REVIEW ARTICLE

GENETIC INFLUENCES ON PAIN MECHANISMS

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ABSTRACT

The aim: To review the available results for genetic influences on pain syndrome development.

Materials and methods: In the period from 2009 to 2020, a total of 45 research papers describing the key points of genetic influences on pain mechanisms in both adults and children were published in Ukrainian and English and they are now included in the PubMed, EMBASE, Cochrane, and Google Scholar research databases.

Conclusions: Pain is a comprehensive characteristic of a person; therefore, it is inevitable that several genes with little individual effect interact with each other and environmental factors, influencing pain susceptibility and chronic pain syndrome manifestation. This requires searching for biomarkers for diagnosing and predicting the development of acute and chronic pain syndromes, especially in pediatric practice.

KEY WORDS: pain, pain genes, chronic pain

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INTRODUCTION

Pain is the main motivating factor forcing people to seek medical care and pain responses are characterized by significant interindividual differences. Over the past decade, there has been a significant breakthrough in the study of genetic aspects of nociception and pain management. Although genetic factors play an important role in the interindividual variability in nociception, there are other factors that influence the pain experience itself: mood, behavior, expectations, prior pain experience, gender, psychosocial and environmental factors. Understanding the role of the genetics is the first and most important step to explaining the discrepancy between pain threshold, pain tolerance and susceptibility to chronic pain.

Nociception, the process of perception of intense thermal, mechanical, or chemical stimuli by a subpopulation of peripheral nerve endings – nociceptor, is the ability of organism to detect damaged tissues. Nociception involves the four processes of transduction, transmission, modulation, and perception [1]. Nociceptive pain is generated by pin prick, touching hot objects, or exposure to any other chemical, thermal, or mechanical stimuli. Lack of the ability to experience nociceptive pain is catastrophic: damaged tips of fingers and toes, lips and tongues, reduced life expectancy, as witnessed in individuals with congenital insensitivity to pain due to rare recessive gene mutations resulting in either loss of the nociceptors or their functional disruption [2].

There are several levels of blocking the nociceptive signal: at the site of generation (transduction) with topical agents, local anesthetics, anti-inflammatory drugs, or by eliminating pain generator (amputation or organ removal, e.g., cholecystectomy); at the level of the paraaortic ganglia (the abdominal ganglion) with local anesthetics; at the site along the pathway of nociceptive pain transmission with regional anesthesia, nerve ablation (radiofrequency ablation), neuromodulation (invasive or non-invasive peripheral nerve stimulation); at the level of the spinal cord (transmission or modulation) with the subarachnoid block and intrathecal drug delivery systems, neuromodulation; at the level of the central nervous system with opioids, general anesthetics.

Nociception involves the following components: the nociceptors, mediators of inflammation; the nociceptive, antinociceptive and pain-modulating neuronal pathways and neurotransmitters; the neuronal ion channels; the neurotransmitter receptors and other messenger systems. They help in transmitting, conducting, and modulating noxious stimuli. Pain is a subjective emotional experience that results from a complex processing of noxious stimulus in the pain matrix. Functional genomics of pain is the study of genetic basis of pain, including the genetics of nociception, hereditary pain conditions (erythromelalgia, congenital insensitivity to pain), chronic pain conditions, genetic background of psychological factors that determine pain experience.

THE AIM

A large number of recent studies on pain require clear structuring. Genetic factors are important components that influence the occurrence and intensity of pain; therefore, the aim and objectives were to review the available results for the influence of genetic factors on the formation of pain processes.

MATERIALS AND METHODS

In the period from 2009 to 2020, a total of 45 research papers describing the key points of genetic influences on pain mechanisms in both adults and children were published in Ukrainian and English and they are now included in the PubMed, EMBASE, Cochrane, and Google Scholar research databases. Evidence review Following an extensive search of electronic databases, we included observational research, a systematic review and meta-analysis, randomized controlled trials, a prevalence study using a nationwide database, analysis of a family-based cohort and twin study covering genetic influences on the formation and perception of pain of varying intensity in patients with identical pathology or disease severity.

A pain gene has been described as 'a gene for which there are one or more polymorphisms that affect the expression or functioning of its protein product in a way that affects pain response.' Although some genetic studies have focused on pain in specific body sites and suggested possible genetic variants associated with pain phenotypes, the overall understanding of pain genetics remains unclear [3].

Current limitations in our knowledge include: the extent to which pain as a phenotype is determined by the additive genetic components, mainly presented by single nucleotide polymorphisms – SNPs); whether the genetic mechanisms of pain are different or similar in various body sites or in different disorders; whether the genetic relations between pain phenotypes and other common comorbidities are different or similar. Many pain phenotypes have been shown to be associated with depression and neuroticism in epidemiological studies. Understanding the genetic correlations between pain, depression and neuroticism may help elucidate the degree of their shared genetic architecture and become the basis for future causal inferences [4].

Catecholamines such as adrenaline, norepinephrine, and dopamine play a key role in the transmission and modulation of pain. Catechol-O-methyltransferase (COMT) is an enzyme that is involved in the breakdown of catecholamines and is a key regulator of pain perception, cognitive functions, and emotional state. Low COMT activity results in elevated catecholamine levels and, therefore, increased pain sensitivity [5, 6]. High dopamine levels result in the depletion of enkephalins, thereby leading to upregulation of opioid receptors and increased pain sensitivity. Three common haplotypes of the human COMT gene, which are divergent in two synonymous and one nonsynonymous position, code for differences in COMT enzymatic activity and are associated with pain sensitivity. They include the low pain sensitivity (LPS) haplotype, the average pain sensitivity (APS) haplotype, and the high pain sensitivity (HPS) haplotype which have been described based on four common single-nucleotide polymorphism genes encoding COMT [7]. COMT polymorphism has been found to affect RNA stability and protein translation [8]. The LPS phenotype demonstrated the greatest COMT activity, while the HPS phenotype exhibited the lowest. Even a single LPS haplotype has been found to decrease the risk of postoperative pain; it also affects the consumption of opioids [9]. In a study of postoperative pain and opioid consumption in children who underwent adenotonsillectomy, the carriers of the minor alleles were found to require more analgesic intervention as compared to heterozygous carriers of the major alleles [10, 11].

Rare conditions associated with pain have been identified by genetic mapping of family-based diseases caused by mutations in a single gene (the Mendelian gene.). Recognized hereditary syndromes associated with reduced pain sensitivity include channelopathy-associated congenital insensitivity to pain; loss-of-function mutations accompanied by the inability of the affected individual to feel pain [12]; hereditary sensory and autonomic neuropathy (HSAN) type I-V which is associated with a number of genetic anomalies and results in various patterns of sensory and autonomic dysfunctions, peripheral neuropathy [13]. These syndromes involve the loss of pain sensitivity or reduced pain sensitivity followed by other autonomic disorders and sensory deficit. Type IV is known as congenital insensitivity to pain with anhidrosis. Recognized hereditary conditions associated with pain intensification [14] include erythromelalgia and paroxysmal extreme pain disorder, familial hemiplegic migraine, hereditary neuralgic amyotrophy, hereditary pancreatitis. In addition to these rare Mendelian disorders, pain sensitivity is considered to change in approximately 50% of the general population due to genetic differences. A lot of genetic variants are associated with pain sensitivity [15].

The most common genes of pain are μ-opioid receptor (OPRM1), COMT, guanosine triphosphate cyclohydrolase-1 (GTPCH-1), transient receptor potential vanilloid type 1 (TRPV1), melanocortin-1 receptor (MC1R). Other genetic variants associated with changes in acute pain sensitivity include ADRB2, HTR2A, IL1RN, KCNJ6, MAOA, MAOB [16], P2RX7 [17]. Wide variability in gene expression and genetic polymorphism can explain some individual variations of acute pain and the efficacy of analgesia in this group of patients [18].

Effective perioperative pain control in children is often challenging; up to 50% of pediatric patients receive inadequate pain management and experience serious opioid side effects [19]. The choice of anesthesia administered to surgical patients includes regional anesthetic techniques and systemic analgesia, their combinations; it depends on the intensity of pain, the route of drug administration and planning the patient's rehabilitation period. Moreover, combinations of anesthetic agents may have various effects in different categories of patients (cancer patients, gynecological patients, trauma patients, neurosurgical patients, etc.) The algorithms for assessing pain and choosing the type of anesthesia administered to surgical patients, including pediatric patients, are not standardized as well.

Postoperative pain in children is still a serious problem as it often cannot be managed for a number of reasons. Prolonged postoperative pain leads to prolonging hospital stay, increasing treatment costs, extending the rehabilitation period. The intensity of acute postoperative pain, especially within the first 6 hours after surgery, is an important predictor of chronic

pain. *Severe acute pain occurring within the first postoperative month may develop into chronic pain [20].* Among patients with chronic pain, 22.5% of individuals note the association of pain with the surgical site. There is less evidence of postoperative chronic pain in children; however, a year after surgery, an estimated 20% of children experience pain in the spine and joints that is most likely due to an inadequate analgesia. A significant proportion of patients with postoperative chronic pain develop sensory anomalies that indicates a neuropathic component of pain development [21].

The best perioperative anesthesia is regional analgesia as it allows for quality pain management with minimal side effects. Local anesthetics act by blocking sodium channels and the mutations in the gene SCN9A encoding sodium channels demonstrate the resistance to lidocaine. Genetic variability is associated with the risk of local anesthetic toxicity as well. A κ-agonist such as buprenorphine can be substituted for a μ-agonist such as morphine in patients with an inactive OPRMI allele. This gene encodes one of at least three opioid receptors in humans; μ-opioid receptor (MOR). The MOR is the main target of endogenous opioid peptides and opioid analgesics such as beta-endorphin and enkephalins. The MOR plays an important role in addiction to other opioid drugs such as nicotine, cocaine, and alcohol through the modulation of the dopamine system. Several transcript variants encoding different isoforms have been found for this gene [22].

Abdominal wall surgeries account for 88% of all pediatric surgeries. To provide analgesia and protect from surgical aggression, due to psychological characteristics of children, general anesthesia is used; however, the main reason for using this type of anesthesia is that pediatric anesthesiologists have insufficient knowledge of the technique and methods of regional anesthesia due to the prevalence of the myth about excessive invasiveness of regional analgesia [23]. Analgesic efficacy of different types of regional anesthetic blocks has not been studied sufficiently. Peripheral nerve blocks can have advantages over central nerve blocks due to their safety and analgesia duration [24]. As the perioperative period may involve long-term and persistent opioid use, the application of regional anesthesia, as a part of multimodal pain management regimen results in reducing opioid use after surgery, thereby providing adequate postoperative analgesia as compared to opioids [25, 26]. According to the recently published data, peripheral nerve blocks were used only in 25.5% out of 12 million surgeries; regional anesthesia techniques were used in 3.3% of these cases only [27]. For success of regional anesthesia, it should be indicated correctly, block the target nerve, and use the appropriate technique and equipment [28]. In addition, regional anesthesia is, or should be, an integral part of any Enhanced Recovery After Surgery (ERAS) program, while opioids should be avoided, if possible, due to their unfavorable side effects [29].

REVIEW AND DISCUSSION

There are a wide range of responses to the administration of agents for postoperative pain management, depending on the patient's age, gender, race, anxiety level, surgery type, prior pain experience, and genetic factors. Two-thirds of the variability in the response to morphine and side effects are currently considered to result from genetic changes in both adults and children. Pain from the internal organs, muscles and bones is described as diffuse, often poorly localized as compared to well-localized pain signals coming from the skin. Visceral pain is rated as more unpleasant than somatic pain and is accompanied by a greater fear [30]. Consequently, it is becoming clear that bone pain and ischemic pain are accompanied by visceral pain. Ischemic pain and bone pain are believed to be transmitted through the afferent nerve fibers which, like visceral pain, are associated with the sympathetic afferent fibers, distributing themselves along the blood vessels [31]. *Transduction, modulation, and perception of visceral and somatic pain are very similar, with a few exceptions. Visceral and somatic pain, however, significantly differ in the transmission [32].* When assessing the impact of visceral pain on the patient's postoperative recovery, one should consider the interindividual variability in visceral pain intensity. Depending on the procedure performed, visceral or somatic pain may predominate. For example, after laparoscopic inguinal hernia repair, the most intense pain is diagnosed on the day of surgery, with visceral pain significantly dominating over superficial pain. As primary somatic pain subsides within the first few postoperative days, visceral pain increases, probably, due to the irritation and inflammation of the parietal peritoneum [33]. In uncontrolled acute perioperative visceral pain, it may progress into chronic pain. Prolonged aggressive stimulation of the internal organs and peripheral sensitization of the visceral nociceptors can result in central sensitization. So far studies on chronic pain have not differentiated acute visceral and somatic pain as a risk factor for developing chronic postoperative pain [34]. A high incidence of chronic pain syndrome is observed in minor and minimally invasive (laparoscopic) surgeries. Probably, physicians consider these surgeries as less painful and, therefore, patients receive inadequate pain management [6]. Chronic pain is pain that occurs on at least 50% of the days for 6 months or pain that persists for longer than 3 months [35].

Low awareness of pain mechanisms is accompanied by little or no treatment for underlying biochemical aberrations including nutritional deficiencies (5.2%), oxidative stress (0.7%), or metabolic abnormalities (0.1%). This is surprising considering the rapidly growing number of high-quality randomized controlled trial data that provide conclusive evidence that treatment with vitamin B, acetyl-L-carnitine, alpha-lipoic acid, coenzyme Q10 (CoQ10), N-acetylcysteine mitigates severe and persistent pain while improving body functions [36, 37, 38]. Some experts assert that chronic pain syndrome occurs in the presence of the three following factors: micronutrient deficiency, metabolic abnormalities, and oxidative stress. The studies have found that elevated homocysteine level causes inflammation by increasing the level of arachidonic acid and the proinflammatory production of prostaglandin E2 [39]. Elevated homocysteine level indicates a correlation between inflammation and chronic pain.

The search for pain biomarkers is now a top priority in pain medicine; however, it is very difficult to identify the objective biomarkers for such a subjective condition as pain [40, 41].

Pain is always subjective; it is an invisible and internal experience, while the neural circuits and biochemistry of the nociceptive pathways can be explored [42]. Today there is no perspective therapy for neuropathic pain management. Modern therapeutic regimens include tricyclic antidepressants, ion channel modulators (gabapentin, pregabalin, carbamazepine, lidocaine) and some anticonvulsants. However, this arsenal of drugs does not provide the expected efficacy and causes side effects. Opioids and other analgesics are considered as less effective in neuropathic pain management [43]. Peripheral nerve injury, traumatic brain injury, toxic neuronal death result in the release of endogenous toll-like receptor (TLR) agonists (fibronectin, gangliosides, mRNA, hyaluronic acid) in the spinal cord. These agonists activate astrocytes, Schwann cells, microglia, and macrophages via TLRs, which can result in the increased expression of proinflammatory mediators. In addition, TLRs located on the other cell surfaces may be involved in the development of pain hypersensitivity [44].

CONCLUSIONS

Today, there are limited clinical and experimental studies on the genetic and immune mechanisms of pain syndrome development. A thorough understanding of the genetic influence on pain response will allow for improving the diagnosis and management of pain. Currently, there are no clear biomarkers for diagnosing and predicting the development of acute and chronic pain syndromes, especially in pediatric practice. Lack of specific pain biomarkers makes impossible to determine the efficacy of pain management and predict disease progression. Further development of genomics and pharmacogenetics of pain will, probably, allow for formulating clear algorithms for diagnosis, management, and prevention of acute pain, as well as the mechanisms of chronic pain syndrome development.

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