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List of Publications

List of Publications

Publication from thesis: Research Article:

1. **Gadepalli, A,** Ummadisetty, O, Akhilesh, Chouhan, D, and **Tiwari, V*.** Loperamide, a peripheral Mu-Opioid receptor agonist, attenuates chemotherapy-induced neuropathic pain in rats. ***International Immunopharmacology*. 2023.** 124, p.110944. **(Impact Factor: 5.6).**
2. **Gadepalli, A,** Ummadisetty, O, Akhilesh, Chouhan, D, Yadav, K.E and **Tiwari, V*.** Peripheral mu-opioid receptor activation by Dermorphin [D-Arg2, Lys4](1–4) amide alleviates behavioral and neurobiological aberrations in rat model of chemotherapy-induced neuropathic pain. ***Neurotherapeutics***. **2024.** 21(1), p.e00302**. (Impact Factor: 5.7).**

Other publications:

1. Ummadisetty O, Akhilesh, **Gadepalli A**, Chouhan D, Patil U, Singh S.P, Singh S, & Tiwari V. Dermorphin [D-Arg2, Lys4] (1-4) Amide Alleviates Frostbite-Induced Pain by Regulating TRP Channel-Mediated Microglial Activation and Neuroinflammation. Molecular Neurobiology, 2024 Jan 26.
2. Ummadisetty O, Akhilesh, **Gadepalli A**, Chouhan D, & Tiwari V. Development and validation of clinically Mimicable model of frostbite injury-induced chronic pain. Cellular Signalling. 2024 Jan 2; 111028
3. Parekh P, Sharma N, Sharma M, **Gadepalli A**, Sayyed AA, Chatterjee S, Kate A, Khairnar A. AMPK-dependent autophagy activation and alpha-Synuclein clearance: a putative mechanism behind alpha-mangostin's neuroprotection in a rotenone-induced mouse model of Parkinson's disease. Metabolic Brain Disease. 2022 Dec;37(8):2853-70.

4. Uniyal A, **Gadepalli A**, Modi A, Tiwari V. Modulation of KIF17/NR2B crosstalk by tozasertib attenuates inflammatory pain in rats. Inflammopharmacology. 2022 Mar 3:1-5.
5. Patel S, Sharma D, Uniyal A, **Gadepalli A**, Tiwari V. Recent advancements in biomarker research in schizophrenia: mapping the road from bench to bedside. Metabolic Brain Disease. 2022 Mar 3:1-5.
6. Akhilesh, Uniyal A, **Gadepalli A**, Tiwari V, Allani M, Chouhan D, Ummadisetty O, Verma N, Tiwari V Unlocking the potential of TRPV1 based siRNA therapeutics for the treatment of chemotherapy-induced neuropathic pain. Life Sciences. 2022 Jan 1;288:120187.
7. **Gadepalli A**, Akhilesh, Uniyal A, Modi A, Chouhan D, Ummadisetty O, Khanna S, Solanki S, Allani M, Tiwari V. Multifarious Targets and Recent Developments in the Therapeutics for the Management of Bone Cancer Pain. ACS chemical neuroscience. 2021 Nov 1;12(22):4195-208.
8. Uniyal A, Thakur V, Rani M, Tiwari V, Akhilesh, **Gadepalli A**, Ummadisetty O, Modi A, Tiwari V. Kinesin Nanomotors Mediated Trafficking of NMDA-Loaded Cargo as A Novel Target in Chronic Pain. ACS Chemical Neuroscience. 2021 Jul 29;12(16):2956-63.
9. Uniyal A, Kotiyal A, **Gadepalli A**, Ummadisetty O, Tiwari V. Epigallocatechin-3-gallate Improves Chronic Alcohol Induced Cognitive Dysfunction in Rats by Interfering with the Neuro-inflammatory, Cell Death and Oxido-nitrosative Stress Pathways. Metabolic Brain Disease. 2021
10. Tiwari V, Uniyal A, **Gadepalli A**, Tiwari V, Agrawal S. Sodium Channels: As an Eye of the Storm in Various Clinical Pathologies. InFrontiers in Pharmacology of Neurotransmitters 2020 (pp. 619-634). Springer, Singapore.
11. Shaw S, Uniyal A, **Gadepalli A**, Tiwari V, Belinskaia DA, Shestakova NN, Venugopala KN, Deb PK, Tiwari V. Adenosine receptor signalling: Probing the potential pathways for the ministration of neuropathic pain. European Journal of Pharmacology. 2020 Oct 2:173619.
12. Chouhan D, Uniyal A, **Gadepalli A**, - A, Tiwari V, Agrawal S, Roy TK, Shaw S, Purohit N, Tiwari V. Probing the Manipulated Neurochemical Drive in Alcohol

Addiction and Novel Therapeutic Advancements. ACS Chemical Neuroscience. 2020 Apr 13.

13. Uniyal A, **Gadepalli A**, Akhilesh, Tiwari V. Underpinning the Neurobiological Intricacies Associated with Opioid Tolerance. ACS Chemical Neuroscience. 2020 Feb 21;11(6):830-9.
14. Parkhe A, Parekh P, Nalla LV, Sharma N, Sharma M, **Gadepalli A**, Kate A, Khairnar A. Protective effect of alpha mangostin on rotenone induced toxicity in rat model of Parkinson's disease. Neuroscience letters. 2020 Jan 18;716:134652.
15. Parekh P, Sharma N, **Gadepalli A**, Shahane A, Sharma M, Khairnar A. A Cleaning Crew: The Pursuit of Autophagy in Parkinson's Disease. ACS chemical neuroscience. 2019 Aug 6;10(9):3914-26.

National/International Conference Presentations/Participation:

1. Participated in **32nd SPSR Webinar on 'From Lab to Life: Unraveling Chemotherapy-Induced Neuropathic Pain with Cutting-Edge Animal Models'** organized by the Society of Pharmaceutical Sciences and Research (SPSR) on 3rd December 2023.
2. Participated and gave an oral presentation on *"Activation of Peripheral μ-Opioid Receptors Alleviates Chemotherapy-induced Evoked and Ongoing Pain in Rats"* at the **37th Annual Meeting of the Society for Neurochemistry - International Conference on "Neuroscience and Neurological Disorders,"** September 8th to 16th, 2023, at North Eastern Hill University in Shillong, Meghalaya.
3. Participated in the **IBRO Supported Meeting and Workshop on "Recent Progress in Brain Research and Drug Delivery"**, organized by ISF College of Pharmacy, Moga, Punjab, 13-15th May, 2022.
4. Participated in the **SPARC sponsored International Workshop on Neurobiology of Pain & Itch**, June 29, 2021 to July 03, 2021, organized by the Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, India.
5. Participated in the **SPARC sponsored Indo US Workshop on Pain Mechanisms & Therapeutics**, May 06, 2021 to May 10, 2021, organized by the Department of

Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, India.

6. Participated in a short-term course on "**Pre-clinical Models in Drug Discovery and Development**", from 30 March- 3 April, 2021; organized by IIT(BHU), Varanasi, India.
7. Participated in the '**IBRO-APRC School on Understanding Neuroscience and the Spectrum of Neurogenetic Disorders',** Kathmandu, Nepal. (Virtual school) August 20-25, 2021.
8. Attended the **27th Napa Pain Conference** Online on 15th August, 2020.
9. Attended the 2020 Global Year Webinar titled "**Pain Prevention After Surgery**" on 4 June 2020.
10. Participated in the Webinar Lecture Series on the topic of **"Pharmacy as the backbone of healthcare system: Brainstorming to restore its glory"** 03 May, 2020, organized by Amity Institute of Indian System of Medicine, Health & Allied Sciences Domain, Amity University Uttar Pradesh, Noida (INDIA).

RECOGNITION: Awards, Achievements and Honors:

1. Have been awarded **Financial Aid** to attend **2022 IASP World Congress**, Toronto, Canada from September 19- 23, 2022.

2. Received **'Best Presentation award'** in the IBRO-APRC School on **"Understanding Neuroscience and the Spectrum of Neurogenetic Disorders",** Kathmandu, Nepal (virtual mode), 20-25 August,2021.

3. Selected for the '**IBRO-APRC School on Understanding Neuroscience and the Spectrum of Neurogenetic Disorders',** Kathmandu, Nepal. (Virtual school) August 20-25, 2021.

4. Have been awarded **Financial Aid** to attend **2021 IASP World Congress**, Amsterdam from June 27- July 1,2021.

5. Have been **awarded travel grant** to attend the **IBRO-APRC Nepal School on "Understanding of Neuroscience and Spectrum of Neurogenetic Disorders"** Kathmandu, Nepal in March 2020.

Dr. Vinod Tiwari, working as Associate Professor at the Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, India. Currently heading the Neuroscience and Pain Research Lab at IIT (BHU), Varanasi, he is also the Ph.D. supervisor of Ms. Anagha Gadepalli. Dr. Tiwari holds a Ph.D. in neuropharmacology, and his groundbreaking research has identified key signaling pathways associated with alcoholic neuropathy, cognitive deficits, diabetic neuropathy, and musculoskeletal pain. His Ph.D. work, published in esteemed international journals such as the International Journal of Neuropsychopharmacology, Journal of Neurochemistry, Pharmacology, Biochemistry & Behavior, PAIN, and The Journal of Pain, has garnered significant citations. During his postdoctoral tenure at Johns Hopkins University, U.S.A., under the mentorship of Prof. Srinivasa N. Raja and Prof. Yun Guan, Dr. Tiwari explored various spinal and supraspinal mechanisms related to peripheral opioid-induced relief of spontaneous ongoing pain after spinal and sciatic nerve injury. His investigations included the study of MOR and DOR heterodimerization in peripheral opioid-induced tolerance and hyperalgesia, addressing a pertinent clinical challenge. These postdoctoral findings were published in renowned journals such as Nature Neuroscience, Proceedings of National Academy of Science (PNAS), PAIN, Anesthesiology, and The Journal of Clinical Investigation. Prior to joining IIT (BHU), Varanasi. Dr. Tiwari served as Assistant Professor at the National Institute of Pharmaceutical Education and Research, Ahmedabad. His impactful contributions to the pain field have gained worldwide recognition, with over 5198 citations, an h-index of 39, and an i10-index of 75. Currently, Dr. Tiwari's research focus centers on chemotherapy-induced neuropathic pain (CINP). The laboratory has recently published the first ever report showcasing the efficacy of a peripheral MOR agonist in mitigating CINP. This milestone underscores the lab's dedication to progressing pain research and development of safer analgesic strategies. Dr. Tiwari is also actively involved in studying TRP channels' mediated regulation of nociceptors and dissecting different neuronal circuitries involved in pain relief and drug addiction. The ultimate goal is to develop improved analgesic drugs devoid of addictive properties.

Ms. Anagha Gadepalli, is a Ph.D. scholar at the Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, India. She joined Dr. Tiwari's lab in July 2019 and, during her Ph.D., successfully worked on demonstrating the therapeutic potential of peripheral GPCR targeting for mitigation of Chemotherapy-Induced Neuropathic Pain. Her research was focused on investigating the efficacy of peripheral MOR and CBR agonists in the management of CINP. Anagha's noteworthy contributions have been published in reputable, high-impact peer-reviewed international journals, including International Immunopharmacology and Neurotherapeutics. Beyond her academic accomplishments, Anagha has been honored with various travel grants and awards from esteemed organizations, including the International Association for the Study of Pain (IASP) and International Brain Research Organization (IBRO). Moving forward, Anagha's post-Ph.D. aspirations center around undertaking advanced training within highly competitive research setting to further enhance expertise in neuroscience and pain research. She envisions a career dedicated to advancing our understanding of intricacies of various neurological disorders. Her ultimate objective is to actively contribute to the forefront of neuroscience and pain research by making meaningful contributions to the field and fostering advancements in pain management and neurological disorder treatments.

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Loperamide, a peripheral Mu-Opioid receptor agonist, attenuates chemotherapy-induced neuropathic pain in rats

Anagha Gadepalli, Obulapathi Ummadisetty, Akhilesh, Deepak Chouhan, Anmol, Vinod Tiwari *

Neuroscience and Pain Research Laboratory, Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, 221005, Uttar Pradesh, India

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ABSTRACT

Opioids are employed in the management of chemotherapy-induced neuropathic pain (CINP) when other pain management approaches have failed and proven ineffective. However, their use in CINP is generally considered as a second-line or adjunctive therapy owing to their central side effects and development of tolerance with their long-term usage. Targeting peripheral sites may offer several advantages over the conventional CNS-based approaches as peripheral targets modulate pain signals at their source, thereby relieving pain with higher specificity, efficacy and minimizing adverse effects associated with off-site CNS actions. Therefore, present study was designed with an aim to investigate the effect of loperamide, a peripherally acting mu-opioid receptor agonist, on paclitaxel-induced neuropathic pain in rats and elucidate its underlying mechanism. Loperamide treatment significantly attenuated mechanical, and cold hypersensitivity and produced significant place preference behaviour in neuropathic rats indicating its potential to treat both evoked and spontaneous pain. More importantly, loperamide treatment in naïve rats did not produce place preference to drug-paired chamber pointing towards its non-addictive analgesic potential. Further, molecular investigations revealed increased expression of ion channels such as TRPA1, TRPM8; voltage-gated sodium channels (VGSCs) and neuroinflammatory markers in the dorsal root ganglion (DRG) and lumbar (L4-L5) spinal cord of neuropathic rats, which was significantly downregulated upon loperamide treatment. These findings collectively suggest that activation of peripheral mu-opioid receptors contributes to the amelioration of both evoked and spontaneous pain in neuropathic rats by downregulating TRP channels and VGSCs along with suppression of oxido-nitrosative stress and neuroinflammatory cascade.

1. Introduction

Chemotherapy-induced neuropathic pain (CINP) is a noteworthy complication stemming from the administration of chemotherapeutic agents, affecting around 50–90 % of individuals undergoing chemotherapy treatment [1]. CINP manifests as a painful condition which can progress in severe cases to loss of sensory perceptions. Impairments in sensory functions can lead to a lowered pain threshold in response to various stimuli giving rise to mechanical allodynia, tingling, burning, paraesthesia and dysesthesia triggered by contact with warm or cool temperatures [2–5]. Despite its increasing recognition, CINP continues to pose a significant challenge, as it currently lacks viable curative approaches [6]. Some of the medications currently being used for CINP include serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, anticonvulsants like gabapentin and pregabalin, tricyclic antidepressants (TCAs) and patches of lidocaine, capsaicin and both weak and strong opioids [1]. Unfortunately, a substantial proportion, approximately 70 %, of patients does not get effective pain relief from these medications [7]. Moreover, most of these drugs primarily work by targeting the higher pain centers, present in the central nervous system and are associated with several unwanted side effects such as hepatic impairment, renal insufficiency, fatigue and central toxicities like anxiety, dizziness, sedation, respiratory depression, cognitive dysfunction, addiction, abuse potential [8].

Nonetheless, a growing body of clinical evidence suggests the involvement of the peripheral nervous system (PNS) in the progression and maintenance of chronic pain [9]. Targeting peripheral nociceptors modulate pain signals at their source, thereby relieving the pain with higher specificity, and minimizing off-target CNS side effects. Thus, targeting the PNS for development of safer therapeutics devoid of

* Corresponding author at: Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (B.H.U.), Varanasi 221005, (U.P.), India.
E-mail address: vtiwari.phe@iitbhu.ac.in (V. Tiwari).

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Original Article

Peripheral mu-opioid receptor activation by dermorphin [D-Arg2, Lys4] (1–4) amide alleviates behavioral and neurobiological aberrations in rat model of chemotherapy-induced neuropathic pain

Anagha Gadepalli, Obulapathi Ummadisetty, Akhilesh, Deepak Chouhan, Krushna Eknath Yadav, Vinod Tiwari *

Neuroscience and Pain Research Laboratory, Department of Pharmaceutical Engineering and Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, 221005, Uttar Pradesh, India

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ABSTRACT

Paclitaxel, a frequently utilized chemotherapeutic agent, often gives rise to severe and distressing sensory neuropathy in patients undergoing chemotherapy. Unfortunately, current therapeutics for chemotherapy-induced neuropathic pain (CINP) demonstrate limited effectiveness and are burdened with the potential for central side effects such as sedation, respiratory depression, cognitive impairment, and addiction, posing substantial clinical challenges. In light of these limitations, present study is designed to investigate the therapeutic potential of Dermorphin [D-Arg2, Lys4] (1–4) amide (DALDA), a preferential peripherally acting mu-opioid receptor agonist, in rat model of CINP. The primary objective was to assess the analgesic properties of DALDA and elucidate the underlying mechanisms governing its therapeutic activity. Our findings revealed that DALDA treatment significantly ameliorated paclitaxel-induced evoked and spontaneous ongoing pain in rats without causing drug addiction and other central side effects. Molecular analyses further unveiled that paclitaxel administration resulted in increased expression of TRP channels, NR2B, voltage-gated sodium channels (VGSCs) and neuroinflammatory markers in both the dorsal root ganglion (DRG) and the spinal cord (L4-L5 region) of rats. DALDA treatment significantly downregulated ion channels (TRPs, VGSCs) and NR2B expressions, concomitant with the inhibition of microglial activation, resulting in the suppression of oxido-nitrosative stress and neuroinflammatory cascade. Findings from the current study suggests that peripheral mu-opioid receptors may offer a potential target for the treatment of patients suffering from CINP, offering new avenues for improved pain relief while minimizing central side effects.

Introduction

Paclitaxel, a widely used chemotherapeutic agent, has demonstrated remarkable efficacy against various malignancies. Despite its success in cancer treatment, a distressing side effect associated with paclitaxel administration is the development of neuropathic pain, which significantly compromises patients' quality of life [1]. Chemotherapy-induced neuropathic pain (CINP) is characterized by sensory abnormalities, such as spontaneous pain, allodynia, and hyperalgesia, burning, tingling, which can persist long after the completion of treatment [2–4]. Overall, estimates of CINP prevalence can range from 30 % to 70 % or more among cancer patients receiving chemotherapy. The current therapeutic options for CINP include gabapentinoids, tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) like duloxetine and weak or strong opioids [5,6]. These medications predominantly work by targeting the pain centers in the central nervous system (CNS) resulting in multiple side effects like dizziness, sedation, addiction and abuse potential [5,7]. Additionally, a significant proportion of patients with CINP do not respond favorably to current therapeutic interventions, and many eventually develop tolerance over time, rendering treatment less effective. Therefore, it becomes imperative to prioritize the development of therapeutic interventions that can produce profound analgesia without causing CNS toxicities.

In recent years, the pursuit of targeting the peripheral nervous system (PNS) has gained prominence as a strategic approach in the development of safer and innovative analgesic treatments. This approach focuses on

* Corresponding author.
E-mail addresses: vtiwari.phe@iitbhu.ac.in, vinodtiwari1980@gmail.com (V. Tiwari).

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