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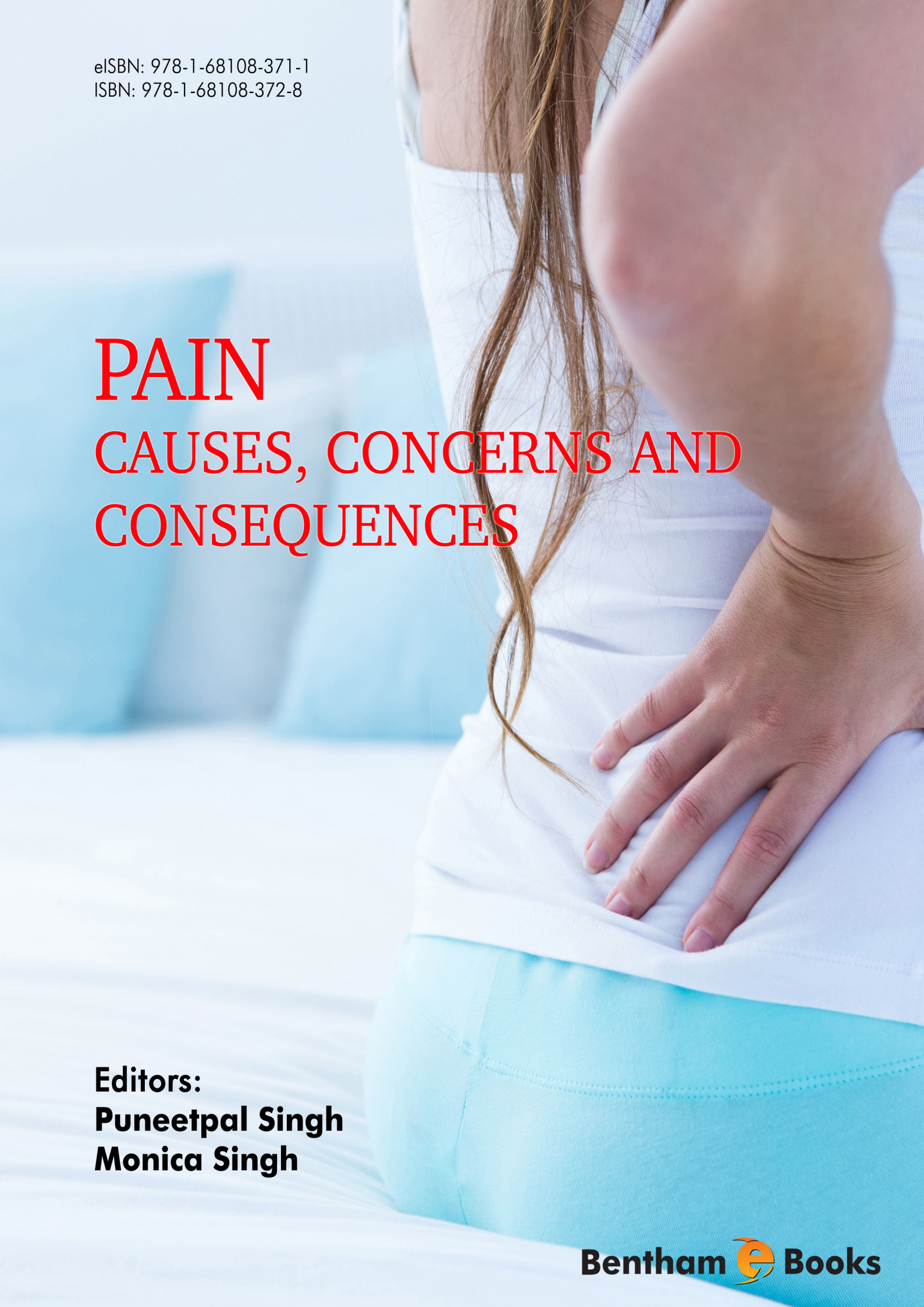

PAIN
CAUSES, CONCERNS AND CONSEQUENCES

Editors:
Puneetpal Singh
Monica Singh

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Pain: Causes, Concerns and Consequences

Edited By:

Puneetpal Singh
&
Monica Singh
Human Genetics Punjabi University
Patiala
India

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PREFACE

The present book is about pain, a vital part but an unwelcome guest in the corridors of human health. If we count the toll of human sufferings, the pain is the forefront perpetrator. It is metastasizing and has tethered directly or indirectly to almost every disease or morbid condition. Its realisation is different by anaesthesiologist on pre-operative condition, neurologist on migraine or headache, rheumatologist on arthritis and oncologist on cancer, however, complex and distinctive appraisals are proclaimed by different patients.

Scientist have exposed constellation of factors and started hunting down all those culprits which contribute but are still absconding from the scene of pain. The physiological, biochemical and genetic role in human pain has been delved, discussed and disseminated in clinical literature but many concerns are still to be unravelled.

This compendium, "Pain: Causes, Concerns and Consequences" is aimed to assimilate and harness scholastic knowledge from the scientists and researchers of high repute, who have been working in this domain of pain research. This treatise has positively brought state of the art knowledge in relation to prognosis and prophylactic measures of pain, which we surmise to be a valuable volume.

In the first chapter Dr. David shares his experiences of understanding pain as a clinician. He trudges along his memory lane and discusses the interdependence of clinician and researcher in the search of indepth perception of explained and unexplained pain. His professional journey as a special orthodontist proffers a novel way of tackling pain by employing not only classical but psychological ways and means.

Dr. Bai Chuang Shyu discussed that central post -stroke pain (CPSP) involves three hypotheses: central disinhibition, central imbalance and central sensitisation, which do not conflict with each other.

He puts forth that, although, neural substrates of CPSP are diverse, but cortical pain matrix (contra lateral somatosensory cortex, bilateral mid and posterior insula, interior insula and posterior cingulate cortex) regulates pain processing in CPSP. He concludes that [^{14}C] iodoantipyrine (IAP) data from the animal model of CPSP with lesions of ventrobasal complex of right thalamus indicate that during pain, significantly higher activation occurs in the medial prefrontal cortex (mPFC), interior cingulate cortex, thalamus, hypothalamus, amygdala and periaqueductal gray (PAG). He proposes that for, CPSP this novel idea of checking [^{14}C] IAP may be used for pharmacological and non- pharmacological interventions of CPSP.

Third chapter emphasises the psychological issues in cardiac and non-cardiac chest pain. In emergency departments and intensive cardiac care units (ICCU), the most common symptoms of these patients are psychological stress, fear and anxiety. If remain unaddressed, these symptoms may lead to worst outcomes with severe ramifications. Psychotherapy especially cognitive and behavioural interventions can substantially lower the pain developed as a consequence of psychological distress.

Fourth chapter presents the facts and figures of several genes that participate in different phases of pain. Pain being a complex manifestation is perceived, processed and promulgated first and foremost through genetic endowment of the individual whereas, physiology, psychology, sociology and environment, later appear on the scene. It is acknowledged in this chapter that the idea of personal medicine for managing pain, based on the genetic profiling of the individual is possible in near future.

Dr Przekop writes about the causes and concerns of chronic non-cancer pain (CNCP) especially when coexisted with substance use disorder (SUD). He professes that, in formulating the treatment plan for CNCP and SUD the concomitant factors of one's psychology, sociology and physiology should be taken care of, so that the patient becomes an active participant in the treatment of his or her chronic pain.

Fifth chapter emerges out from a query that whether microRNAs (miRNAs) play role in pain pathophysiology and targeting them can be useful in managing pain. The chapter diligently explores the role and relevance of miRNAs in anti-nociceptive therapeutics. Apropos to the query, the chapter reveals that understanding the miRNA expression profile in almost every component of somatosensory system from peripheral neurons to higher central system, plays promising role in modulation of pain perception.

Dr Muthuraman investigates the analgesic potential of 7-hydoxy-4-methyl-coumarin (HMC) in acrylamide induced pain in rats. By conducting acrylamide induced nociceptive pain sensation and biochemical estimation, he documents that pre-treatment of rats with HMC and cyclosporine; ameliorate the acrylamide induced changes in biochemical and behavioural parameters in dose dependent manner.

He suggests that this ameliorative effect of HMC is because of its antioxidant, anti-lipid peroxidative, calcium ion regulatory and mitochondrial permeability transition pore inhibitory action.

We are deeply indebted to Ms. ShalluKhullar for her extended help in style editing of the book. We extend our heartfelt gratitude to Mrs. Humaira Hashmi, Editor In-charge, eBook department and Editorial Manager Publications, Ms. Hira Aftab, Incharge Publications, Ms. Maria Baig, Manager Publications and especially Mr.MahmoodAlam, Director Publications,

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Dr. Puneetpal Singh
Department of Human Genetics
Punjabi University, Patiala, India
Dr. Monica Singh
Department of Human Genetics
Punjabi University, Patiala, India

List of Contributors

Andrew Chih Wei Huang	Department of Psychology, Fo Guang University, Yilan, Taiwan, Republic of China
Arunachalam Muthuraman	Neuropharmacology Division, Department of Pharmacology and Toxicology, Akal College of Pharmacy & technical Education, Mastuana Sahib, Sangrur 148002, Punjab, India
Bai Chuang Shyu	Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, Republic of China
David S. Basser	53 Bennetts Road Mountain River, Tasmania 7109, Australia
Harjot Dhillon	Department of Human Genetics, Punjabi University, Patiala, India
Hsiang-Chin Lu	Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, India
Jaspreet Kaur	Neuropharmacology Division, Department of Pharmacology and Toxicology, Akal College of Pharmacy & technical Education, Mastuana Sahib, Sangrur 148002, Punjab, India
Masoumali Masoumi	Professor of Cardiac Surgery, Bistoon Hospital, Kermanshah, Iran
Mozhgan Saeid	Cardiac Rehabilitation Center, Imam Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
Muthusaamy Ramesh	Neuropharmacology Division, Department of Pharmacology and Toxicology, Akal College of Pharmacy & technical Education, Mastuana Sahib, Sangrur 148002, Punjab, India
Peter Przekop	Betty Ford Center, Rancho Mirage, CA 92270, USA, Departments of Pediatrics, Neurology, and Psychiatry. Loma Linda University School of Medicine, Loma Linda, CA 92350, USA
Puneetpal Singh	Department of Human Genetics, Punjabi University, Patiala, India
Saeid Komasi	Cardiac Rehabilitation Center, Imam Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran
Yogita K. Adlakha	Cellular and Molecular Neuroscience, National Brain Research Centre, Manesar-122051, India

DEDICATION

Our Parents and Dear Son Bunny

CHAPTER 1

Pain: A Clinician's Journey

David S. Basser*

22 High Street New Norfolk, Tasmania 7140, Australia

Abstract: Pain is a percept: it is an unpleasant sensory and emotional experience, a product of the brain's abstraction that might be considered an activity mediated event: the activity being the message and pain the messenger warning of imminent or actual injury or imbalance yet to be avoided or resolved. There are no 'painful stimuli' that is stimuli that invariably elicit the perception of pain in all individuals and it is this highly individual and subjective nature of pain that makes it difficult to define and to treat clinically. The key to understanding and therefore appropriate treatment is in deciphering the message. Recognising and respecting the interdependence of both the clinician and researcher in the search for deeper discernment proffers the potential for synergistic evolution in understanding and treatment with the promise of bringing relief to many sufferers of both explained and unexplained pain.

Keywords: Allodynia, Central sensitisation, Chronic pain, Clinical application, Clinical experience, Global syndrome, Idiopathic pain, Neural activity, Neuroplasticity, Occlusion, Orofacial pain, Pain, Patient centred, Persistent pain, Precision medicine, Psychoneuroimmunology, Psychosocial, TMD.

INTRODUCTION

Pain and suffering are integral to the transformative journey that is life. In humans pain may be initiated at the physical, psychosocial and/or spiritual level(s) and experienced at any one or combination of these levels.

* **Corresponding author David S. Basser:** Specialist Dentist, 22 High Street New Norfolk, Tasmania 7140, Australia; Email: dbasser@ozonline.com.au.

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PART 1

Pain: a Clinician's journey

There is an abundance of information in the scientific literature, the relevance of which is often beyond the scope of understanding of the general clinician. Likewise much of the clinical experience and effectiveness of the clinical generations is not part of the scope of conception of the general scientific researcher. In an age, demanding evidence based biomedicine, it would seem prudent to afford equal respect to the expertise developed in both clinical and research areas and acknowledge, through action, their interdependence to affect mutual synergistic evolution. This then may re-establish the balance, as called for by Besedovsky and Del Rey [1], between deduction and induction, analysis and synthesis (the essence of science) in biomedicine. Benjamin Moffett [2], Professor of Orthodontics at the University of Washington, School of Dentistry, afforded much respect in 1978: he stated, "As a professional scientist working in dentistry for the past 25 years, I have been impressed by the progress, which clinicians make with time in solving their patient's problems. These advances are often accomplished empirically without prior benefit of needed biological data from non-clinicians. Such gains are hard fought victories and are slowly recognized both within and outside the profession for several reasons. They are usually founded on individual clinical experience – a process that is not easily evaluated by others. Also the biological significance of these clinical advances is often obscured by the emphasis which clinicians naturally place on clinical procedures. But for those who are willing to learn from the trials and errors of others, the resulting insights are rewarding ... Because I am not a clinician ... you may be wondering why I opened the paper with a purely clinical observation. My reason is that when asked for a biological appraisal ... I ask the clinician in turn 'Does it work at the clinical level?' Whether a procedure or concept succeeds clinically is a big factor in determining its biological validity ... my question should (then) be (not if but) 'Why does it work?'"

I come to an understanding of pain having directly experienced two generations of clinical expertise in resolving patient's acute and chronic orofacial pain, the latter usually being classified as "idiopathic" or, to quote Woolf [3], "unexplained

clinical pain".

In 2002, I embarked on a scientist's path in the quest for an explanation of the "unexplained". In November 2004, whilst completing a library based research paper in fulfilment of a unit for the formal neuroscience degree in which I was enrolled, I happened upon a theoretical explanation; the result of a distillation of the scientific literature combined with the experience and deliberations of two generations of clinicians. In line with Moffett's commentary, the paper (in a slightly updated form) did not find publication until 2012 [4]. Here, I present an updated theoretical understanding of pain based upon the clinical and scientific experience of the intervening years.

Pain; A Theoretical and Applied, Integrative Clinical and Research Understanding

"The sensation we call pain – pricking, burning, aching, stinging, and soreness - ... is a submodality of somatic sensation like touch, pressure and position sense and serves an important protective function. It warns of injury that should be avoided or treated. Pain is a percept: it is an unpleasant sensory and emotional experience... a product of the brain's abstraction and elaboration of sensory input... there are no 'painful stimuli' – stimuli that invariably elicit the perception of pain in all individuals"... thus... "The highly individual and subjective nature of pain is one of the factors that make it difficult to define and to treat clinically" [5].

All pain, might be considered an activity mediated event: the activity being the message and pain the messenger warning of imminent or actual injury or imbalance yet to be avoided or resolved. The key to understanding, and therefore appropriate treatment, will be in deciphering the message. When attempting to do so, it should be remembered that pain is not a site specific phenomenon, but a perception of activity mediated by the neural pain matrix which comprises a vast interrelated network of peripheral and central neural components acting as a functional unit [4].

From a neuroscientific perspective there are two aspects to consider, the pain threshold and the level of activity. The pain threshold might be thought of as an activity switch, the parameters of which are unique to each individual, being

CHAPTER 2

Functional Brain Circuitry in Central Post-stroke Pain

Andrew Chih Wei Huang[1], Hsiang-Chin Lu[2] and **Bai Chuang Shyu[2,*]**

[1] *Department of Psychology, Fo Guang University, Yilan, Taiwan, Republic of China*

[2] *Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, Republic of China*

Abstract: Central post-stroke pain (CPSP) results from lesions or dysfunction of the spinothalamocortical pathway. Pathophysiological mechanism of CPSP may include contralateral somatosensory cortex or bilateral mid- and posterior insula, anterior insula, posterior cingulate cortex and spinothalamocortical pathway. Our [^{14}C] iodoantipyrine data from animal model of CPSP indicated that significantly higher activation occurs in the medial prefrontal cortex (mPFC), anterior cingulate cortex, thalamus, hypothalamus, amygdala and periaqueductal gray (PAG). We propose a neural correlation hypothesis of CPSP, in which the mPFC-amygdala pathway, hypothalamus and PAG interact with each other and the spinothalamocortical pathway, resulting in the manifestation of CPSP symptoms. These symptoms can include depression, anxiety, motor disturbances and cognitive dysfunction in thalamic stroke patients, in addition to CPSP. Alterations in different brain activation and circuitry connections in CPSP may help in understanding the pathophysiological mechanisms underlying multiple aspects of CPSP symptoms. Such novel ideas may be applied to develop pharmacological and non-pharmacological interventions for CPSP.

Keywords: CPSP, Nociceptive stimuli, Spinothalamocprtical pathway.

INTRODUCTION

Based on the definition of the International Association for the Study of Pain, central pain is attributable to primary lesions or dysfunction of the central nervous system [1]. The clinical characteristics of central pain are severely confounded by

* **Coresponding author Bai Chuang Shyu:** Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, Republic of China; Email: bmbai@gate.sinica.edu.tw

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the characteristics of peripheral pain, with the exception of the location of neuropathic damage in the central or peripheral nervous system [2]. Distinguishing between central pain and peripheral pain is important, in which damage or dysfunction of spinothalamocortical mechanisms is critical for central pain but not peripheral pain [3]. Despite the distinctions between central and peripheral pain, "deafferentation pain" is suggested to be common to both central and peripheral pain. Both types of pain involve deficits or decreases in sensory inputs to the nervous system; thus, they share some clinical characteristics [4]. The essential characteristics of central pain consist of dysesthesia or paresthesia, persistent or paroxysmal pain, and spontaneous or evoked pain. When central pain is caused by stroke, with damage or dysfunction of the central nervous system, central pain is referred to as central post-stroke pain (CPSP) [5].

1. CLINICAL SYMPTOMS OF CENTRAL POST-STROKE PAIN

Previous studies thought that CPSP results from thalamic lesions, referred to as thalamic symptoms [6]. However, recent findings have shown that CPSP is also associated with extra-thalamic lesions [7]. The prevalence of CPSP is uncertain. Klit *et al.* [6] reported prevalence between 1% and 12% whereas another study reported it to be 8-35% [5]. Although the prevalence of CPSP is diverse, it appears to be > 8% in stroke patients. The cardinal symptoms of CPSP include pain that is attributable to impairments in the spinothalamocortical pathway. This impairment of the spinothalamocortical circuitry is resulted in the neuropathic pain. In general, peripheral sensitization and central sensitization are two major neuronal mechanisms underlying the neuropathic pain. Previous evidences have reported that the noxious stimuli may sensitize the peripheral nervous structure resulted in sensitization development, wind-up or expansion of receptive fields of nociceptive neurons. Moreover, molecules such as prostaglandin and bradykinin have been seen as pain mediators to affect peripheral sensitization and peripheral pain. These molecules are resulted from the tissue damage or inflammation, and they are suggested to involve peripheral sensitization and hyper-activation from peripheral signaling of sensory neurons. CPSP is primarily due to the central

sensitization mechanism. Hyper-excitability of the central neuronal circuitry in the central pain involves abnormal neurotransmission of glutamate, substance P and nitric oxide. Central sensitization can be reduced by the brain GABA receptor agonism or the glutamate (such as NMDA) receptor antagonism. GABA or NMDA categories of drugs have been developed to treat CPSP patients. For example, carbamazepine, which was a typical antiepileptic drug and GABA receptor agonist, are frequently used to reduce abnormal hyperactivity for the involvement of central neuronal disinhibition. Ketamine is another treatment method for CPSP that is one of NMDA receptor antagonists. It was evident that intravenous ketamine administration can effectively reduce the CPSP symptom. In addition, oral administrations of ketamine can alleviate dysphoria when using to combine with oral diazepam. On the other hand, pain perception may be spontaneous or evoked. In spontaneous pain, some cases present a continuous way and some are shown a paroxysmal way. Regardless of continuous or paroxysmal conditions, patients with CPSP often suffer from sensations of burning, aching, squeezing, pricking, lacerating, shooting, throbbing, heaviness, and cold. Evoked pain in CPSP is caused by nociceptive or non-nociceptive stimuli. Nociceptive stimuli can induce hyperalgesia in punctuate and thermal conditions. Non-nociceptive stimuli elicit allodynia in thermal, static, and dynamic conditions. Therefore, allodynia and hyperalgesia are likely important features of CPSP symptoms.

In addition to pain symptoms, some psychological, social, and physiological functions are also impaired in patients who suffer from stroke hemorrhage and consequently CPSP [8]. For example, previous studies showed that stroke hemorrhage patients may present motor dysfunction and clinical depression [9, 10]. Patients with stroke hemorrhage have been shown to present affective and apathetic symptoms, such as anxiety and depression [11]. Moreover, clinical data have shown that patients with thalamic lesions exhibited cognitive dysfunction [12]. After focal thalamic lesions, explicit memory and implicit memory can also be impaired [13]. Moreover, amnesia was present following thalamic hemorrhage [14]. Quality of life and motivation also deteriorate after stroke. Patients with CPSP may present blunting of thought processes that affects mood and intellect and produces neurotic tendencies [15]. Additionally, patients with CPSP have an

CHAPTER 3

The Role of Psychological Factors in Cardiac and Non-Cardiac Chest Pain

Masoumali Masoumi[1], Mozhgan Saeidi[2] and **Saeid Komasi[2,*]**

[1] *Cardiac Surgery, Bistoon Hospital, Kermanshah, Iran*

[2] *Cardiac Rehabilitation Center, Imam Ali Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran*

Abstract: Chest pain as a common symptom in general population is considered to be the second most common cause of presentation to emergency departments of medical centers. Such pains are categorized broadly into cardiac chest pain (CCP) *vs.* non-cardiac chest pain (NCCP). In patients with cardiac diseases, the main symptoms of psychological reactions to pain include psychological stress, fear and anxiety, pain resulting from anxiety, and anxiety and depression as a result of pain. Furthermore, there is a relationship between perceived psychological factors and the psychological distress, and sustained NCCP could lead to the development of depression, stress and low mental quality of life. Controlled clinical trials on treating CCP and NCCP have shown that these relatively extensive interventions have been effective in reducing psychological distress, periods of chest pain frequency, and lowering functional problems.

Keywords: Angina pectoris, Cardiac chest pain, Cardiovascular diseases, Cognitive - behavior therapy, Non-cardiac chest pain, Psychological distress, Psychological factors, Psychotherapy.

INTRODUCTION

Since life-threatening events in patients with or without established cardiovascular diseases (CVDs) occur suddenly, chest pain experience could be horrifying for

[*] **Coresponding author Saeid Komasi:** Cardiac Rehabilitation Center, Imam Ali Hospital, Kermanshah University of Medical Sciences, Shahid Beheshti Boulevard, Kermanshah, Iran; E-mail:S_komasi63@yahoo.com

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anyone [1]. Chest pain as a common symptom in general population is considered to be the second most common cause of presentation to emergency departments (ED) of medical clinics and hospitals [2]. In the US, six million patients present to ED annually. This imposes over eight billion US$ on healthcare system [3]. Chest pain, with a life time prevalence of 39%, affects the quality of life of suffering patient severely and results in decreased working ability, physical exercise and serious sleep problems [4 - 7]. Chest pain, especially as it may herald serious cardiac conditions like heart attack, cause nervousness and consequently lead in apparent complaining by patients [8]. Chest pain presents itself in various forms such as phrictopathic sensation, hot flashes, tingling, pressure sensation, and choking. It also varies in terms of duration and severity [9]. Such pains are categorized broadly into cardiac chest pain (CCP) *vs*. non-cardiac chest pain (NCCP).

CARDIAC CHEST PAIN (CCP)

Cardiovascular diseases (CVDs), as one of the most common conditions, are responsible for disability in 151 million patients and death in 17 million cases of the world population. Even though 14% of disabilities and 30% of mortality cases in developed countries are attributed to CVDs, about 82% of disabilities and 75% of death cases in developing countries are the result of such diseases [10]. One of the symptoms of cardiac disease is chest pain which is considered as one of the most prevalent cause of presentation of patients to cardiovascular clinics [11]. CCP are usually the result of acute coronary syndrome (ACS), myocardial infarction (MI) or ischemia, aortic dissection, pericarditis, cardiac arrhythmias, anxiety and panic attacks.

The pain of MI, myocardial ischemia, pericarditis, and greater vessels disease are considered as one of the most common causes of CCP. The pain of MI or myocardial ischemia happens when the required oxygen of the myocardium is not supplied. But infectious pericarditis pain always involves the surroundings of the pleura and cause pleuritic pain in patients. This pain aggravates with inspiration, coughing, and bodily position change. However, in patients with vascular diseases, acute aortic dissection causes a sudden, tearing, and severely distressing pain [12]. Pain is a mental phenomenon associated with unpleasant feelings and

causes distress. Pain-related complaints are the most common symptoms experienced by patients [13].

Epidemiology

Annually, seven million Americans present to ED because of acute chest pain. About 15-25% of such presentations are due to CVDs [12]. The prevalence of angina pectoris increases with aging in both males and females and it is estimated that 2-4% of adult population in the Europe experience CCP [14]. According to Modi *et al.* (2015), of patients who admit in ED because of chest pain, less than 50% are discharged in a short time and only 7.2% of those who are admitted have CVDs [15]. In another study, it has been reported that in 9.6% of the cases, the cause of chest pain is CADs [16].

Etiology

CCP is the result of decreased blood supply by coronary arteries or increased demand for oxygen by the myocardium [17]. The most common cause of acute chest pain in patients with CVDs is MI or myocardial ischemia and happens when enough oxygen is not supplied to the heart [12]. This pain which can be continuous or intermittent is known as angina pectoris. Angina can be affected by factors other than cardiac diseases such as psychological factors.

Cardiac Chest Pain and Mechanism of Pain

Chest pain, while having many etiologies, is generally considered to be most lethal when related to a cardiac cause [18]. Cardiac chest pain or angina pectoris can be either acute or chronic and usually is a result of imbalance between myocardial oxygen supply and myocardial oxygen demand. Atheroma formation and atherosclerotic plaques seem to affect coronary flow, given that multivessel flow-limiting obstructions are observed in patients with chronic coronary syndrome. In addition, morphological changes of diseased arteries related to significant atherosclerosis, such as vascular remodeling may also result in stable angina or claudication [19].

Although, angina pectoris has a variety of physiological correlates, including the type of triggering activity, the severity of ischemia or ventricular dysfunction,

CHAPTER 4

Genetic Explorations of Pain

Harjot Dhillon and **Puneetpal Singh***

Department of Human Genetics, Punjabi University, Patiala-147002, India

Abstract: Pain is the most prevalent form of human health malady which, if remain unaddressed, exerts formidable impact. Pain research has tried hard to unravel the possibilities in the direction of diagnosis and management of pain conditions, but knowledge of genetic consequences of pain is still in infancy. During pain, sensory input is realized, processed and regulated, first and foremost through ones genetic composition and then different characters of physiology, psychology, sociology and environment come in the scene. The present exposition demonstrates the precise details of various genes and genetic variants that participate in different phases of pain and pain conditions, disseminating an idea that in future, diagnosis and treatment of pain by harnessing indepth genetic knowledge has startling revelations in store for us.

Keywords: Chronic pain, Conduction, Genes, Modulation, Synaptic transmission, Transduction.

INTRODUCTION

Pain is a complex sensation where sensory, affective and cognitive dimensions of pain alongwith parallel neural networks in brain are associated with constellation of factors. Though pain occurs to show protective gesture, but when it surpasses threshold, exerts debilitating effect upon health and triggers concomitant physiological and psychological concerns of perilous ramifications. Right from the activation of primary afferent nociceptors upto the cortical processing of the pain in the higher regions of the brain, pain trajectory can be dissected into transduction, conduction, synaptic transmission and modulation.

* **Coresponding author Puneetpal Singh:** Department of Human Genetics, Punjabi University, Patiala; Email: singh.puneet@rediffmail.com

Besides, environmental, behavioral and psychological risks involved, all these stages of pain sensitivity, severity and analgesic responses are mediated by different sets of genes and genetic variants.

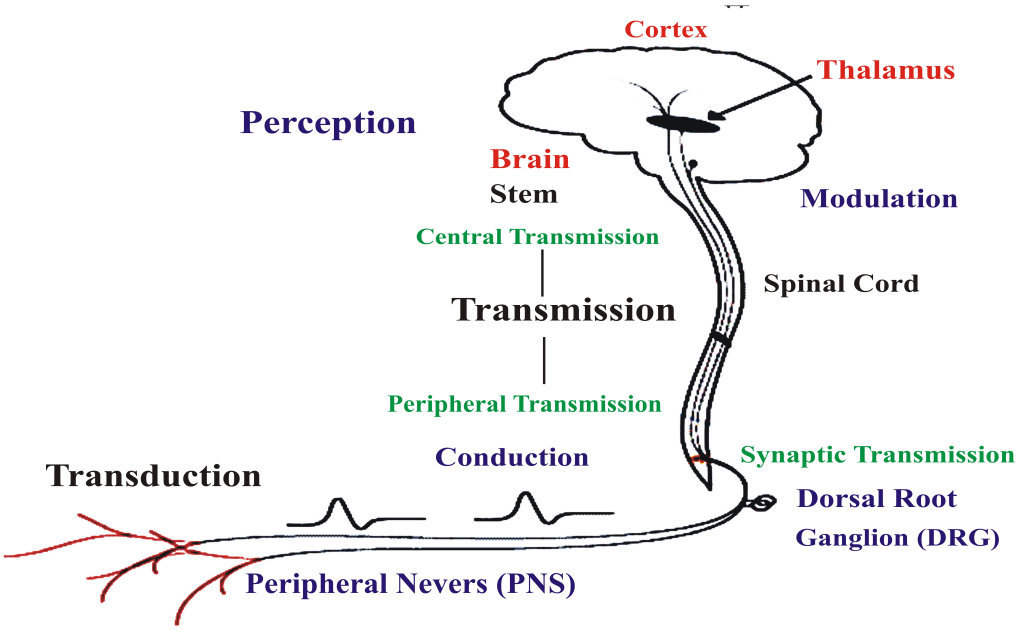

Fig. (1). Showing different phases of pain

1. TRANSDUCTION

Transduction marks the cardinal process for the pain realization. It involves detection of noxious stimuli by the peripheral nociceptors by sensing various substances such as substance P, bradykinin, *etc.* leading to the depolarization of the neurons causing generation of a receptor potential [1].

Heat Pain

The nociceptors detect four major types of noxious stimuli namely; heat, cold, mechanical and chemical. The detection of these various types of stimuli is further regulated by numerous genes. Amongst the most studied one in relation to heat related sensitization are the transient receptor potential (TRP) family genes. TRP

family is a calcium gated channel protein family comprising 6 subfamilies; TRPA, TRPV, TRPM, TRPML, TRPP and TRPL. While the majority of TRP gene family members detect specific types of noxious insults, some of them are polymodal in function. A class of TRP gene family; TRPV1 is activated by both heat and capsaicin found in hot chilli pepper [2]. It is highly associated with detection of thermal, mechanical and pH shifts. The polymodal function of TRPV1 has been confirmed by various gene knockouts, siRNA knockout and inhibition studies [3]. In human, TRPV1 Met315Ile and Ile585Val polymorphism has been examined and Met315lle is found to be associated with greater susceptibility to chronic neuropathic pain [4]. TRPV1 acts in close amity with Protein kinase beta type II (PKCβII), as the activation of the latter by TRPV1 causes phosphorylation of Thr705, setting the pain and itch thresholds below normal ranges [5]. TRPV1 also regulates calcitonin gene related peptide (CGRP) functioning as TRPV1 knockouts show enhanced metabolism and longevity due to suppression of CGRP activity [6].The TRPV1 knockout shows reduced thermal sensitivity while TRPV2 knockout shows normal function. Surprisingly, 1911A>G (rs8065080) polymorphism is found to be associated with cold hypoalgesia, less heat, pin prick and mechanical hyperalgesia, whereas, 1103C>G (rs2222747) is associated with reduced cold hyaesthesia. None of the TRPV polymorphisms give impaired functions, suggesting its indirect linkage to pain *via* somatosensory abnormalities than direct function in pain [7]. In a complex manner, inflammatory mediator bradykinin enhances mechanical pain through Purinoreceptor 2X (P2X2,3) receptors mediation, and upregulates TRPV1 activation and Adenosine triphosphate (ATP) production *via* keratinocytes, Nerve growth factor (NGF) signaling *etc.*, thus causing mechanical hyperalgesia [8, 9]. However, inflammation induced hyperalgesia involves several other inflammatory mediators besides bradykinin alone [10].

Following the footprints of TRP gene family, Anoctamin 1(ANO1), a calcium activated chloride channel senses heat related pain detection. It depolarizes the neuron, causing generation of action potential. Animal studies confirmed its role in propagating heat stimuli, but not mechanical noxious stimuli by gene knockout, tail flick tests and chemical inhibition methods [11, 12].

CHAPTER 5

Non-Pharmacological Treatment Options for Coexisting Chronic Non-Cancer Pain and Substance Use Disorder

Peter Przekop[1,2,*]

[1] *Betty Ford Center, Rancho Mirage, CA 92270, USA*

[2] *Departments of Pediatrics and Psychiatry, Loma Linda University School of Medicine, Loma Linda, CA 92350, USA*

Abstract: Chronic non-cancer pain (CNCP) presents significant challenges to physicians and when combined with co-occurring diseases such as substance use disorder (SUD) the challenge becomes magnified. It is important that the physician realizes that both CNCP and SUD are diseases of the brain, mind, body, and spirit and, therefore, consideration of the whole person and their life experience is essential. In formulating a treatment plan, the physician should remember the cognitive and emotional changes that have occurred as a result of the disease's effect upon the and mind. The proper treatment of the patient should also include treatment of chronic stress and its consequences. The physician should be aware of the alternative modalities such as mind-body, psychosocial, and technology based treatments. Many are available to the patient locally and can also be accessed through the internet. Physicians who treat complex CNCP patients should begin to implement these modalities in a comprehensive treatment plan that restores balance to the patient with CNCP and SUD and allows the patient to become an active participant in their care.

Keywords: Brain, Chronic non-cancer pain, Cognition, Mind-body therapy Nociceptor, Substance use disorder.

[*] **Coresponding author Peter Przekop:** Betty Ford Center, 39000 Bob Hope Drive, Rancho Mirage, CA 92270, USA; E-mail: pprzekop@llu.edu

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INTRODUCTION

Many physicians are faced with difficult challenges when treating chronic non-cancer pain (CNCP) and the many occurring processes that it is associated with. This situation has become somewhat easier since new research that has occurred over the last two decades has made it clear that CNCP is a fundamentally different disease process when compared to acute pain. Indeed, CNCP is a disease process in which the brain has transformed, reorganized, and has become capable of generating pain spontaneously [1 - 3]. It is now clear that CNCP is very complex which explains why the simplistic Cartesian approach in which a peripheral nociceptive input is treated is ineffective [4 - 6]. Effective treatments must consider the mind, brain, body, and spirit [7]. The current lack of such treatments has left many physicians in a difficult position especially those who treat patients with CNCP and co-occurring substance use disorder (SUD) [8].

This apparent gap in treatment options can be filled by alternative treatment options which range from mind-body therapies, to psychosocial treatments, to technology based therapies, all of which can offer healing to complex CNCP patients. These treatments are effective and popular because they support healing as opposed to chronic disease management, add balance, and well-being, and are devoid of adverse effects [7]. An estimated 62% of Americans take advantage of them [9, 10].

The Scope of the CNCP Problem

CNCP confers considerable suffering to many and is currently at epidemic levels [11]. An estimated half of all patients with SUD also have CNCP [12]. Patients with CNCP and SUD are very difficult to treat with conventional Western medicine, generally pharmacologic methods because they seek help for much more than just physical pain [13, 14]. Most suffer from co-occurring anxiety, symptoms of depression, chronic stress, multiple problems, and the culmination of adversity they have and do suffer from [15]. Most of these patients will be improperly selected for chronic opioid therapy in an attempt to relieve their suffering. However, historically, they have been excluded from opioid clinical trials [16] and thus, there is virtually no evidence to guide opioid-based treatment

choices [17]. To complicate matters, it is essential that CNCP is adequately treated in these patients because 60% of them report that pain significantly contributes to the development of SUD [18]. Moreover, effective treatment has been shown to normalize the changes which occur in the brain as a result of CNCP [19].

The Patient with CNCP and SUD

When approaching the patient with CNCP and SUD it is important for the physician to realize that the brain, mind, body, and spirit have been transformed and reorganized. The structural, functional, and connectivity changes of the brain have been extensively reported [20 - 22]. The reorganization of neural networks involved in goal-directed behavior, attention, internal surveillance, emotional regulation, and the ability to enjoy natural rewards have all resulted in significant changes [21] in the patient's ability to think, regulate emotions, regulate behavior, and maintain a positive outlook [23, 24].

Patients with CNCP and SUD have biased acquisition and processing of information that distorts thinking and continues to activate and sustain both disease states. The patient has lost attentional control and attention has been captured by the pain signal which makes it difficult to disengage attention from drug related cues. This results in a bias towards pain-related and drug-related cognitions. In addition, self-referential thought focuses on poor health and poor well-being further contributing to a loss of emotional regulation. Therefore, emotions are negatively valanced and thinking is skewed towards prolonged suffering, poor self-efficacy, pain catastrophizing, and fear of future pain [25].

These factors manifest in the patient as increases in the perception of pain and increases in the areas of the body in which the pain manifests. On days in which the above symptoms are especially severe the patient's perception of physical pain worsens. All is exacerbated by increases in acute and chronic stress.

Patients with both CNCP and SUD report high levels of current suffering and 96% of these patients report a history of unresolved adversity [17, 23, 26]. This results in a dysregulated chronic stress response [27, 28]. Patients display poor coping and report a lack of optimism [25]. In approaching these patients all of

CHAPTER 6

MicroRNAs: The Tiny Robust Players Unraveling the Multifaceted Channels of Pain

Yogita K. Adlakha*

Cellular and Molecular Neuroscience, National Brain Research Centre, Manesar-122051, India

Abstract: Pain is a debilitating condition which is the leading cause of cognitive, mood and anxiety disorders. It is one of the major medical burdens on human health which obstructs the quality life of a person as the appropriate therapeutic solution is not available. Due to advancement of new genomic technologies, it is now possible to view genome wide changes during chronic pain in different cell types from the somato-sensory system to the neurons in central nervous system. Tremendous research over recent years has enlightened the magical potential of small non-coding RNAs, mainly microRNAs in modulating numerous pathophysiological processes including proliferation, apoptosis and oncogenesis. They target a wide range of molecules and refine their protein output and thus, fine tune distinct cellular processes including pain signaling. Recently, animal models depicting inflammatory and neuropathic pain and patient subjects complaining distress due to pain have shown deregulations of miRNAs in affected tissues and systemic circulation. Although various painful conditions *viz*. spinal cord injury, peripheral nerve injury, cancer and inflammatory diseases have been recognized with genome-wide changes in microRNA signatures, yet the gene regulatory networks underlying pathological significance of individual microRNAs are sparsely studied. Hence, this chapter summarizes the latest findings addressing the role of microRNAs in various inflammatory or neuropathic pain conditions. How can miRNA research be expedited in revealing new aspects of pain pathophysiology is also addressed. The chapter also uncovers the novel potentials of miRNAs as well as roadblocks in the path of miRNA based anti-nociceptive therapies.

Keywords: DRG, miRNA, Nociceptive pathway, Pain, Spinal cord, TG.

* **Coresponding author Yogita K. Adlakha:** Cellular and Molecular Neuroscience, National Brain Research Centre, Manesar-122051, India; E-mail: yogita@nbrc.ac.in

Puneetpal Singh (Ed.)

INTRODUCTION

Although pain is one of the fundamental alarming systems of the body yet chronic pain may devastate the quality of one's life, leading to disturbances in the cognitive and emotional functions. Thus, human disorders associated with the chronic pain including osteoarthritis (OA), post-herpetic neuralgia, diabetic polyneuropathy and migraine represent a large socioeconomic burden. Although recent research has provided fundamental insights into pathological pain, yet effective therapeutic treatments are least available till date. In recent years, accumulating reports have introduced a novel entity in pain that is known as microRNAs (miRNAs) for being small, functional non-coding RNAs in nature that have been playing an instrumental role in regulating pain-processing in various pain settings ranging from experimental models to clinical pain disorders [1 - 4]. These studies have provided the basic understanding for the development of microRNA therapeutics for the treatment of pathological chronic pain in future. The main objective of this chapter is to discuss various implications of miRNAs in pain and to explore ways to expedite the miRNA research in pain pathophysiology. Attention has also been paid to exploring opportunities for the development of miRNAs as a therapy for chronic pain.

Pain

Pain is such an unpleasant feeling which cannot be described in words. It is an obnoxious sensation that is not only associated with sensory experience due to actual or potential tissue damage but also with the elements which alter cognitive and emotional circuitry [5]. Pain can be categorized into two types depending upon the length of stimulus: acute and chronic. Acute pain lasts till the applied stimulus and resolves promptly, thus functions as a central alarming system for the body and protects from damage [6]. However, chronic pain is devastating and outlasts the period of initial injury and thus reduces patient's quality of life. Therefore, there is an urgent call for effective clinical intervention for such unfortunate pain. However, till date, therapeutic solutions are distant from sight due to the hindrance by large numbers of mediators and signaling pathways in the etiology of pain and presence of functional redundancy between them [6]. Further, pain can be divided into two groups depending upon the type of stimuli:

Nociceptive and Neuropathic pain. Nociceptive pain is initiated by signals from damaged tissues or injury which get transferred through peripheral nerves to the brain *via* the spinal cord. This type of pain works as an alerting system for the organism and prepares organism against potential damage. Mostly back, leg and arm pains are nociceptive pains. However, aberrations in somatosensory system can cause damage or disease in the nervous system which is the root cause of neuropathic pain [7]. Chronic neuropathic pain is completely pathological and does not have beneficial aspect. This pain occurs after a stroke or after cutting of nerves and include shingles and diabetic peripheral neuropathy.

The nociceptive pain signaling initiates upon the detection of a nociceptive stimulus by nociceptors. These nociceptors are the primary neurons that have their cell bodies in dorsal root ganglion (DRG) or trigeminal ganglion (TG). However, their peripheral axons sense this stimulus and send this information to DRG or TG *via* their cell bodies. The information is relayed from DRG or TG to the spinal or medullary dorsal horn *via* primary sensory neurons to secondary neurons [5]. Interaction between excitatory and inhibitory inter neurons, glial cells and descending axons from the brainstem form the complex circuits in the dorsal horn, and then process this information and relay the processed information to the higher brain areas which are mainly involved in pain sensation and associated emotions [8, 9]. Somatosensory cortices, prefrontal cortex, amygdala, insular cortex and anterior cingulate cortex form higher brain areas where pain is perceived and sensory and emotional processing of pain occurs [10]. Thus, chronic pain can negatively affect important brain functions including cognition and mood and hence, it is also associated with mood, comorbid cognitive and anxiety disorders [11].

MicroRNA

MicroRNAs (miRNAs) are the small, non-coding pieces of RNA, which were once misunderstood as cellular detritus, have now popped up as master players in the regulation of gene expression in the past decade. MiRNAs comprise a novel class of endogenous, evolutionarily conserved, non-coding single-stranded RNAs of ~19-25 nucleotides in length which mainly operate at post-transcriptional level. They were first discovered in *Caenorhabditis elegans* and since then they have

CHAPTER 7

The Ameliorative Potential of 7-Hydroxy-4-Methylcoumarin in Acrylamide Induced Neuropathic Pain *via* Improving of Mitochondrial Function in Rat

Jaspreet Kaur, Arunachalam Muthuraman* and **Muthusamy Ramesh**

Neuropharmacology Division, Department of Pharmacology and Toxicology, Akal College of Pharmacy & technical Education, Mastuana Sahib, Sangrur 148002, Punjab, India

Abstract: The present study was designed to investigate the analgesic potential of 7-hydroxy-4-methylcoumarin (HMC) in acrylamide induced neuropathic pain in rats. Acrylamide (30 mg/kg, *i.p.*; once in three days, for 24 consecutive days) was administered for inducing neuropathic pain. The acrylamide induced nociceptive pain sensation, *i.e.,* acetone drop, plantar, hot plate, Von Frey Hair and tail immersion tests have been assessed at different time intervals, *i.e.,* 0, 6, 12, 18 and 24th day. Furthermore, the biochemical estimation, *i.e.,* thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH), total calcium, cytochrome c oxidase activity and ATP content levels were estimated from the sciatic nerve tissue sample on 24th day. The HMC (10 and 20 mg/kg, *p.o.*) and cyclosporin A (CsA, 50 µM/kg; *p.o.*) was administered for 24 consecutive days, one hour before each injection of acrylamide. The treatment of acrylamide resulted in significant ($P < 0.05$) changes of behavioral and biochemical changes. Pretreatment of HMC ameliorate the acrylamide induced changes of behavioral and biochemical parameters in a dose dependent manner. These results are similar to that of CsA treated group. Based on these findings, it may conclude that, HMC possesses the potential ameliorative effect against acrylamide induced neuropathic pain, it may be because of its therapeutic potential of anti-oxidant, anti-lipidperoxidative, calcium ion regulatory and mitochondrial permeability transition pore inhibitory action.

* **Coresponding author Arunachalam Muthuraman:** Neuropharmacology Division, Department of Pharmacology and Toxicology, Akal College of Pharmacy & technical Education, Mastuana Sahib, Sangrur 148002, Punjab, India. E-mail: arunachalammu@gmail.com

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Keywords: 7-hydroxy-4-methylcoumarin, Acrylamide, Adenosine triphosphate, Allodynia, Calcium, Cyclosporin A, Cytochrome c oxidase, Electron transport chain, Hyperalgesia, Mitochondrial dysfunction.

INTRODUCTION

According to the International Association for the Study of Pain (IASP), neuropathic pain is defined as *"pain initiated or caused by a primary lesion or dysfunction or transitory perturbation in the peripheral or central nervous system"* [1]. It is characterized by affecting the somatosensory system leading to produce the spontaneous pain, hyperalgesia, hypothesia, dysthesia and allodynia [2]. In addition, the Food and Drug Administration (FDA) approved few drugs to manage the neuropathic pain syndrome, *i.e.,* anti-convulsants, anti-depressants, topical medicines and opioids [3, 4]. However, these medications give partially relief from the symptoms, induce wide spectrum of adverse effects and lack specificity. Thus, clinical usage of these drugs is limited in the management of neuropathic pain [5, 6]. The various animal models are well established for evaluating newer agents in the management of neuropathic pain syndrome. Acrylamide is one of the chemical methods for inducing neuropathic pain [7].

Acrylamide (prop-2-enamide) is an odourless white crystalline solid. It is widely used in various chemical industries for preparing polyacrylamides, water-soluble thickeners, sugar manufacturing, pesticide formulations, preparing permanent cement, press fabrics/plastic products, dyes and ore processing [8, 9]. It is also used as binding, thickening / flocculating agent, cosmetic preparation and gel electrophoresis process in pharmaceutical science [10, 11]. In addition, acrylamide was found in many roasted starchy foods [12 - 14]. Furthermore, it is present in black olives, prunes, dried pears, coffee, cocoa powder, roasted almonds, whole wheat bread and Pringles [14, 15]. The precise mechanism of acrylamide formation in foods remains unclear, but it is believed that, it is a byproduct of the Maillard reaction between asparagine and reducing sugars (*i.e.,* fructose and glucose) or reactive carbonyls at temperatures above 120 °C [16, 17]. Various studies have reported that, acrylamide is known to have potential neurotoxic effect [18, 19]. In fact, it produces the potential distal multifocal axonal degeneration, which is also known as "dying back" neuropathy. Generally,

dying back" neuropathy is a progressive loss of peripheral and central neuronal axon which is observed in both humans as well as animal species [20 - 22]. Acrylamide (30 mg/kg, *i.p.,* for 24 consecutive days) induced neuropathic pain is one of the common experimental models of the neuropathic pain disorder. It is a clinically relevant model for neurotoxic chemical associated neuropathic pain and is widely accepted model due to its similar pathophysiological mechanism in humans as well as in rodents [20, 23].

Recently, various herbal constituents are employed in the management of neuropathic pain, *i.e.,* quercetin [24]; geraniol and curcumin [25]; safranal [26]; puerarin [27]; thymoquinone [28] which have been documented to produce the attenuation of neuropathic pain. Coumarin is one of the important flavonoid in herbal plants [24]. Higher concentrations of coumarin are present in *Dipteryx odorata*, *Anthoxanthum odoratum*, *Galium odoratum* and *Albizia antunesiana* [29, 30]. It has various pharmacological actions such as anti-diabetic [31], hepatoprotection [32], anti-coagulant [33], anti-tumor, and anti-fungal activity [34, 35]. Coumarin is one of the major constituents of the various herbal plants and has various therapeutic actions against ulcerative colitis [36], psychosis [37], thrombosis [38] and diabetes [39]. Recently, various reports have documented that, coumarin derivatives also possess the potential pharmacological actions, *i.e.,* anti-cancer [40], anti-inflammation [41] and improvement of learning and memory function [42]. The molecular mechanism of coumarin is known to have the free radical scavenger, *i.e.,* reactive oxygen species, reactive nitrogen species and reactive chlorine species, calcium channel blocking actions [43].

Furthermore, coumarin derivative is known to possess the potential action on mitochondrial functional regulation [44]. In addition, cyclosporine A is also documented to produce the neuroprotection *via* regulation of mitochondrial function by inhibition of mitochondrial permeability transition pore (MPTP) opening and release of cytochrome c [45]. Thus, cyclosporine A served as positive control in this study. Acrylamide is known to cause the mitochondrial dysfunction in the nervous system *via* opening of MPTP [46, 47]. Therefore, the present study has been designed to investigate the molecular mechanism and therapeutic potential of 7-hydroxy-4-methylcoumarin in acrylamide induced neuropathic pain in rats.

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