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Theory

The Effects of Lithium on the Endogenous Opioid System: A Model for Nonsuicidal Self-Injury Behavior

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ABSTRACT

Lithium and the opioid system have been studied extensively in the field of neuroscience due to their potential therapeutic applications in treating a range of psychiatric disorders. Lithium's mechanism of action is not fully understood, but it is believed to involve multiple neurotransmitter systems. The opioid system may also be involved, as lithium has been shown to modulate the effects of opiates in animal studies. Lithium is commonly used to treat bipolar disorder, while opioid receptors have been implicated in analgesia, regulation of mood and behavior. Studies from the last four decades have suggested that lithium may modulate the activity of the opioid system, and this interaction may play a role in the therapeutic effects of this ion. This review will explore the current understanding of the interaction between lithium and the opioid system, and discuss the potential clinical implications of this relationship. The Nonsuicidal Self-Injury (NSSI) is a behavior that has been spreading significantly in the adolescent population, especially in the last 10 years, probably due to the influence of the media and social networks available on the web. Lithium would modulate the opioid system in the cessation of NSSI, and the endorphin release mechanism would be more evident as a behavioral reward system aimed at attenuating psychiatric symptoms. The hypothesis described here could suggest the use of lithium for the specific behavior of the NSSI, regardless of the mental disorder in which it appears and relate the action of this medication to a possible effect on the opioid system.

Keywords: Lithium; Opioid receptor; Opiate; Nonsuicidal self-injury; Deliberate self-harm

INTRODUCTION

The intracellular signaling pathways involving the opioid system have components that are affected, *in vitro* and *in vivo*, by lithium. Even though all these models have their weaknesses due to the lack of replications and studies that consistently confirm the results, clinical observations of the effects of lithium on mood disorders and suicidal behavior deserve a theorization that offers more meaning to clinical practice [1-3]. Therefore, we would find a theoretical formulation involving models of the endogenous opioid system and lithium action mechanisms. There are no publications relating the effects of lithium on the endogenous opioid system and its clinical implications on mental disorders in humans. Understanding the opioid system goes through the basic definition of what neuroscientists call neuropeptides. These correspond to small proteins that act directly mediating or regulating synaptic neurotransmission in the Central Nervous System (CNS) and peripheral nervous system [4].

The term opiate refers to components structurally related to the products found in opium, a word derived from the Greek "opos", in the Latin described as "opium", meaning the "juice" of a species of the poppy plant, the *Papaver somniferum*. Opiates include natural plant alkaloids such as morphine, codeine, thebaine, and various semi-synthetic derivatives. An opioid is any agent that has the functional and pharmacological properties of an opiate. Endogenous opioids correspond to ligands for opioid receptors found in animals. The term endorphin is not only used synonymously with endogenous opioid peptides, but also refers to a specific endogenous opioid: β-endorphin [5]. The 1970's heralded a new era in the field of the opioid system with the discovery that opiates produce their effects by binding to specific sites in the brain, followed by the discovery that neurons

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also synthesize opioid-like peptides that produce similar effects through of actions on the same receptors. Coupled with the findings that reversible analgesia with naloxone could be produced by stimulating specific brain regions, this solidified the transformative idea that opiates act by mimicking the endogenous opioid system. Gene cloning and brain mapping revealed three opioid peptide systems encoded by individual genes for pre-pro-enkephalin, pre-pro-opiomelanocortin and pre-pro-dynorphin, that have distinct brain distributions. Likewise, three distinct receptors were cloned, μ (MOR), κ (KOR) and δ (DOR), with different affinity for the individual endogenous peptides and for the various pharmacologically used opiate drugs [6-11].

The location of the opioid receptors shows distinct but overlapping and similar distributions for the three types of them. These findings are shaping our evolutionary understanding of how different opioids produce their rewarding or dysphoric effects, pro- and anti-stress effects, cognitive effects that govern decisions, analgesic effects, and respiratory depression. For example, the rewarding effects of MOR activation were thought to be mediated by inhibition of GABA (Gamma-Aminobutyric Acid) interneurons in the Ventral Tegmental Area (VTA), disinhibiting dopaminergic neurons. However, recent evidence has revealed that this is primarily due to inhibition of potent GABA entry into the rostromedial tegmental nucleus and, to a lesser extent, inhibition of GABA entry to type 2 dopaminergic neurons in the Nucleus Accumbens (NAC). A similar inhibition of MOR receptors at GABA neurons in the Periaqueductal Gray Matter (PAG) and raphe magna may contribute to analgesia. Inhibition of GABA interneurons in the hippocampus by MOR and DOR agonists increases pyramidal cell activity, an effect that may facilitate learning and memory associated with drug use [7].

The direct inhibition of Locus Coeruleus (LC) noradrenergic neurons by action on the MOR attenuates the activation and promotes recovery of this central stress response system. In contrast, intense activation of neurons in the LC associated with opioid withdrawal may underlie the hyperarousal and sleep disturbances that interfere with the recovery process. Remarkably, the habenula, a brain region with especially high MOR density, is central to a circuit that mediates aversion and inhibits the reward system through inhibition of VTA dopaminergic neurons. MOR activation in the lateral habenula has mixed excitatory and inhibitory effects, and the effects in the medial habenula are not yet well characterized [7,12].

Although MOR is the primary target of opioid analgesics, DOR and KOR also regulate pain and analgesia, and the relative affinities of opioid analgesics for these receptors give them unique properties. The rewarding effects of opioids also depend on MOR, although DOR and KOR modulate them through regulation of hedonic response, mood and stress. Specifically, while MOR agonists produce euphoria and promote stress coping, KOR agonists produce dysphoria, stress-like responses, and negative affect, while DOR agonists reduce anxiety and promote positive affect. The multiplicity of opioid receptors inspired the design of agonists and antagonists with different potencies, efficiencies and selectivities for MOR, DOR and KOR, based on structural activity relationships and with different pharmacokinetics, in an effort to develop analgesics with fewer adverse effects [7,13,14].

OPIOD RECEPTORS

Opioid receptors are expressed by central and peripheral neurons, neuroendocrine (pituitary, adrenal), immune, and ectodermal cells. Human opioid receptors have been mapped to chromosomes 1p35-36 (DOR), 8q11.23–21 (KOR) and 6q25-26 (MOR) [17]. Opioid receptors belong to the Class A, gamma subgroup, of seven G-Protein Coupled Transmembrane Receptors (GPCRs) and show 50%-70% homology between their genes [6,18].

Although there is significant complexity in opioid-receptor interactions, some general principles are important for this work: (a) functional interactions between opioid receptors first suggested the existence of heterodimers of opioid receptors [19]. Heterodimers composed of different opioid receptors (e.g. DOR-MOR, DOR-KOR and MOR-KOR) or between opioid and non-opioid receptors (e.g. DOR-CB1 - with cannabinoid receptor type 1-CB1) have been reported, but the DOR-MOR heterodimer is the best studied [20]; (b) the gene for human MOR has at least two promoters and multiple exons, which generate at least 11 variants encoding multiple morphine binding isoforms, varying widely at their carboxyl termini. These alternative bindings would be crucial for the diversity of receptors and responses [21]; (c) MOR cloning discovered the complexity of its OPRM1 gene and the existence of multiple splice variants. Some of these variants are truncated and lack traditional G protein-coupled receptor structures. Specifically, OPRM1 contains two independent promoters: the exon 1 (E1) and exon 11 (E11) promoters, which generate multiple variants. The E1 promoter generates seven variants of the transmembrane domain of the G protein-coupled receptor, while the E11 promoter generates six truncated transmembrane domains; (d) genetic models in which splice variants are deleted are revealing the functional importance of different receptor components. These studies demonstrated that variants can influence the degree of tolerance, physical dependence and reward and the degree of signaling bias of certain agonists. This line of research could explain individual variability in opioid responses and be a basis for individualized therapy [21].

The differentiation of agonist/antagonist binding by sodium ions (ie, the “sodium effect”) was first reported with opioid receptors, an observation that has now been accepted as a widespread feature of GPCRs. The proposal would be: interchangeable conformations of receptors could be “forced” into a state of antagonism by sodium ions and neutralized by the divalent magnesium and manganese cations, but not by calcium. Crystallographic studies have now identified the sodium ion binding site within a GPCR, while modeling studies have suggested a similar location within the MOR. The ability of divalent cations to stabilize the agonist receptor conformation, counteracting the effect of sodium, proved particularly intriguing, leaving open the question of where within the

receptor divalent ions would bind [6,22]. Another topic referring this work would be the role of lithium on this "sodium effect" at the opioid receptor, considering the known transit of lithium in places occupied by sodium. Hypothetically, lithium would occupy the sodium site in the GPCR, but would not lead to antagonistic effects, that is, in this case, it would facilitate agonism or an agonist tonus of the receptor, potentiating the actions of agonist ligands, such as β-endorphin. But this hypothesis must be extensively studied and confirmed, serving at the moment only as a theoretical speculation.

INTERCELLULAR SIGNALING MECHANISMS OF THE OPIOID SYSTEM

The ligands correspond to the main endogenous opioids (endorphin and enkephalin), which will bind to their respective receptors: DOR, MOR and KOR, which are G protein-coupled receptors. G proteins they are so named because of their ability to bind to the Guanine nucleotides: Guanosine Triphosphate (GTP) and Guanosine Diphosphate (GDP). With receptor activation and G protein coupling, there is a resultant of intracellular events that are mediated by α and βγ subunits, including: inhibition of Adenylate Cyclase (AC) activity; reduced opening of voltage-gated calcium channels (reduces neurotransmitter release from presynaptic terminals); stimulation of potassium current through various channels (hyperpolarizes and inhibits postsynaptic neurons); activation of Protein Kinase C (PKC) and Phospholipase C (PLC); decrease in cellular Cyclic Adenosine Monophosphate (cAMP); and decreased Protein Kinase A (PKA) activation [5,19].

LITHIUM

Lithium salts share some characteristics with sodium and potassium. It is found in biological fluids and can be detected in brain tissue by magnetic resonance spectroscopy. Trace ions occur normally in animal tissues, but have no known physiological role. Clinically, lithium is known for its role in the treatment of bipolar disorder, the reduction of cluster headache symptoms, as an antidepressant enhancer in the treatment of refractory depression, and in the reduction of suicide attempts in patients with various mental disorders. There is also a description of a potential effect on reducing inflammation [23].

The main indications for lithium with consistent evidence of efficacy: acute manic episode; episode of major depressive disorder in Bipolar Disorder (BD)-(associated or not with antidepressants); prophylaxis of depressive and manic episodes in BD; prophylaxis of unipolar depressive episodes; prophylaxis of manic, hypomanic and depressive episodes in BD types I and II; reduced risk of suicide; potentiation of antidepressants in unipolar depressive episodes; decreased overall mortality in patients with mood disorders; cyclothymic disorder; and schizoaffective disorder (associated with antipsychotics) [24].

The literature shows that lithium acts on several and complex targets: possible substitution of sodium for lithium, impacting homeostasis of electrolyte balance and therefore, neuronal activation; modulation of membrane transport of different ions and neurotransmitter precursors; opioids can reduce the entry of Ca^{2+} into neurons, which can contribute to the analgesic effects of opioids - treatment with lithium can modify this effect by enhancing the opioid-mediated reduction of Ca^{2+} entry. This suggests that lithium may enhance the analgesic effects of opioids by modulating their effects on Ca^{2+} entry into neurons; it is a modulator of nitric oxide production in the brain; inhibits Gi and Gs proteins, leading to the initiation of adenylate and guanylate cyclases and different protein kinases; affects GSK-3β (Glycogen Synthase Kinase 3) and, therefore, both in Akt signaling (Protein kinase B) and in the Wingless integration site (Wnt); it is capable of inhibiting an inositol monophosphatase and an inositol polyphosphate-1-phosphatase, influencing inositol-dependent regulatory processes; reduces CREB (cAMP response element-binding protein) phosphorylation and decreases CREB-dependent gene expression; the anti-inflammatory properties of lithium lead to a negative regulation of pro-inflammatory cytokines and interleukin TNF-alpha; regulate the biosynthesis of different neurotransmitters and/or associated receptors (for example, modulation of the synthesis and intensity of serotonin and glutamate) [25-33].

LITHIUM AND THE OPIOID SYSTEM IN CLINICAL PRACTICE

There are few studies in the literature evaluating the relationship between lithium and the opioid system in mental disorders. However, in clinical practice, we can observe that the use of lithium carbonate, associated or not with other medications (such as antidepressants and antipsychotics), is associated with a reduction (and also disappearance), not only of thoughts of suicide, but also various psychiatric symptoms [34]. In this sense, conditions characterized by mood swings and affective instability, impulsivity, recurrent self-harm and recurrent suicide attempts could be practical examples of the proposed pharmacodynamics effect.

Taking the opioid system as the basis of this paradigm in the treatment of mental disorders, the symptomatology and vulnerability of certain patients could be explained by the following alterations: a low basal level of opioids associated with hypersensitivity of the MOR, where an opioid discharge after a painful stimulus would lead to an exacerbated response when compared to patterns with normal baseline opioid levels. The low baseline level could be observed clinically as a chronic dysphoria, lack of a sense of well-being and the feeling of "being dead inside", while the exacerbated stimulation of the MOR (through self-harm, for example) would take to an important relief of pain and restoration of a sense of well-being. This model is based on observational studies: Stanley et al. observed low levels of opioids in the Cerebrospinal Fluid (CSF) of patients with Cluster B personality disorder and a history of self-mutilation [35]; Schmhal, et al. observed an increase in the pain threshold after stressful events in patients with borderline personality disorder [36]; Sher and Stanley observed some positive effect of using naltrexone, an opioid antagonist, in the treatment of self-injury [37]; Yang et al. found a possible decrease in neuropathic pain [38].

Affective dysregulation and self-mutilation seem to be associated with a poor perception of physical pain. Recently, van der Venne

et al. found that both reduced pain sensitivity and basal opioid deficiency were independent biological correlates and potential risk-factors for nonsuicidal self-injury [39].

Simeon et al. suggested that self-mutilation would work as a "self-treatment" process, since it drives to an improvement in affection, even if briefly [40]. This suggestion was based on clinical observation that patients with borderline personality disorder show a decrease in negative affect, an increase in positive affect, and an increase in dissociative symptoms after self-injury.

Nonsuicidal Self-Injury (NSSI) is a behavior that has been spreading significantly in the adolescent population, especially in the last 10 years, probably due to the influence of the media and social networks available on the web [41]. Therefore, it is considered that the behavior of self-mutilation is influenced by culture and, once started, would promote changes in the endorphin system, favoring the repetition of these acts with a consequent feeling of relief for suffering.

The voluntary execution of a skin wound leads to the stimulation of type Aδ fibers, which activates the projection neurons of the posterior horn of the spinal cord, with the stimuli being forwarded to the thalamus, primary somatosensory cortex and limbic system, where the feeling of pain would become conscious [5]. Patients who perform self-injury, there would already be a previous dysfunction of the endogenous opioid system. The cuts would trigger an intense release of endorphins, which would occupy their sites in the central MOR, with a consequent improvement in affective changes. The action of cutting oneself is generally described as generating a sense of relief for different types of feelings: anger, "emotional pain", anguish, sadness, intense anxiety and fear, thoughts of death and suicide. The most frequent cuts are superficial and are not necessarily linked to the desire to die or commit suicide. They are carried out in moments of intense suffering, associated with the feeling of despair, which impel the individual to mutilate himself and mitigate the condition. Some teens describe the effects as being immediate.

Therefore, lithium would modulate the opioid system in the cessation of NSSI, and the endorphin release mechanism would be more evident as a behavioral reward system aimed at attenuating psychiatric symptoms. The hypothesis described here could suggest the use of lithium for the specific behavior of the NSSI, regardless of the mental disorder in which it appears (depression, bipolar disorder, dysthymia, phobic and anxiety disorders, personality disorders, impulse disorders and substance related disorders) and relate the action of this ion to a possible effect on the opioid system. In this hypothesis, lithium would have its action (1) modulating the existing imbalance between the decreased baseline levels of endogenous opioids and MOR, and (2) reducing the activity of the dopaminergic reward circuit involving the substantia nigra and nucleus accumbens, activated by the hyperstimulation of the endogenous opioid system during recurrent self-mutilation or self-stimulation.

According to several hypotheses about the etiology of mental disorders, the models arise from the clinical observation of some drugs, their mechanisms of action, which are extrapolated to neurobiology. Inferences are made since the drugs act on certain neurotransmitters, and they would consequently be involved in the pathophysiology of these disorders. There are studies with mice that observed a decrease in the tolerance of morphine used continuously after lithium administration. Several research groups have reported pharmacodynamic interactions between lithium and the opioid system [42-54]. In particular, lithium affects analgesia, reduces tolerance and dependence on morphine. It has been shown that lithium inhibits morphine withdrawal signs in morphine-dependent mice, reduces the self-stimulation facilitated by morphine and the expression of tolerance to morphine [1,55-57]. Lithium attenuates thermal hyperalgesia and mechanical allodynia in different models of neuropathic pain in rats through a naloxone-sensitive mechanism, suggesting that the action of lithium is dependent on the opioid receptor.

Studies that have examined the role of lithium in pain responses are, unfortunately, contradictory to date. On one hand, some studies suggest that lithium can actually make pain worse (hyperalgesia) and decrease the effectiveness of pain-relieving drugs like morphine. In fact, in some cases, lithium overdose can cause nerve damage or muscle weakness (peripheral neuropathy or myopathy) in patients [58-61].

In animal studies involving rats, it has been suggested that lithium can have a biphasic effect on morphine-induced pain relief. This means that at certain concentrations of lithium and under certain pain test conditions, lithium can either enhance or reduce the pain relief provided by morphine. It's important to note that animal studies do not necessarily translate directly to humans, and the effects of lithium on pain responses in humans may be different [47,62-64].

Interestingly, lithium has been shown to alleviate cluster headaches, which are characterized by episodes of extreme pain. Additionally, both acute and chronic administrations of lithium have been shown to induce direct analgesia in neuropathic pain states, and to potentiate morphine analgesia in animal models. The mechanism behind these analgesic effects is not well understood, although lithium may play a role in the selective regulation of neurotrophins, which are proteins that support the growth and survival of nerve cells [38,65].

Studies have shown that lithium has the potential to reverse thermal hyperalgesia, mechanical allodynia, and cold allodynia induced by partial sciatic nerve ligation in rats. These findings suggest that lithium has an analgesic effect on neuropathic pain, which is typically resistant to standard analgesics such as opioids. Interestingly, the mechanism of lithium-induced analgesia appears to be naloxone-responsive. Naloxone is a medication used to reverse the effects of opioids, which suggests that lithium may act on the same pathway as opioids to produce its analgesic effects. Finally, it has been demonstrated that lithium can prevent paclitaxel-induced peripheral neuropathy in mice, which

is a common side effect of chemotherapy that can cause pain and sensory dysfunction [66-71].

However, the exact mechanisms underlying the interaction between lithium and the opioid system are not fully understood. Further research is needed to determine the potential clinical implications of this relationship. In this regard, if the behavioral mechanism involving patients with NSSI is associated with changes in the opioid system, mainly β-endorphin, we would have a pathophysiological model of repetitive self-injury in patients with mental disorders, which would be directly associated with the effect of lithium in this same system, attenuating the desire and impulse for self-aggressiveness through still unknown mechanisms. Another focus of the model would be the identification of which patients would be more responsive to lithium treatment in the cessation of NSSI. Then, assuming the background of lithium and opiate system as a possible hypothesis, new studies would be necessary to clarify the mechanisms toward the identification of those patients that would benefit from the different responses to treatment.

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