PN in this issue of the *Journal*. Two articles focus on particular clinical conditions associated with PN: diabetes mellitus (O'Brien et al. 2013) and autoimmune disease (Soliven 2013). An additional two articles are concerned with neuropathy from infectious agents: human immunodeficiency virus (Mangus et al. 2013) and leprosy (Truman et al. 2013). Animal models to explore PNS toxicity as a result of environmental and chemical exposure (Rao and Sills 2013) and standard-dose chemotherapy (Höke 2013) are explained. *Drosophila* can model peripheral nerve degeneration (Freeman 2013), a consequence of some PN. International, national, and local institutional monitoring of laboratory animal welfare is clarified (Brabb et al. 2013), with illumination of NIH guidelines and resources for use and care of animal model research supported by the NIH (Brown et al. 2013). As outlined in this issue, animal models expand our knowledge of PN in conjunction with extension of technology and behavioral research.

Concluding Thoughts

The predictive ability of animal models will be enhanced by further collaborations among basic, translational, clinical, and behavioral scientists that focus on PN symptom perception by the models. Multiple types of models are necessary to investigate particular neuropathies. Clinical research priorities include the significant disability that results from anesthesia and paresthesias, in addition to NeP. Advances in the science of PN-induced neural degeneration will aid development of neuropathic disease–modifying agent strategies, such as regeneration. Prevention of PNS damage and, subsequently, abnormal sensation is the ultimate goal. If a common process for nerve damage is discovered, treatment/prevention strategies may still need to be specifically devised for each type of condition. For example, metabolic control of diabetes is feasible as potential prevention/treatment of neuropathy; however chemotherapy-induced PN must be prevented or managed while the insult on normal neuronal tissue continues with repeated doses of anticancer therapy. Animal models continue to provide a window to experienced symptoms and physiology and impact the translation of bench discoveries to the

bedside. In this issue of the *Journal*, researchers describe and refine their current models and, with new animal models, move neurosciences forward to impact patient care.

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