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ELECTROPHYSIOLOGICAL METHODS IN NOCICEPTION RESEARCH

A wide range of experimental models has been developed to elucidate the complex mechanisms underlying nociception, spanning from isolated cellular systems to whole organisms. In vitro methods, including heterologous expression systems and primary cell cultures, enable detailed investigation of the biophysical and pharmacological properties of nociceptive ion channels and receptors. Ex vivo preparations preserve native tissue architecture and critical intercellular interactions, offering a physiologically relevant environment for electrophysiological recordings. In contrast, in vivo rodent models integrate peripheral and central nervous system processes with endocrine, immune, and vascular influences to capture the full spectrum of pain behavior. Each of these approaches presents distinct advantages and limitations. As the level of biological organization increases–from in vitro to ex vivo to in vivo–the experimental conditions more closely mimic natural physiology, but they also introduce additional variables that can influence outcomes. Relying solely on a single method to study specific receptors or assess pharmacological effects may lead to incomplete or misleading conclusions. Therefore, a comparative analysis that integrates data from multiple experimental models is essential for obtaining a more objective and comprehensive understanding of nociception.

K e y w o r d s : ***nociception, sensory neurons, extracellular recording, patch-clamp, behavioral response to pain.***

Background

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Raja et al., 2020). The initial phase of pain perception, known as nociception, involves the transduction of harmful or potentially harmful stimuli into nerve impulses at the terminal ends of sensory neurons. The resulting pain signal–its intensity proportional to the frequency of action potentials–is relayed via the spinal cord to the brain, where it is ultimately perceived as pain.

Effective pain management is a critical concern in medicine, primarily relying on pharmacological interventions. Consequently, the discovery of novel analgesic agents remains an active and vital area of research. Experimental data on analgesic efficacy not only guide therapeutic development but also enhance our understanding of the molecular mechanisms underlying pain. Although genetic and electrophysiological studies have successfully identified key nociceptive receptors, the complex mechanisms of nociception in native sensory neurons continue to elude full characterization.

A diverse array of experimental assays is employed in pain research, spanning various levels of biological organization–from isolated proteins to intact organisms. *In vitro* cellular models, for instance, facilitate the investigation of specific molecular pathways but often fail to replicate the complexity of intercellular interactions. Techniques such as heterologous receptor expression in CHO cells, HEK293 cells, or Xenopus oocytes, etc. enable detailed examination of the activation mechanisms and pharmacological profiles of individual receptors and ion channels. Additionally, cultured dorsal root ganglion (DRG) neurons are widely used to investigate the functional properties of ion channels and G protein-coupled receptors, including TRPV1, ASIC, P2X, and P2Y. Research with these neurons has demonstrated that nociceptive signaling is regulated at multiple levels–through protein phosphorylation cascades, specific protein–protein interactions, calcium current modulation, and changes in gene expression–all of which contribute to the complex modulation of pain (Lacinova, 2022; Zhen et al., 2023). *Ex vivo* tissue models further incorporate intercellular interactions by maintaining the native tissue architecture. For example, intact nerve ganglia preserve the interactions between sensory neurons and glial cells (Tewari, Michalski, & Egan, 2024), while rodent skin-nerve preparations allow the study of interactions between sensory nerve terminals and keratinocytes (Erbacher et al., 2024).

In vivo rodent models of pain behavior offer the most comprehensive view by engaging multiple physiological systems, including the endocrine, immune, and vascular systems. Although these models provide a broader context for understanding pain, they also introduce complexity that can complicate data interpretation. Thus, each experimental approach to studying nociception has its distinct advantages and limitations, which must be carefully weighed during experimental design.

This review outlines the most prevalent methodologies for assessing nociceptive skin sensitivity in research laboratories. These methods encompass electrophysiological recordings from cultured neurons *in vitro*, measurement of single afferent activity *in vivo* and *ex vivo*, and behavioral

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assays in animal models. In addition, the review offers a critical analysis of the factors that influence the interpretation of experimental data in pharmacological research, thereby guiding the selection of appropriate methodological approaches for investigating specific mechanisms of sensory sensitivity.

Intracellular recordings techniques in pain research

Patch-clamp recordings on heterologous expression systems. Heterologous expression systems-such as HEK293 cells, Xenopus oocytes, and Chinese hamster ovary (CHO) cells-provide robust platforms for the study of a wide array of ion channels and receptors. These systems allow detailed investigations into the functional properties of these proteins, facilitating direct comparisons across species by enabling the analysis of human proteins and various mutants.

The patch-clamp technique, especially in voltage-clamp mode, is considered the gold standard for studying ion channels because it precisely measures ion flux or ionic currents through open channels. Among its various configurations, the whole-cell recording is most commonly used. This method monitors the activity of all ion channels present on the cell surface of an isolated cell while allowing precise control over both intracellular and extracellular solutions. Additionally, patch-clamp can be performed manually for detailed mechanistic studies in research laboratories or via automated systems for high-throughput pharmacological screening of chemical compounds against ion channels (Fig. 1).

Furthermore, heterologous expression systems facilitate the monitoring of intracellular ion concentration changes using fluorescent dyes (Jiang, & Roger, 2020), a technique that is also employed in high-throughput screening of chemical libraries. By expressing membrane proteins in non-neuronal cells, researchers can study the biophysical and pharmacological properties of individual transmembrane proteins in isolation, free from the confounding effects of other membrane structures. This isolation enhances experimental reproducibility but also represents a limitation; in native sensory neurons, nociceptive receptors and other membrane complexes operate within an integrated system for the perception, excitation, and transmission of sensory information (Grundy et al., 2018).

Patch-clamp recordings on primary cultures of rodent DRG neurons in vitro. Primary cultures of rodent dorsal root ganglion (DRG) neurons are extensively used to investigate signal transmission, ion channel and receptor dynamics, neurotransmitter release, intracellular ion visualization, and biochemical changes at the single-cell or network level. This *in vitro* approach addresses several limitations of *in vivo* experiments (Altinok et al., 2025; Lin, & Chen, 2018) while preserving many characteristics of the membrane proteins of native sensory neurons.

DRG cultures are particularly valuable for electrophysiological studies using the standard patch-clamp technique. Sensory neurons can be analyzed immediately following isolation or after several days in culture, offering flexibility in experimental design. Although receptor-channel complexes on the neuronal soma are assumed to mirror those on the nerve terminals, it remains uncertain whether their functional responses are identical. Additionally, similar to heterologous expression systems, ion influxes can be monitored optically using fluorescent dyes (Fig. 1).

Despite of many advantages, the method has notable restrictions. First of all, we cannot study human ion channels and receptors, which can have distinct from rodents pharmacological and biophysical characteristics. The process of establishing primary DRG neuron cultures involves enzymatic digestion and mechanical dissociation, which remove axons and satellite glial cells (SGCs) that normally function as integrated units with neurons in intact ganglia (Chen et al., 2022). This dissociation and axon removal induce phenotypic alterations and modify membrane excitability (Renthal et al., 2020). The loss of neuron-SGC interactions-integral to normal physiological functions and responses to pathological conditions such as chronic pain (Hanani, & Spray, 2020) – further compromises the physiological relevance of the cultured neurons. *In vitro* conditions can also alter the composition of neuronal membrane proteins (Bhave, & Gereau, 2004), further distinguishing cultured neurons from their *in vivo* counterparts.

Patch-clamp recordings on intact sensory ganglia ex vivo. Recording neuronal activity from intact sensory ganglia *ex vivo* enables the study of DRG neurons in their native environment while preserving the association between neuronal cell bodies, surrounding satellite glial cells, and the basal lamina of the sensory ganglion – a preservation not possible in dissociated DRG neuron cultures. Satellite cells envelop neuronal cell bodies completely (Chen et al., 2022), forming a metabolic barrier that not only protects and supports neurons but also establishes a microenvironment for neuroglial communication through the release of neurotransmitters and hormones, thereby modulating neuronal activity (Hanani, & Spray, 2020). Studies have shown that small neurons in intact DRG *ex vivo* exhibit a higher rheobase and input resistance compared to neurons cultured *in vitro*, suggesting that dissociation increases neuronal excitability (Gong, Ohara, & Jasmin, 2016). Moreover, neurons surrounded by satellite glial cells display a weaker response to adenosine triphosphate (ATP), glutamate, γ-aminobutyric acid (GABA), and bradykinin than those without glial coverage (Qarot, Guan, & Hanani, 2024).

This *ex vivo* method offers additional advantages. It allows axons to remain within the sensory ganglion and requires minimal enzymatic treatment, unlike complete dissociation *in vitro*. Intact DRG preparations from adult rats maintain good viability for 6–8 hours, providing a stable window for recordings. Extracellular electrophysiological recordings from a ganglion region can be performed using suction or metal electrodes, while individual neurons and glial cells can be studied using the patch-clamp technique. Furthermore, chemical stimulation of ganglion cells is feasible, as is stimulation of preserved afferent and efferent nerve roots using suction electrodes, which effectively mimics *in vivo* nerve fiber excitation.

However, this method does have certain limitations. The metabolic barrier formed by glial cells can impede the penetration of the patch pipette to the neuronal soma and restrict the diffusion of applied chemical agents. Additionally, the necessity to sever dorsal roots and spinal nerves during DRG removal compromises axonal integrity, which may introduce recording errors. Maintaining a consistent electrical potential between the neuronal soma and the axon is quite challenging leading to artifacts during voltage-clamp recordings. Finally, to access DRG neurons, residual connective tissue on the ganglion surface must be removed using proteolytic enzymes, which may inadvertently affect neuronal properties or result in excessive digestion of neurons in the superficial layers (Gong, Ohara, & Jasmin, 2016).

Extracellular recordings techniques in pain research

Recording electrical activity of afferents from the skin-nerve preparation ex vivo. The skin is the largest sensory organ, densely innervated by nerve endings that

form a continuous receptive field, transmitting information about touch, temperature, burning, itching, and pain to the central nervous system. This intricate innervation makes the skin an excellent model for both electrophysiological and pharmacological studies of primary sensory perception, performed *in vivo* and *ex vivo*.

One of the earliest approaches in electrophysiology was the extracellular recording of afferent nerve fiber activity in anesthetized animals. This method allows researchers to study nerve fibers within their natural physiological environment. However, a major challenge is the controlled application of substances directly to the sensory endings.

In contrast, the *ex vivo* extracellular recording technique offers enhanced control over the concentration of chemicals applied directly to nerve endings. Various skin-nerve preparations have been developed for rodents, typically involving the excision of a skin area along with its innervating nerve. The most common model uses the upper hairy skin of the hind paw in mice or rats, innervated by the saphenous nerve (Tkachenko et al., 2023; Zimmermann et al., 2009). Comparative studies have shown that recordings of saphenous nerve afferent activity, both *in vivo* and *ex vivo* over 12 hours, yield similar properties (Kress et al., 1992). This region is also a common site for subcutaneous formalin injections, which elicit a characteristic biphasic pain-related behavioral response during the formalin test *in vivo* (Scuteri et al., 2020). Notably, the biphasic pain response in rodents correlates with two distinct phases of nociceptive afferent activity observed in the rat skin-nerve *ex vivo* model (Hoffmann et al., 2022). This correlation allows direct comparisons between behavioral outcomes and nociceptive activity recorded *ex vivo*, as well as with data from *in vivo* and *in vitro* sensory neuron studies, thereby providing a comprehensive understanding of nociceptive mechanisms and pain sensitivity.

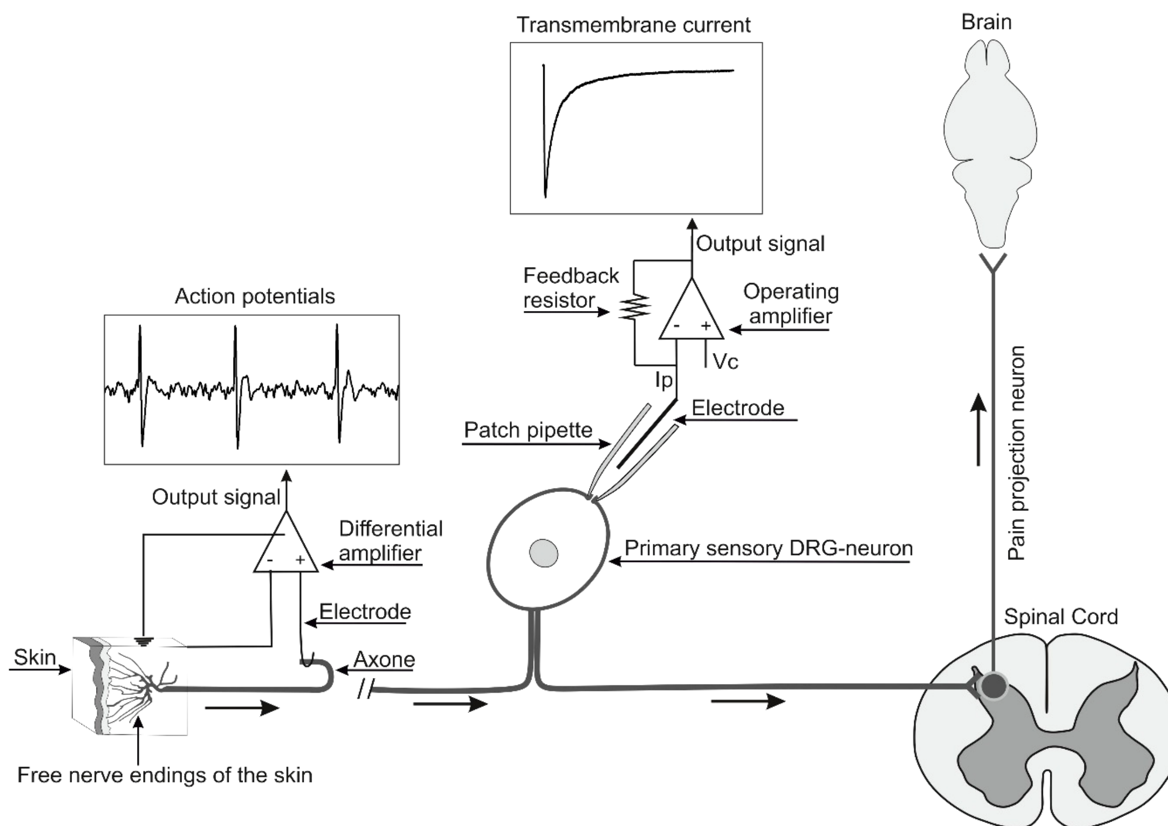

Fig. 1. The pain signal generated at the sensitive distal endings of axons in the skin and internal organs is transmitted via lightly myelinated Aδ-fibers and unmyelinated C-fibers to the synaptic endings of the central branch, where they form synapses with secondary neurons in the dorsal horn of the spinal cord. The signal is transmitted through these neurons along ascending pathways to the brain. Changes in the membrane potential of nerve fibers during the passage of nerve impulses (action potentials) along the axon can be recorded using a differential amplifier. The electrical activity of neuron somas can be measured using the patch-clamp method (a simplified schematic of a patch-clamp amplifier in voltage-clamp mode is provided)

The *ex vivo* recording method has significant advantages over *in vivo* approaches. It permits the precise stimulation of sensory receptive fields using controlled, quantitative stimuli of various modalities. Continuous perfusion of the skin ensures the accurate application of substances at defined concentrations and enables rapid solution exchange, facilitating controlled chemical stimulation during pharmacological tests. Although nociceptive axons in the keratinocyte layer form "naked" nerve endings, it remains unclear whether the receptor properties of sensory neurons recorded *in vitro* fully match those of native nerve endings embedded within the skin's natural architecture (Erbacher et al., 2024). Traditionally, these nociceptive endings were thought to function autonomously without specialized receptor cells; however, recent studies indicate that keratinocytes may actively participate in transmitting or modulating nociceptive signals (Tracey, 2017).

Recording single afferent nerve fiber activity from skin-nerve preparations *ex vivo* is a powerful tool for investigating the properties of sensory nerve endings, the

mechanisms underlying peripheral sensitivity, and the efficacy of analgesic drugs targeting nociceptive terminals. Although this technique successfully registers action potentials along nerve fibers, it does not allow direct measurement of electrochemical gradients or membrane potentials at the exact sites of action potential generation in the skin. Consequently, native peripheral nociceptive nerve endings remain inaccessible to direct measurement by the patch-clamp method.

Recording of neural activity from the skin-nerve-DRG preparation. The *ex vivo* mouse skin-nerve-DRG preparation is a sophisticated model that combines the strengths of patch-clamp and extracellular recording techniques, offering a unique opportunity to monitor the electrophysiological activity of dorsal root ganglion (DRG) neurons in a setting that preserves much of their natural connectivity. In this preparation, the intact skin along with its innervating nerve and attached DRG are maintained, which allows researchers to apply precisely controlled stimuli directly to the receptive fields of skin nerve endings while simultaneously recording neuronal responses. This dual recording capability facilitates detailed investigations into how sensory signals are integrated at the level of the DRG, capturing both the intrinsic electrical properties of the neurons via patch-clamp techniques and the overall afferent activity using extracellular methods (Ru et al., 2017).

One of the key advantages of this approach is its ability to preserve the natural microenvironment of the sensory neurons. Unlike dissociated cell cultures, the *ex vivo* preparation maintains the anatomical and functional relationships between neurons, satellite glial cells, and connective tissue, which is critical for understanding the integrative functions of intact DRG neurons. This model enables the study of complex interactions that contribute to sensory processing, including the modulation of neuronal excitability by surrounding glial cells and extracellular matrix components.

When this skin-nerve-DRG preparation is combined with *ex vivo* spinal cord segments, the entire pathway from peripheral sensory input to central signal processing is preserved. This integrated model is particularly valuable for investigating how peripheral afferent signals are transmitted to the spinal cord and for examining alterations in this pathway following pathological conditions such as spinal cord injury. For example, studies have used this combined preparation to characterize changes in afferent response properties and synaptic transmission after injury, providing insights into the mechanisms of pain and sensory dysfunction (Eller et al., 2022).

Despite its significant advantages and its status as one of the best models for studying nociception, the *ex vivo* skin-nerve-DRG and spinal cord preparation is technically demanding. The surgical procedures required to isolate and maintain the integrity of these tissues are complex and require precise dissection skills to preserve the functional connectivity of the sensory pathway. Additionally, the preparation must be carefully maintained under optimal physiological conditions to ensure viability, as any disruption can affect the accuracy and reliability of the electrophysiological recordings.

Overall, this integrated *ex vivo* model offers an invaluable tool for dissecting the complex mechanisms of sensory transduction and pain, bridging the gap between *in vitro* studies and *in vivo* physiology, while also posing significant technical challenges that must be addressed through meticulous experimental design and execution.

In vivo rodent pain models. Experimental models for evaluating analgesic effects employ behavioral assays that measure responses to noxious stimuli. Among these, acute pain tests are widely used to determine the reaction thresholds of experimental animals to high-intensity mechanical or thermal stimuli. Standard assays include the hot plate test and its analogue, the tail flick test, which assess thermal nociception (Raup-Konsavage et al., 2023), as well as the paw withdrawal threshold test, which measures sensitivity to mechanical stimulation (Zumbusch et al., 2024). Additionally, models that simulate prolonged peripheral injury or inflammation–such as the formalin test (Hoffmann et al., 2022) and carrageenan-induced paw edema–are utilized to study sustained nociceptive and inflammatory responses (Mancipe et al., 2023).

Despite their utility, interpreting data from these behavioral assays presents several challenges. It is often difficult to ascertain whether an analgesic agent exerts its effects on peripheral nociceptors or central neural circuits. Furthermore, distinguishing true analgesic action from sedative effects is problematic. Rodents, which are predominantly used in these studies, exhibit complex social behaviors, including emotional contagion and observational fear learning (Keum, & Shin, 2016). As natural prey species, they are predisposed to mask pain behaviors, thereby complicating the assessment of nociception.

To address these issues, it is essential to allow animals to habituate thoroughly to their testing environment and to minimize the visibility of the observer during experiments (Burkholder et al., 2012). Moreover, the localized administration of pharmacological agents poses an additional challenge. For example, subcutaneous injections, while effective in delivering substances to a specific skin area, may cause local tissue damage that alters nociceptor sensitivity (Steen, Issberner, & Reeh, 1995). Another complicating factor is the vasoactive nature of many pharmacological agents, such as bradykinin, histamine, and acetylcholine. When these substances are administered, particularly via arterial injection into the target region, they can induce vasoconstriction or vasodilation. Such changes in local blood flow can influence the distribution and concentration of the agent, potentially confounding the interpretation of the observed analgesic effects.

Discussion and conclusions

This review highlights a diverse array of experimental models for studying nociception, each providing unique insights into pain mechanisms while also exhibiting distinct limitations. *In vitro* approaches, including heterologous expression systems and primary cell cultures, enable precise investigation of the biophysical and pharmacological properties of ion channels and receptors such as TRPV1, P2X, and ASICs. These models offer excellent control over experimental variables and are particularly well-suited for high-throughput pharmacological screening to identify novel analgesic compounds. However, their reductionist nature omits critical intercellular interactions and the complex microenvironment characteristic of native tissues (Lacinova, 2022; Zhen et al., 2023).

Ex vivo tissue preparations, including intact ganglia, skin-nerve, and skin-nerve-DRG models, bridge the gap between *in vitro* and *in vivo* studies by preserving the anatomical and functional relationships among neurons, satellite glial cells, and surrounding connective tissues. These models enable more physiologically relevant recordings and allow the application of controlled chemical and mechanical stimuli directly to sensory nerve endings. Nevertheless, challenges such as limited tissue viability,

difficulties in maintaining axonal integrity, and technical constraints in accessing neuronal somata can impact data interpretation (Gong, Ohara, & Jasmin, 2016).

In vivo rodent pain models represent the most comprehensive approach to studying nociception, as they integrate peripheral and central nervous system processes along with contributions from the endocrine, immune, and vascular systems. Behavioral assays, ranging from acute tests like the hot plate and tail flick to prolonged models such as the formalin test, provide valuable insights into organism-wide responses to painful stimuli. However, the complexity of *in vivo* models introduces additional variables, including non-specific drug effects, stress responses, and the animals' innate tendencies to mask pain, which complicate the attribution of observed outcomes solely to analgesic efficacy (Mancipe et al., 2023; Raup-Konsavage et al., 2023).

The comparative analysis of these methodologies underscores a fundamental trade-off between experimental control and physiological relevance. While *in vitro* models excel in mechanistic detail and reproducibility, *ex vivo* and *in vivo* approaches capture the integrated responses of intact systems. Relying on a single method can therefore yield incomplete or potentially misleading conclusions. A multimodal strategy that integrates data from cellular, tissue, and whole-animal models provides a more robust framework for understanding nociception and evaluating the analgesic potential of pharmacological agents.

Future research should focus on refining these models and developing integrative approaches that reconcile discrepancies between experimental systems. Advances in technology, such as enhanced recording techniques and sophisticated imaging methods, promise to further our understanding of pain mechanisms. Ultimately, a comprehensive, cross-methodological approach is essential for translating preclinical findings into effective clinical therapies for pain management.

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ЕЛЕКТРОФІЗІОЛОГІЧНІ МЕТОДИ В ДОСЛІДЖЕННІ НОЦИЦЕПЦІЇ

Для вивчення складних механізмів, що лежать в основі ноцицепції, було розроблено широкий спектр експериментальних моделей – від ізольованих клітинних систем до цілих організмів. Методи in vitro, зокрема гетерологічні системи експресії та первинні клітинні культури, дозволяють детально досліджувати біофізичні та фармакологічні властивості ноцицептивних іонних каналів і рецепторів. Препарати ex vivo зберігають природну архітектуру тканин та критичні міжклітинні взаємодії, забезпечуючи фізіологічно релевантне середовище для електрофізіологічних досліджень. У свою чергу, моделі in vivo на гризунах інтегрують периферійні та центральні механізми обробки ноцицептивної інформації з впливами ендокринної, імунної та судинної систем, забезпечуючи комплексне відображення больової поведінки. Кожен із цих підходів має свої переваги та обмеження. Із підвищенням рівня біологічної організації – від in vitro до ex vivo і далі до in vivo – експериментальні умови стають більш подібними до природної фізіології, проте одночасно зростає кількість змінних, що можуть впливати на результати. Використання лише одного методу для дослідження певних рецепторів або оцінки фармакологічних ефектів може призвести до неповних або хибних висновків. Тому для об'єктивного та комплексного розуміння ноцицепції необхідний порівняльний аналіз, що інтегрує дані з різних експериментальних моделей.

К л ю ч о в і   с л о в а : ***ноцицепція, сенсорні нейрони, зовнішньоклітинний запис нервової активності, patch-clamp, больова поведінка.***

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