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THE ANIMAL MODELS OF PAIN

ŽIVOTINJSKI MODELI BOLI

Alagić-Džambić Larisa, Bečić F., Bečić Ervina, Rakanović-Todić Maida, Džambić M.

Abstract – According to International Association for Study of Pain, pain is uncomfortable sensory and emotional experience associated with actual or potential tissue damage. Pain can be a warning that protects the body from possible injury and raises some answers. Also, pain is important health problem. Pain studies are importantly affected by a wide range of modulatory factors including genotype, sex and social communication. All of these factors have to be taken into account when using animal models.

Key words**:** animal models, pain, chronic pain, inflammatory

Sažetak – Prema Međunarodnoj asocijaciji za bol, to je neugodno osjetno i osjećajno iskustvo, praćeno i povezano sa oštećenjem tkiva. Bol je zapravo upozoravajući mehanizam organizma, i kao takav predstavlja ozbiljan zdravstveni problem. Studije koje se bave proučavanjem boli uključuju različite faktore, kao što su genotip, spol i socijalizacija. Svi ovi faktori se moraju uzeti u obzir kada se koriste životinjski modeli boli.

Mr. sc. Larisa Alagić-Džambić, mr. ph., Bosnalijek d.d. Sarajevo, larisatravnik@gmail.com; dr. sc. Fahir Bečić, profesor, Farmaceutski fakultet Univerziteta u Sarajevu, fbph95@hotmail.com; mr. sc. Ervina Bečić, mr. ph. spec., Farmaceutski fakultet Univerziteta u Sarajevu, ervinafarmacy@gmail.com; dr. sc. Maida Todić-Rakanović, docent, Medicinski fakultet Univerziteta u Sarajevu, maida@dic.unsa.ba; Mirsad Džambić, dipl. ing. teh., Bosnalijek d.d. Sarajevo, dzamba2002@gmail.com

Larisa Alagić-Džambić, M. Pharm., MSc, Bosnalijek d.d. Sarajevo, larisatravnik@gmail.com; Fahir Bečić, PhD, Professor, Faculty of Pharmacy, University of Sarajevo, fbph95@hotmail.com; Ervina Bečić, M. Pharm., MSc, Faculty of Pharmacy, University of Sarajevo, ervinafarmacy@gmail.com; Maida Todić-Rakanović, MD, PhD, Assistant Professor, Faculty of Medicine, University of Sarajevo, maida@dic.unsa.ba; Mirsad Džambić, Tech. Eng., Bosnalijek d.d. Sarajevo, dzamba2002@gmail.com

Ključne riječi: životinjski modeli, bol, hronična bol, upala

Introduction

Pain experiments with human subjects have proven to be practically challenging, fundamentally subjective and ethically self-limiting. For these reasons, there is a need for use the animal models of pain. Pain is subjective in humans and interpretation of animal model results requires careful attention (18).

There are many examples where simple intuitive models predict with fair accuracy therapeutic efficacy in humans. By injecting chemicals into the paws of rats or mice and causing swelling and sensitivity, we can predict efficacy of drugs used to relieve inflammatory conditions in humans (for example, rheumatoid arthritis). Animal model should be similar to human disease by the following parameters: similar phenotype, a common cause, a similar pathophysiology and similar response to therapy, however, there are many difficulties in practice. For example, drugs were effective in animals but had no effect on humans. Psychiatric diseases are characterized by human-specific phenomena that are difficult or impossible to observe at animals. Also, the cause of many diseases in humans is unknown (5).

What exactly is an „animal model"? When animal models of pain are discussed, the confusion can result from the use of the single word „model" to refer to three distinctive entities: subject, assay and measure. The choice is crucial and depends on the purpose of the study. Animal models have been used extensively in basic pain research based on premise that these models can serve as surrogate assays that can reliably predict the potency and efficacy of the pharmacologic action and, in some cases, the molecular response to agents that work in human pain states (23, 29).

Accoriding to manuscripts published in *Pain*, there are four pain assays waves development:

1. Acute assay- classical assay developed in the middle of the past century based on human tests. It involves applying a noxius stimulus, which may be thermal, mechanical, electrical or chemical, to a conventional body part usually the hindpaws, tail or abdomen (19, 20).
2. Inflammatory assay- involves supraspinal organization such as formalin test.

Besides formalin, also used are capsaicin and carrageenan (4, 6).

3. Neuropathic assay- introduced in the late 1980´. The first model was called neuroma model.

This assay has been adapted for use in mouse to study orofacial pain (15, 27).

4. Painful disease assay- the first three assays were not similar enough to the clinical syndromes (9, 11). That is why this assay is more directly model-prevalent in clinical pain syndromes. This assay includes burn-related pain, cancer pain, chemotherapeuthic-induced neuropathic pain, labour pain,

pancreatitis pain, multiple sclerosis pain, post-operative pain, etc. (1, 14, 22, 25, 28).

Siddall et al. classified spinal cord injury pain (SPI pain) from spinal cord injury into two broad types (nociceptive and neurophatic pain), with three regions of pain (above level, at level and below level) (3).

Nociceptive pain is caused by stimulation of peripheral nerve fibers that respond only to stimuli approaching or exceeding harmful intensity (nociceptors), and may be classified according to the mode of noxious stimulation; the most common categories being "thermal" (heat or cold), "mechanical" (crushing, tearing, etc.) and "chemical" (iodine in a cut, chili powder in the eyes). Nociceptive pain may also be divided into visceral, deep somatic and superficial somatic pain. Visceral structures are highly sensitive to stretch, ischemia and inflammation, but relatively insensitive to other stimuli that normally evoke pain in other structures, such as burning and cutting. Visceral pain is diffuse, difficult to locate and often referred to a distant, usually superficial, structure.

Neuropathic pain is caused by damage or disease affecting any part of the nervous system involved in bodily feelings (the somatosensory system). Peripheral neuropathic pain is often described as burning, tingling, electrical, stabbing or pins and needles (24).

Short duration stimuli test- acute phasic pain

Acute test, such as hot-plate, tail flick and paw pressure tests, require a high-intesity stimulus, such as thermal, mechanical or chemical (2). Tail-flick method of D'Amour and Smith (1941) as modified by Dewey et al. (1970) using analgesiometar. Reaction time in seconds was used as the unit for measurment of pain and an increase in reaction time was indicative of analgesia. Time between placing the tail of the rat on the radiant heat source and sharp withdrawal of the tail is recorded as *reaction time* (13).

Another acute pain test that uses a thermal stimulus is the Hot-plate assay. The method is an adaptation of that described by Eddy and Leimbach (1953) and Atwell and Jacobson (1978). In this test, a rat or a mouse is placed in an open-ended cylindrical space with a floor capable of being precisely heated. The plated floor heated to an constant temperature, produces two responses measured in terms of their reaction times: paw licking and jumping (21).

The paw-pressure (mechanical hyperalgesia) test uses a pressure of increasing intensity applied to a punctiform area on the hindpaw or far less commonly on the tail. The application of increasing pressure is interrupted when the animal removes its tail, an action that is read out as force in grams for the threshold of response (16).

Long duration stimuli test- tonic pain

These tests use an irritant, foreign chemical agents as noncieptive stimulus. They are usually based on intradermal or intraperitoneal injections of the agent. Formalin, capsaicin or carrageenin can be used (26). Such long-term tonic pain in rats has been used to model human arthritis and to examine the safety and efficacy of various nonsteroid anti-inflammatory drugs (NSAIDs) including the COX-1 and COX-2 inhibitors commonly used by patients for inflammatory pain (7, 8). A 0.5 to 15% formalin, injected into the dorsal or plantar surface of the rat fore-or hindpaw, produces a biphasic painful response of increasing and decreasing intensity for about 60 minutes after the injection. Typical responses include the paw-being lifted, licked, nibbled or shaken (12). The initial phase of the response, which lasts 3 to 5 minutes is probably due to direct chemical stimulation of nociceptors (10). The second phase of this response starts about 15 to 20 minutes after the formalin injection and lasts 20 to 40 minutes. The intensities of these nociceptive behaviors depend on the concentration of formalin used. Opioid analgesics provide analgesia for both phases of the behavioral response, while agents such as NSAIDs only suppress the second phase (17).

Conclusion

These models have been used successfully to produce new drugs. Also, animal models are important for investigating pathogenesis. Animal models of pain play central role in analgesic drug development and the fundamental mechanisms that drive it. Final point is that analgesic drug development requires not only valid and reliable models of efficacy, but also valid and reliable models of toxicity, so that therapeutic indices might be accurately estimated. In summary, animal models have contributed much to the understanding of the mechanisms of pain and spasticity in humans.

REFERENCES:

1. Aicher SA, Silverman MB, Winkler CW, Bebo BF. Hyperalgesia in an animal model of multiple sclerosis. Pain. 2004; 110: 560-570.
2. Argoff CE. Pharmacologic menagement of chronic pain. J Am Osteopath Assoc. 2002; 102: 7-21.
3. Borsook D, Bacerra L. Phenotyping central nervous system circuitry in chronic pain using funcional MRI: considerations and potential implication in the clinic. Curr. Pain Headache Rep. 2007; 11: 201-207.
4. Caterina MJ, et al. The capsaicin receptor: a heat-activatedion channel in the pain patway. Nature. 1997; 389: 816-824.

5. Dale RR, Dale MM. Method and measurment in Pharmacology. Pharmacology. 2012; 89-97.
6. Dubuisson D, Denis SG. The formalin test: a quantitative study of the analgesic effects of morphine, meperidine and brain stem stimulation in rats and cats. Pain. 1977; 4: 161-174.
7. Fiorucci S, Antonelli E, Burguad JL, Morelli A. Nitric oxide-releasing NSAIDs: a review of their current status. Drug safety. 2011; 24: 11-801.
8. Giulianao F, Warner TD. Origims of prostagladinis E2: involvements of cyclooxygenase COX-1 and COX-2 in human and rat system. J Pharmacol Exp Ther. 2002; 303: 6-1001.
9. Hall GC, Carroll D, Parry D, McQuay HJ. Epidemiology and treatment of neuropathic pain: the UK primary care perspective. Pain. 2006; 122: 156-162.
10. Humnskarr S, Fasmer OB, Hole K. Formalin test in mice, a useful technique for evaluating mild analgesics. J Neurosci Methods. 1985; 14: 69-76.
11. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006; 367: 1618-1625.
12. Lariviere WR, Melzack R. The bee venom test: a new tonic-pain test. Pain. 1996; 66: 77-271.
13. Le Bars D, Gozariu M, Cadden SW. Animal models of nociception. Pharmacol Rev. 2001; 53: 597-652.
14. Lynch JL, Gallus NJ, Ericson ME, Beitz AJ. Analysis of nociception, sex and peripheral nerve innervation in the TMEV animal model of multiple sclerosis. Pain. 2008; 136: 293-304.
15. Malmberg AB, Basbaum AI. Partial sciatic nerve injuri in the mouseas a model of neuropathic pain: behavioral and neuroanatomical correlates. Pain. 2000; 76: 215-222.
16. Mary E. Common animal models for spasticity and pain. Jor Of Rehab Res and Devel. 2003; 40: 41-54.
17. McCormack K, Prather P, Chapleo C. Some new insights into the effects of opoids in phasic and tonic nociceptive tests. Pain. 1998; 78: 79-98.
18. Mogli JS, Davis DD, Derbyshire SW. The necessity of animal models in pain research. Pain. 2010; 151: 12-17.
19. Mogli JS, et al. Screening for pain phenotypes: analysis of three congenic mouse strains on a battery of nine nociceptive assays. Pain. 2006; 126: 24-34.
20. Mogli JS, Simmonds K. Pain research from 1975 to 2007: a categorical and bibliometric meta-trend analysis of every research paper published in the journal Pain. Pain. 2009; 142: 48-58.
21. O´Callaghan JP, Holzman SG. Quantification of the analgesic activity of narcotic antagonists by a modofied hot plate procedure. J Pharmacol Exp Ther. 1975; 192: 497-505.
22. Pacharinsank C, Beitz A. Animal models of cancer pain. Comp. Med. 2008; 58: 220-233.

23. Race A, et al. Animal models and prediction of efficacy in clinical trials of analgesic grugs. Pain. 2008; 139: 24-245.
24. Siddall PJ, Yezierski RP, Loeser JD. Pain following spinal cord injury: clinical features, prevalence and taxonomy. IASP Newsletter. 2000; 3: 3-7.
25. Tong C, Conklin DR, Liu B, Ririe DG, Eisenach JC. Assesment of behavior during labor in rats and effect of intrathecal morphine. Anesthesiology. 2008; 108: 1081-1086.
26. Tonussi CR, Ferreira SH. Rat kne-joint carrageenin incapacititation test: an objective screen for central peripheral analgesics. Pain. 1992; 48: 27-421.
27. Vos BP, Strassman AM, Maciewitc RJ. Behavioral evidence of trigeminal neuropathic pain following chronic constriction injuri to the rats infraorbital nerve. J. Neurosci. 1994; 14: 2708-2723.
28. Wright-Williams SL, Courade JP, Richardson CA, Roughan JV, Flecknell PA. Effects of vasectomy surgery and meloxicam treatment on faecal corticosterone levels and behaviour in two strains of laboratory mouse. Pain. 2007; 130: 108-118.
29. Yaksh TL. Spinal systems and pain processing: develpment of novel analgesic drugs with mechanistically defined models. Tips. 1999; 20: 37-329.

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