OPIOID AS A TREATMENT FOR CHRONIC PAIN AND ITS CONSEQUENCES

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ABSTRACT

Pain is transmitted by peripheral neurons called primary afferent fibers. These fibers become active in the presence of damage to the periphery and send electrochemical signals to the spinal cord. In the spinal cord a second order of neurons transfer these signals to different areas in the brain allowing us to locate where the damage is and perceive pain. Chronic pain is long lasting pain that may be caused by a wide range of factors including strokes, spinal injury, arthritis and even amputation. Opioids are one of the most popular and perhaps one of the most controversial treatments to chronic pain. Opioid consumption can lead to physiological dependence, addiction and in some cases opioid induced hyperalgesia.

INTRODUCTION

An action potential from a pre-synaptic neuron triggers release of neurotransmitters which regenerates it on the post-synaptic neuron, through a synaptic cleft. This functionality is particularly useful in pain relief medicine as the “pain impulse” can be blocked from being transmitted in towards the central nervous system. However, such interference usually leads to knock-on effects such as feelings of euphoria.

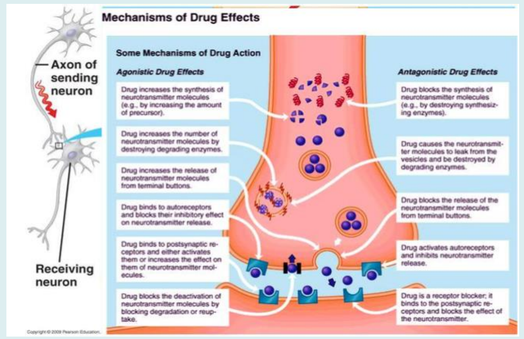
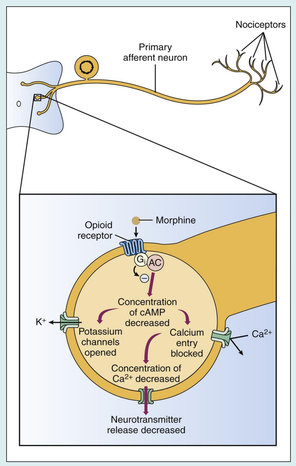


Figure 1. The influence of drugs on the transmission of neurotransmitters across the synaptic cleft (*from http://cmapspublic.ihmc.us/rid=1L2F26FZ6-1LWCH5L-1SHN/28_06aNeuronCommunicat-L.jpg*)

MECHANISM OF OPIOID-INDUCED PAIN RELIEF



- Opioids produce their analgesic effect by binding to specific receptors found on the membrane of neurons that are distributed in the central and peripheral nervous system.
- Painful stimulus activates nociceptors, also known as primary afferent fibres. These transmit the signal to neurons in the spinal cord (Figure 1).
- The inhibition of pain happens in the presynaptic membrane, where the opioid molecule binds with a specific opioid receptor.
- Morphine binds to opioid receptor causing the inhibition of neurotransmitters release (Figure 2).

Figure 2. Mechanisms of Opioid induced pain relief (*from https://basicmedicalkey.com/opioid-analgesics-and-antagonists-2)*

METHODS

- **In-vivo electrophysiology** allows us to record electrical signals from spinal cord neurons in anaesthetized rats **(Figure 3).** This allows us to measure the response to neurons in the spinal cord that transmit pain signals to the brain. We can also see the responses of these neurons to different types of painful mechanical stimuli by using von Frey filaments or hot water as a thermal stimuli. Von Frey filaments are nylon filaments of different weights that range between 0g-60g. The higher the weight the more painful it will be.

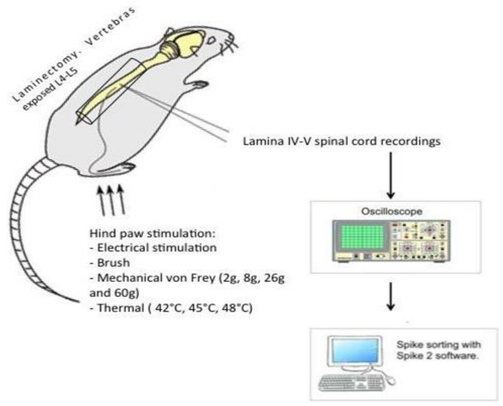


Figure 3. (*from Montagut-Bordas et al., poster figure 2017*) . In-vivo electrophysiological recordings of spinal cord neurons in rats.

- **Paw withdraw behaviour** allows us to measure the response of awake animals to mechanical sensitivity by using calibrated von Frey Filaments. Awake rats are placed in separated transparent plexiglass chambers with a wire mesh floor **(Figure 4A)**. Filaments of different weights can be applied to the hind-paw **(Figure 4B)** for 5s or until a withdraw response occurs. Withdrawal of the hind paw is then scored according to the up-down method (Luo et al., 2008). This allows us to measure if the animal is suffering from mechanical hypersensitivity.

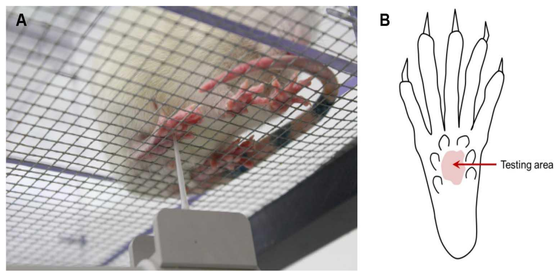


Figure 4. *(from Ferrier, J., Marchand, F. and Balayssac, D. et. al., (2016))* . (A) Animal placed in transparent chamber and electrical von Frey application. (B) Hind-paw showing von Frey application area in red.

RESULTS

Electrophysiological effects of morphine in a rat model of chronic pain.

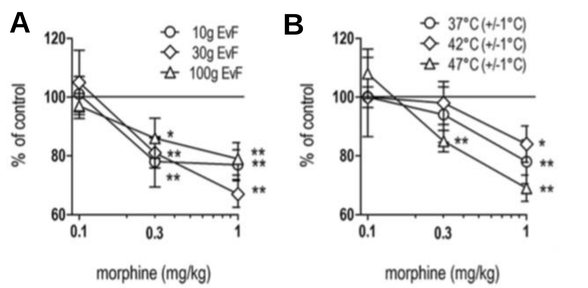


Figure. 5. Neuronal responses to mechanical (A) and thermal (B) stimuli in an rat model of chronic pain *(from S.J Hirsche. A.H. Dickenson/Neuroscience Letters 562(2014) 97-101)* . (A) Neuronal responses to 10g, 30g and 100g of Electrical von Frey are significantly reduced after 0.3 mg/kg and 1mg/kg of morphine administration. (B) Thermal responses to 47°C are significantly reduced at 0.3mh/kg of morphine administration. In addition 37°C, 45°C and 47°C are significantly reduced after 1mg/kg morphine administration.

Neuronal responses to mechanical and thermal stimuli in morphine treated rats.

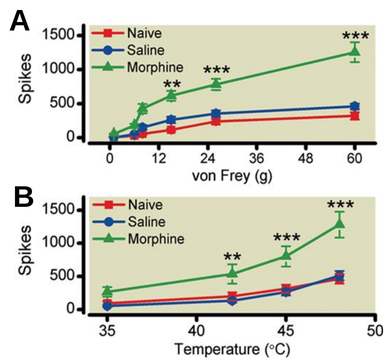


Figure 6. Neuronal responses to mechanical (A) and thermal (B) stimuli in Naïve, Saline and Morphine treated rats (from Bannister et al., 2011). (A)Animals chronically treated with morphine show a significant increase to 15g, 26g and 60g von Frey compared to Saline treated and Naïve animals. (B) Animals chronically treated with morphine show a significant increase to 42°C, 45°C, 48°C thermally evoked stimuli compared to Saline treated and Naïve animals.

Behavioural responses to mechanical stimuli during the course of repeated treatment of morphine.

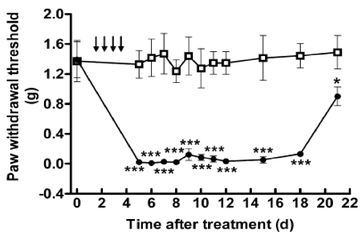


Figure 7. Behavioural responses to mechanical) stimuli in Saline and Morphine treated mice *(from Chen et al., 2010)*. Paw withdraw threshold is significantly reduced during repeated morphine administration over time in mice. Thus these animals exhibit increased mechanical sensitivity.

OPIOID DEPENDENCE

Repeated exposure can induce changes in the brain that drive the compulsive seeking and taking of opioids, despite disastrous consequences. Factors affecting include, but are not limited to:

- Genetic and epigenetic health
- Stress
- Introduction to “gateway drugs”, such as nicotine

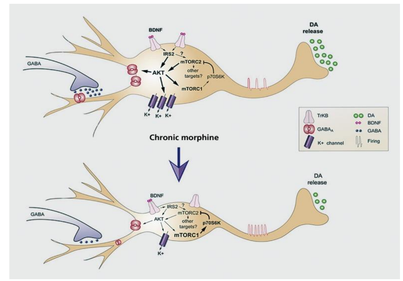


Figure. 8. Chronic morphine decreases neuron size but increases neuronal excitability (*from Eric J. Nestler, 2013 Dec, Whole Cell Plasticity, Cellular basis of memory for addiction)*

PROS OF OPIOID TREATMENT FOR CHRONIC PAIN

- Opioid analgesics have been shown to provide relief in moderate to severe pain, in humans, when compared to a placebo ***(From Furlan, Sandoval, Mailis-Gagnon, & Tunks, 2006).***
- Some opioids can relieve pain extremely rapidly, eg: oxymorphone takes 5-15 minutes for peak effects. ***(From Cherny, Nathan I. 1996. “Opioid Analgesics: Comparative Features and Prescribing Guidelines.” Drugs 51(5):713–37)***

CONS OF OPIOID TREATMENT FOR CHRONIC PAIN

- Increasing number of deaths due to overdose; there were 5 times more deaths due to opioid overdose in 2016 than in 1999
- Patients on chronic opioid therapy shown to have relatively higher levels of clinical depression of up to 38% ***(from Sullivan MD, Von Korff M, Banta-Green C, et al. Problems and concerns of patients receiving chronic opioid therapy for chronic non-cancer pain. Pain. 2010;149(2):345–353)***
- Can lead to development of other complications, eg: opioid induced hyperalgesia.
- Opioid therapy can adversely affect respiratory, gastrointestinal, musculoskeletal, cardiovascular, immune, endocrine, and central nervous systems. ***(from AnGee Baldini, Michael Von Korff, Elizabeth H. B. Lin, A Review of Potential Adverse Effects of Long-Term Opioid Therapy: A Practitioner's Guide, 2012 June)***

CONCLUSIONS

1. Opioids reduce the sensation of pain. Treatment with opioids reduces neuronal responses to mechanical and thermal evoked stimuli in the animal model of chronic pain.
2. Chronic opioid treatment can induce opioid-induced hyperalgesia, thus making painful stimuli even more painful. Neuronal responses to thermal and mechanical stimuli were increased in animals that have been chronically treated with morphine. In addition. paw withdrawal thresholds were decreased in mice that were repeatedly treated with morphine.
3. Opioids can lead to addiction. Thus, even though they are extremely useful in treating chronic pain, doctors should consider prescribing opioids as a last resort, as they also have unwanted side effects that can cause harm in both a patient’s body and life.