



Neuro Effects of Opioids on the Human Brain

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Abstract

This paper is an examination of the neuro effects of opioids on the human brain. The research examines the brain receptors, region, enzymes, agonists involved, and the results of its interaction with opioids. Examination of the pharmacological effect on receptors located in the neural cell membranes shows that the most important aspect is the modulation of the K and Ca ions channels. This is mediated by the activation of the delta, kappa and mu opioid receptors in the peripheral and central nervous systems. The study found that opioid receptors are coupled by guanine nucleotide binding proteins (G-proteins) to the K⁺ channel and voltage sensitive Ca⁺⁺ channel, particularly, the N-type channel. The channels are inhibited if K⁺ outwards release is increased leading to short polarization time. The outward movement occurs in several regions of the spinal cords, brain, and the myenteric plexus. The rapid K⁺ outward movement is associated with the observed hyperpolarization and inhibition caused by opioids. While the brain has naturally occurring opioids peptides (the b endorphin, the enkephalins and the dynorphin which preferentially interact with the m-receptor, d-receptors and k-receptors respectively), morphine was found to produce exaggerated stimulation of the m-receptor which induce tolerance, addiction, and dependency. The results of opioid interaction with the brain were found to cause depression, nausea, sedation, dysphoria, and impaired cognition, modulation of emotions, stress, rewards, memory and learning.

Keywords: Opioids and the brain, Neuro effects of opioid, Opioid receptor, Opioids modulation, Analgesic effect of opioids

Introduction

Previous researchers have explored the effect of opioids on the brain. Its adverse effects include respiratory depression, nausea, sedation, dysphoria, and impaired cognition. Opioids also modulate emotions, stress, rewards, emotions, memory, and learning (Feng et al., 2012). The euphoria and pain-relieving properties of opioids have been discussed since the Sumerian times. Research trace the mechanism of action of opioids to the coupling of receptors and inhibitors like the G-protein. The couple is activated by an agonist such an exogenous, or an endogenous μ -opioid peptide endorphin, the $G\alpha$, and $G\beta\gamma$ dissociate and act on effector pathways (van Rijn, DeFriel & Whistler, 2013). Pharmacological research found that pertussis-toxin-sensitive G proteins coupled with all the four types of opioid receptors. However, the most important aspect of the mode of action of the opioid receptor is its modulation of the K and Ca ions channels (Kaye et al., 2018). The effect of opioids is mediated by the activation of the delta, kappa and mu opioid receptors in the peripheral and central nervous systems (Drewes et al., 2012). Previous researchers have characterized these peptides and receptors and their genes; this study will use a secondary source to explore neuro effects opioids' on the brain.

Material and Methods

A literature review approach is used to explore the impact of opioids on the human brain. The library directory, internet, and computers

were essential to the completion of the research. The data was gathered from online databases including PubMed, EMBASE, and MedLine. The following search terminologies were used:

- Opioids AND Neurological effects ON brain
- Opiates AND brain effects
- Opioids AND Human Brain receptors.
- Opioids AND brain receptor modulation
- Opioid-mediated effects AND brain
- Effects of opioids AND Brain

A total of 54 secondary sources were identified from the online research. The sources were scrutinized to determine their relevance and usability in the study. Sources were eliminated based on sample characteristics. Only sources based on human subjects were identified for use in the study, 43 studies passed the test. Only sources that used unique approaches were included, studies with duplicate approaches were removed (27 studies qualified). The third criteria were the language of publication, only studies published in English were used in the research; 19 studies met the criteria. The search was limited to studies published from January 2014; 11 articles met the criteria. Moreover, the paper will be supplemented by discussions on pain management. The discussion below presents the results of this literature search. **Figure 1** outlines the selection criteria.

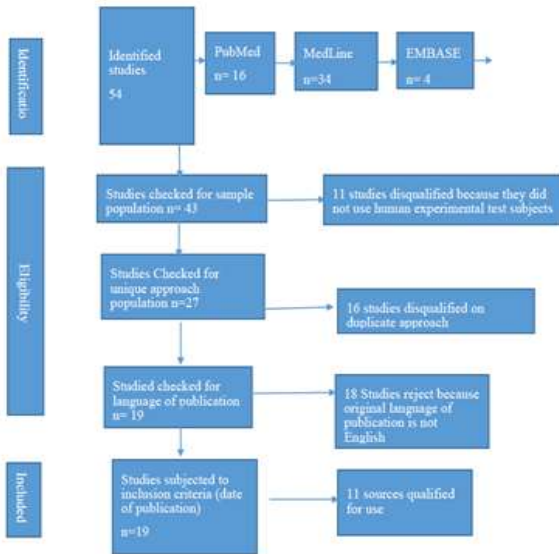


Figure 1: The selection criteria.

Results

Sites of Action and Inhibition of Neurotransmitters Release

Pasternak & Pan (2013) found that opioids act on two sites of the brain, the presynaptic nerve terminal, and the postsynaptic neuron. In the presynaptic region, opioids have an inhibitory effect on neurotransmitter release; this is considered its most pronounced effect on the nervous system (Pasternak & Pan, 2013). However, the summation of opioid action is not limited to its excitatory and inhibitory effect on the presynaptic region, but also its effect on the postsynaptic region (Lee, Wanigasekera & Tracey, 2014). For instance, the action of opioids causes an inhibitory effect on neurotransmitter release this may have an excitatory effect if the neurotransmitter usually causes inhibition in the target neuron (Pasternak & Pan, 2013). However, if the opiate has an inhibitory effect on the postsynaptic region, the excitation may not occur.

Studies characterized the impact of opioid on neurotransmitter release by studying the Ca and K channel. Neurotransmitters release follows depolarization of nerve terminal Ca⁺⁺ across its volt-sensitive Ca⁺⁺ channels (Lamberts & Traynor, 2014). Three types of Ca⁺⁺ type channels exist, the L-type, T-type and the N-type. The release can be inhibited by the increasing outwards K⁺ release leading to short polarization time and action potential (Gendron, Cahill, von Zastrow, Schiller & Pineyro, 2016).

This effect is as a result of the G-protein linking receptors to the K⁺ channel and voltage sensitive Ca⁺⁺ channel, particular, the N-type channel (Lamberts & Traynor, 2014). However, this effect alone does not completely describe the effect of Opioids on neurotransmitters. Opioids open the voltage sensitive potassium ion channels thus increasing outwards flow (Lamberts & Traynor, 2014). The outward movement occurs in several regions of the spinal cords, brain, and the myenteric plexus. The rapid K⁺ outward movement is associated with the hyperpolarization and inhibition resulting from opioids. Opioid interactions with the adenylate cyclase systems lead to inhibition; the AC is responsible for the conversion of ATP to Camp. Lamberts & Traynor (2014) noted that all the three opioid receptors bind to the adenylate cyclase.

Location Bias in Opioids

Al-Hasani & Bruchas (2011) found that morphine has a higher affinity for the m-receptor than other opioids. While all the three receptors produce an analgesic effect when bound to opioids, the k-receptor cause a lesser dependence than m-receptor (Drewes et al., 2012). Both medically used and natural occurring opioids, the surface mu-receptors are activated, and the receptor molecules enter the endosome and receptor remains active for several minutes (Drewes et al., 2012). However, for opioid drugs, there is a unique rapid induction of nanobody signaling (in the range of tens of seconds) in the Golgi apparatus present in the main body the neuron (Drewes et al., 2012). Activation of Golgi outpost located in the branched structure was also observed (Lamberts & Traynor, 2014). The researcher concluded that opioid drugs distort normal spatial sequence and time of mu-receptor signaling.

Pain Modulation

Lee, Wanigasekera & Tracey (2014) studied the effect of opioids on the central and peripheral nervous system. The study noted that there are critical spinal and supraspinal opioid-mediated activities leading to a descending pathway. A study by Garland, Froeliger, Zeidan, Partin & Howard (2013) studied the analgesic effect opioids. As illustrated in the figure below, pain perception results from neural activation in the interconnected brain region shown by the yellow arrows; these regions have sensory-discrimination and effective motivation shown by the blue and red lines.

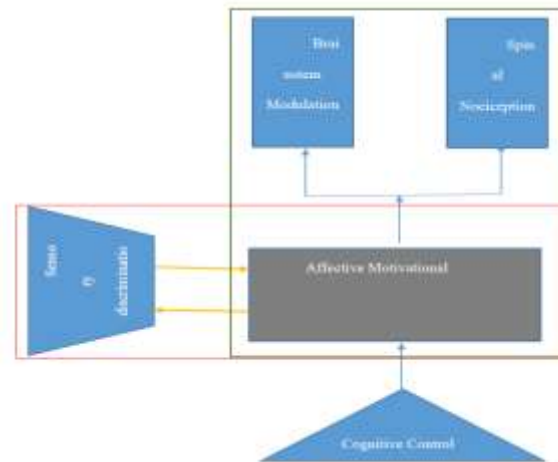


Figure 2: The selection process.

From the illustration, opioid alter brain perception of pain through preferential targeting of the limbic region highlighted in grey. Cognitive control of pain involving the prefrontal cortex is achieved by opioid activation of limbic-brainstem inhibition. Figure 2 illustrates the selection process.

Discussion

From the literature, review, opioids are found to modulate several physiological functions. The degree of impacts is affected by the distribution of opioids receptors in the brain. The regions documented to show most responses were the rostral, medial and inferior frontal gyri, cortex, cingulate cortex, and the precuneus. The prefrontal cortex, insula, amygdala and the cingulate cortex are parts involved in



pain management and are involved in opioid circulation. The presynaptic effect of opioids in neurotransmitter release is the primary mode of action of opioids. The mu-opiate receptor is responsible for most of the observed actions. Opioids trigger a wide range of effect since it interacts with multiple pathways (Pasternak & Pan, 2013). When opioids infiltrate into the locus cereleus the user experience slow respiration, low blood pressure, constipation, and decreased alertness. After long-term use, opioids can alter the neurological processes, and the brain requires more opioid to achieve the same reactions, this leads to addiction. Withdrawal is coupled with an extensive firing by neurons. Thus, rather than constipation and slowed respiration, the brain begins to trigger elevated blood pressure, and diarrhea (Müller-Lissner et al., 2016). Instead of happiness, the amygdala triggers feelings of anxiety and dysphoria. The negative reaction feeds the prefrontal cortex further promotes the desire opioids. As noted in the research, opioids can cause profound mood changes, analgesic, tolerance, dependency, and hedonics effects. Thus, patients taking opioids have to be under strict monitoring, with their dose and intake always within the recommended levels and period.

Conclusion

Most research on the mechanism of action is based on neurological effects. Cortical and subcortical brains are directly altered by opioids thus mediating emotions, impulses, rewards, and motivation. Studies on opiate addicts show alteration of the white and grey matter morphometric and functional properties. Opioids are one of the most explored drugs yet, researchers continue to be divided on its mechanism of action. For decades, it was assumed that opiates have one mode of action the studies have been refuted by subsequent research that pointed out differences in mechanisms of action. The involvement of endogenous peptides brought a new understanding of how opioids interact with the brain discussed in this paper.

References

1. Al-Hasani R and Bruchas M. Molecular Mechanisms of Opioid Receptor-dependent Signaling and Behavior (2011) *Anesthesiol* 115: 1363-1381.
2. Drewes A, Jensen R, Nielsen L, Droney J, Christrup, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives (2012) *British J Clini Pharmacol* 75: 60-78.
3. Feng Y, He X, Yang Y, Chao DH, Lazarus L, et al. Current Research on Opioid Receptor Function (2012) *Current Drug Targets* 13: 230-246.
4. Garland E, Froeliger B, Zeidan F, Partin K and Howard M. The downward spiral of chronic pain, prescription opioid misuse, and addiction: Cognitive, affective, and neuropsychopharmacologic pathways (2013) *Neuroscience and Biobehavioral Reviews* 37: 2597-2607.
5. Gendron L, Cahill C, von Zastrow M, Schiller P and Pineyro G. Molecular Pharmacology of μ -Opioid Receptors (2016) *Pharmacological Reviews* 68: 631-700.
6. Kaye A, Cornett E, Patil S, Gennuso S, Colantonio M, et al. New opioid receptor modulators and agonists (2018) *Best Practice & Research Clini Anesthesiol* 32.
7. Lambert J and Traynor J. Opioid Receptor Interacting Proteins and the Control of Opioid Signaling (2014) *Current Pharmaceut Design* 19: 7333-7347.
8. Lee M, Wanigasekera V, and Tracey I. Imaging opioid analgesia in the human brain and its potential relevance for understanding opioid use in chronic pain (2014) *Neuropharmacol* 84: 123-130.
9. Müller-Lissner S, Bassotti G, Coffin B, Drewes A, Breivik H, et al. Opioid-Induced Constipation and Bowel Dysfunction: A Clinical Guideline (2016) *Pain Medicine* 18: 1837-1863.
10. Pasternak G and Pan Y. Mu Opioids and Their Receptors: Evolution of a Concept (2013) *Pharmacological Reviews* 65: 1257-1317.
11. Van Rijn R, DeFriel J, and Whistler J. Pharmacological traits of delta opioid receptors: pitfalls or opportunities? (2013) *Psychopharmacol* 228: 1-18.