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Case Study

Δ^9-Tetrahydrocannabinol and Morphine as Potential Modulators of STAT3 and IL-6 in Ischemic Stroke: A Case Study and *In Silico* Approaches

Hasnae Houmman[1,2]*, Mohamed Chebaibi[2,3], Siham Bouchal[4], Faouzi Belahcen[4], Sanae Achour[1,2]

1. *Toxicology-Pharmacology Service, Hassan II University Hospital, Fez, 30000, Morocco*
2. *Biomedical and Translational Research Laboratory, Faculty of Medicine and Pharmacy of Fez, Sidi Mohamed Ben Abdellah University, Fez, 30000, Morocco*
3. *Higher Institute of Nursing Professions and Health Techniques, Fez 30000, Morocco*
4. *Medical Neurology Service, Hassan II University Hospital, Fez, 30000, Morocco*

**Corresponding author: Hasnae Houmman ; hasnae.houmman@usmba.ac.ma*

Abstract

Ischemic stroke is a leading cause of mortality and disability worldwide, with inflammation playing a central role in its pathophysiology. STAT3 and IL-6 are key players in the neuroinflammatory response that underlies neuronal injury and repair processes. Δ^9-tetrahydrocannabinol (THC), the primary psychoactive in cannabis, and morphine, a widely used opioid, are well known to modulate these pathways. Here, we present a combined case study of ischemic stroke and *in silico* analyses to assess the involvement of THC and morphine in stroke pathogenesis. The case study concerns a young man with confirmed cannabis and opiate use and acute ischemic stroke. *In silico* studies reveal that STAT3 is a common target of THC and ischemic stroke, while IL-6 is the key target of morphine in relation to stroke. THC demonstrates a dual capacity to both activate and inhibit the JAK/STAT3 pathway, while IL-6, via JAK/STAT3 signaling, exhibits both neuroprotective and destructive properties in ischemic stroke. Our results highlight the complex interplay between STAT3, IL-6 and external agents such as THC and morphine in stroke pathology. They highlight the need for further experimental studies to validate these molecular interactions and assess the therapeutic and pathological implications of targeting these pathways in the management of ischemic stroke.

Keywords: Ischemic stroke, case study, *in silico* approaches, STAT3, IL-6

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Abbreviation

CNR1: Cannabinoid Receptor 1
CRHR1: Corticotropin-Releasing Hormone Receptor 1
DRD2: Dopamine Receptor D2
GSK3B: Glycogen Synthase Kinase 3 Beta
HDAC1: Histone Deacetylase 1
IDH1: Isocitrate Dehydrogenase 1
IL6: Interleukin 6
IS: Ischemic Stroke
JAK: Janus Kinase
JAK2: Janus Kinase 2
MAOA: Monoamine Oxidase A
MAOB: Monoamine Oxidase B
MAPK14: Mitogen-Activated Protein Kinase 14
MDM2: Mouse Double Minute 2 Homolog
NOS3: Nitric Oxide Synthase 3
NR3C1: Nuclear Receptor Subfamily 3 Group C Member 1 (Glucocorticoid Receptor)
OPRM1: Opioid Receptor Mu 1
PARP1: Poly (ADP-Ribose) Polymerase 1
PKM: Pyruvate Kinase M1/2

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STAT3: Signal Transducer and Activator of Transcription 3

TNF-α: Tumor Necrosis Factor-α

TXN: Thioredoxin

Δ^9-THC: Δ^9-Tetrahydrocannabinol

1. Introduction

Ischemic stroke is a medical condition characterized by the interruption of blood flow to the brain, leading to a reduction in oxygen and nutrient supply. This deprivation results in cellular injury, which, if prolonged, causes irreversible neuronal death. The primary causes include thrombotic or embolic occlusions of cerebral arteries, which are often associated with atherosclerosis or cardiovascular disorders (Dirnagl et al., 1999). Clinically, ischemic stroke manifests sudden neurological deficits, such as motor weakness, speech disturbances, and cognitive impairments (Gottesman and Hillis, 2010). Stroke ranks as the second leading cause of mortality worldwide, contributing to 11.6% of total deaths in 2019 (Feigin et al., 2021). Ischemic stroke, the predominant type, constituted 62.4% of all stroke cases globally during the same year (Feigin et al., 2021). In France, 25% of ischemic strokes occur before the age of 65. Ischemic stroke is the most common form of acquired disability; the second most prevalent cause is dementia, and it is the third leading cause of death in industrialized countries (Lecoffre et al., 2017). In an epidemiological study conducted in Casablanca and Rabat, two Moroccan cities, crude stroke prevalence was determined to be 284 per 100,000 people, with ischemic stroke accounting for 70.9% of total stroke cases (Engels et al., 2014). The most frequent causes of strokes were atherosclerosis and cardioembolic disease. Mortality rates were between 3% and 13% during the acute phase. Three-month mortality ranged from 4.3% to 32.5% (Kharbach et al., 2019).

Signal Transducer and Activator of Transcription 3 (STAT3; **2.1.1.** is a major transcription factor engaged in inflammation and apoptosis and pierces the main pathophysiology process of ischemic stroke; thus, the application of ischemic stroke in this study is justified (Millot et al., 2020). In ischemic stroke, STAT3 has dual functions: generally, it tends to activate neuroinflammation but also leads to tissue repair (Zhong et al., 2021). On the other hand, the overactivation of STAT3 increased neuroinflammation by expressing several inflammatory mediators, including TNF-α. This condition will finally enhance neuronal damage and blood-brain barrier disruption (Zhu et al., 2021).

Multiple studies have shown STAT3 inhibition to be beneficial in ischemic stroke outcomes and neuroinflammation. These studies highlight the role of the JAK/STAT3 signaling pathway in reducing the expression of pro-inflammatory mediators, neuronal apoptosis, and oxidative stress, all of which contribute to the pathophysiology of ischemic stroke (Li et al., 2019; Xu et al., 2019; Zhu et al., 2021). Interleukin-6 (IL-6), the mediator inflammatory, is a cytokine that participates in many activities, hence playing a complex role in the pathophysiology of ischemic stroke. IL-6 is a pro-inflammatory mediator, rapidly increasing after cerebral ischemia (Cojocaru et al., 2009). Studies proved that activating IL-6 and other cytokines fostering cooperation within ischemic regions contributes to the exacerbation of damage (Zhu et al., 2022).

This paper presents a case study of ischemic stroke triggered by toxic agents. Toxicology reports show positive results for Δ^9-Tetrahydrocannabinol and Opiates, which contributes toward the possibility of these drugs in the development of ISC. To comprehend the molecular mechanisms underlying this association, we designed an *in silico* study to analyze how THC and opiates could be implicated in the development of ischemic stroke.

2. Materials and Methods

2.1. *In silico* study

2.1.1.Potential Targets of Δ^9-Tetrahydrocannabinol and opiates

ChEMBL database (https://www.ebi.ac.uk/chembl/) and the SwissTarget Prediction tool (http://www.swisstargetprediction.ch/) were used for the identification of potential targets for Δ^9-Tetrahydrocannabinol and Morphine (the primary opiate). SwissTargetPrediction determines compound targets by examining similarities in chemical structures, while ChEMBL provides a more extensive range with its larger database of compounds and their corresponding targets. The results from both sources were merged, with duplicates removed. To ensure consistency, the identified targets were mapped to gene symbols using the UniProt database (https://www.uniprot.org/) (Xian et al., 2021).

2.1.2. Potential Targets of Ischemic Stroke

The GeneCards database (https://www.genecards.org/) was utilized to identify targets linked to Ischemic Stroke by searching the term "Ischemic Stroke." GeneCards offers a comprehensive collection of genomic, proteomic, and disease-related information. Higher scores in GeneCards indicated a more significant correlation between a target and the related disease (Xian et al., 2021).

2.1.3. Protein-Protein Interaction (PPI) Network for Δ^9-Tetrahydrocannabinol-Ischemic Stroke and Morphine-Ischemic Stroke

To investigate the interactions between targets linked to Δ^9-Tetrahydrocannabinol-Ischemic Stroke and Morphine-Ischemic Stroke, a Venn diagram was created to pinpoint common targets. These shared targets were examined through the STRING database (https://string-db.org/) to build a protein-protein interaction (PPI) network, showcasing their connections. Cytoscape software was then used to rank the most critical targets by evaluating the degree

values of the interaction nodes in the network (Xian et al., 2021).

3. Clinical Observation and In-Silico Study Results

3.1. Clinical Observation

A 30-year-old male smoker for five years presented to the emergency department with sudden-onset heaviness in the left hemibody. Clinical examination revealed a conscious patient with left hemiparesis involving facial muscles. The remainder of the clinical examination, including cardiovascular assessment, was unremarkable and did not aid in identifying the etiological diagnosis.

A CT scan performed 12 hours after symptom onset showed a right parietal hypodensity consistent with a superficial right middle cerebral artery infarction (Figure 1).

MRI at 24 hours revealed no additional abnormalities. A comprehensive etiological workup including Doppler ultrasound of the supra-aortic trunks, transthoracic and transesophageal echocardiography, 48-hour ECG monitoring, and laboratory tests (complete blood count, prothrombin time, activated partial thromboplastin time, antithrombin, vitamin B12, proteins C and S, HbA1c, lipid profile, TSH, HIV, hepatitis B and C serologies, and syphilis) was normal.

The toxic origin was suspected, and a toxicological test was carried out in the blood and urine using multi-drug screening cassettes from InTec PRODUCTS, INC. The results were positive for cannabis and opiates in the urine.

The patient later admitted to having recently used cannabis significantly. The patient was hospitalized in a neurovascular unit and showed good progress after functional rehabilitation. A consultation to assist with withdrawal was offered to the patient before he was discharged from the hospital.

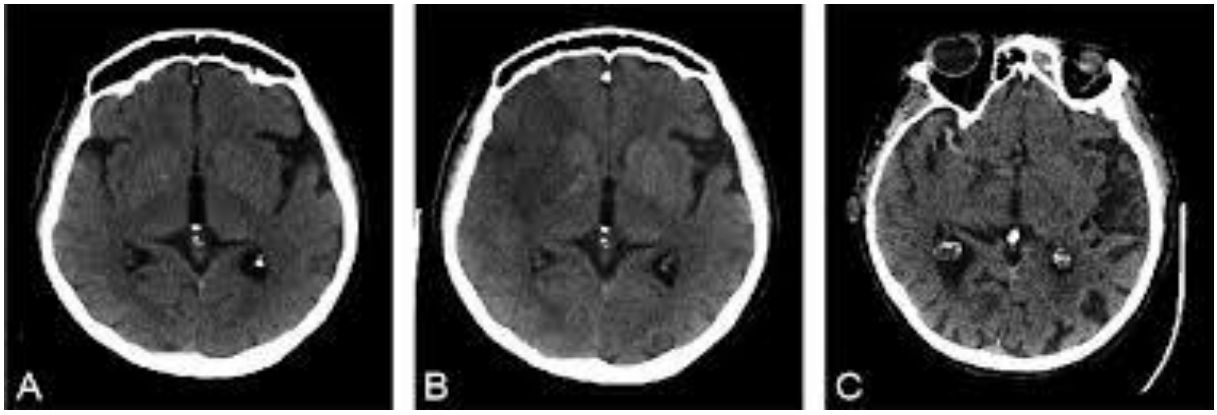

Figure 1: Brain scan showing right parietal hypodensity consistent with right superficial Sylvian infarction

3.2. *In silico* results

After standardization in UniProt and eliminating duplicate entries, we identified 100 potential targets for Δ^9-tetrahydrocannabinol using the SwissTargetPrediction and ChEMBL databases. Similarly, 100 potential targets for morphine were identified. Additionally, 7,381 ischemic stroke-related targets were extracted from the GeneCards database. Seventy-seven overlapping targets were identified between the Δ^9-Tetrahydrocannabinol-associated targets and ischemic stroke-related genes, and 84 overlapping targets were identified between morphine and ischemic stroke targets (Figure 2).

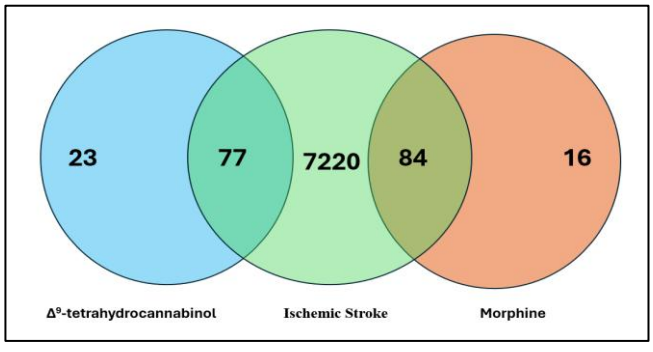

Figure 2: Screening analysis of overlapping genetic symbols between Δ^9-Tetrahydrocannabinol and morphine and ischemic stroke

Correlation analysis revealed strong interrelations among the shared targets (Figure 3). Cytoscape software was used to evaluate these targets further and compute their correlation degree values (Table 1).

For Δ^9-Tetrahydrocannabinol, targets such as STAT3, PARP1, and PKM exhibited notably higher degree values,

suggesting their significant roles as key contributors to Δ^9-Tetrahydrocannabinol-induced ischemic stroke. For morphine, targets including IL6, GSK3B, and NR3C1 presented the highest degree values.

Table 1: Correlation degree values using Cytoscape software

Δ^9-tetrahydrocannabinol - Ischemic Stroke interactions			
Gene name	Degree	Gene name	Degree
STAT3	20	CNR1	10
PARP1	13	TXN	10
PKM	13	JAK2	10
CRHR1	12	MDM2	9
IDH1	12	MAPK14	9
Morphine - Ischemic Stroke interactions			
Gene name	Degree	Gene name	Degree
IL6	36	MAOB	17
GSK3B	22	OPRM1	15
NR3C1	19	NOS3	15
MAOA	19	HDAC1	14
DRD2	18	JAK2	14

4. Discussion

Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that mainly participates in many physiological and pathological processes, such as cell survival, proliferation, differentiation, and immune response (Hillmer et al., 2016; Hirano et al., 2000). It gets activated by upstream signaling pathways, particularly through the Janus kinase (JAK) pathway; after that, it translocates to the nucleus, where it regulates the expression of genes involved in those activities (Bhattacharya and Schindler, 2003). Dysregulation of STAT3 has been implicated in some diseases, including ischemic stroke (Vogel et al., 2015; Zhu et al., 2021).

Many studies have shown that STAT3 gets activated in experimental stroke models, both *in vivo* and *in vitro*. After it is activated, STAT3 controls the expression of many genes involved in several cell activities, which are believed to greatly affect neural harm and healing processes (Liang et al., 2016; Raible et al., 2014). Furthermore, there is debate regarding whether activating this pathway enhances neurological recovery. Some research indicates that interventions targeting STAT3 signaling post-stroke may improve functional outcomes and/or reduce cell death (Zhu et al., 2013).

A) **B)**

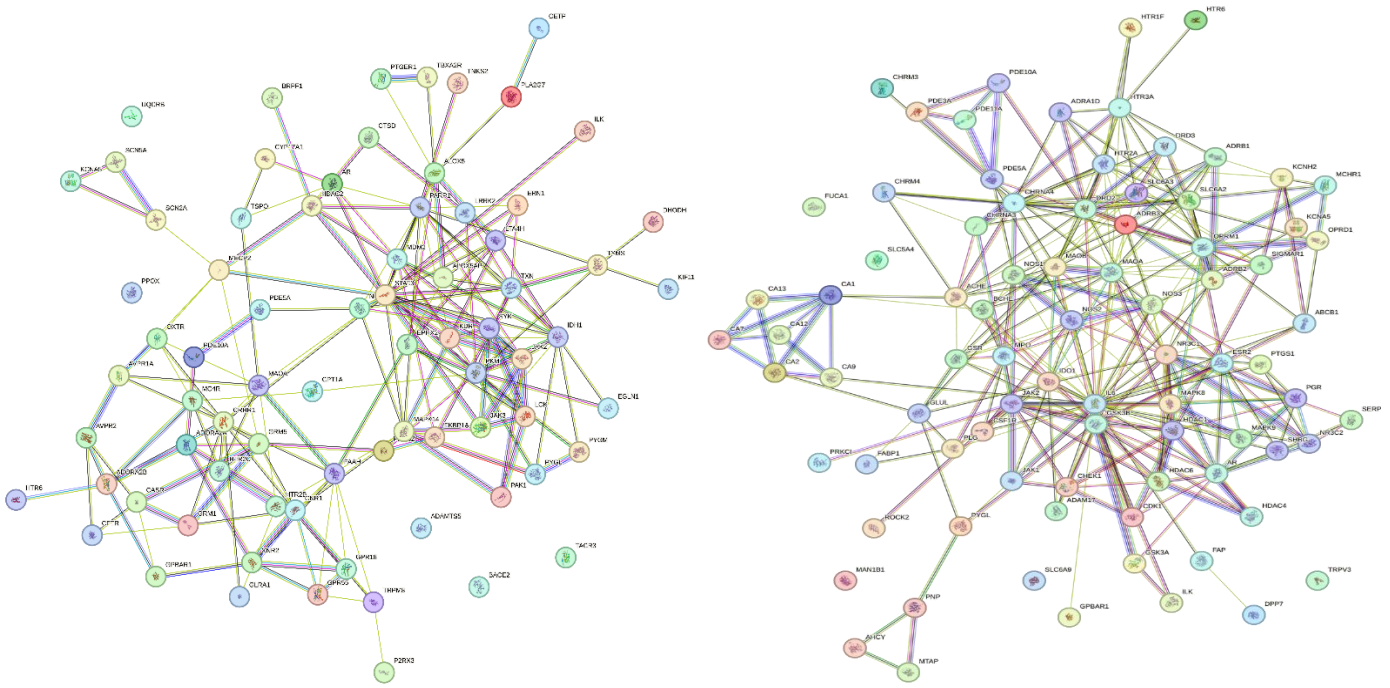

Figure 3: Protein-protein interaction (PPI) network analysis. (A): Overlapping genes between Δ^9-tetrahydrocannabinol and ischemic stroke. (B): Overlapping genes between morphine and ischemic stroke

Conversely, according to author studies, activation of STAT3 can exacerbate neuroinflammation, contributing to secondary brain injury, following ischemia, activated microglia and expression of many genes that encode proinflammatory mediators, including cytokines, chemokines, adhesion molecules, and inflammatory enzymes (Yi et al., 2007). Persistent STAT3 activation may amplify the production of inflammatory mediators, increase oxidative stress, and promote neuronal damage (Yu et al., 2013).

Cannabis has become the most commonly used illicit drug globally since the 1990s. Behind its reputation as a "soft drug" lie numerous somatic and psychiatric complications. Given its widespread use, any pathology, particularly in young individuals, should prompt consideration of its potential role (Mallaret et al., 2005). A temporal relationship between cannabis consumption and neurovascular events is frequently reported (Desbois and Cacoub, 2013; Jouanjus et al., 2014; Thomas et al., 2014), often with increased drug use hours or days before the stroke (Lawson and Rees, 1996; Mateo et al., 2005). Several pathophysiological hypotheses attempt to link cannabis to stroke. Vasospasm was initially suspected following reports of recurrent transient ischemic attacks (TIA) during cannabis use (Lawson and Rees, 1996) or ischemic strokes resolving rapidly (Finsterer et al., 2004). Moreover, the risk of myocardial infarction is 4.8 times higher within an hour of cannabis consumption in patients with angina (Mittleman et al., 2001).

Δ^9-Tetrahydrocannabinol (THC), the primary psychoactive constituent of cannabis, modulates various cellular signaling pathways. The primary molecular targets of THC are cannabinoid receptors CB1 and CB2 (Matsuda et al., 1990; Munro et al., 1993). CB1 receptors are predominantly located in the central nervous system, whereas CB2 receptors are mainly distributed in the peripheral nervous system and immune cells. These cannabinoid receptors belong to the G-protein-coupled receptor family and regulate various physiological functions (Maia et al., 2023).

THC has the capability to activate Janus kinases (JAKs)/signal transducer and activator of transcription proteins (STATs) families (Carmona Rendón et al., 2023; Sido et al., 2015). The activation of Janus kinases (JAKs) leads to the phosphorylation of STAT3 at tyrosine residues, facilitating its dimerization and nuclear translocation. STAT3 regulates genes involved in anti-inflammatory responses, cell cycle progression, and apoptosis in the nucleus. On the other hand, several studies have shown the ability of THC to inhibit the JAKS/STAT signaling pathway (Chang et al., 2017; Ngaotepprutaram et al., 2013).

In our *in-silico* study, STAT3 emerged as a shared target between THC and ischemic stroke, highlighting the necessity for *in vivo* and *in vitro* investigations to evaluate THC's potential to activate the JAK/STAT pathway and its role in the pathogenesis of ischemic stroke.

In this case study, toxicological analysis also detected opiates, which may induce cerebral lesions through hemodynamic mechanisms. Iterative use causes systemic effects, including abrupt changes in blood pressure and heart rate (Frishman et al., 2003). Respiratory depression, symptomatic in overdose cases, may result in hypoxic leukoencephalopathy, occasionally associated with localized ischemia in areas sensitive to hypoxia (Büttner et al., 2000).

We selected morphine as the representative opioid for our *in silico* study, and the results identified IL6 as the primary target of morphine most strongly associated with ischemic stroke.

Interleukin-6 (IL-6) is a multifunctional cytokine that plays a central role in immune regulation, inflammation, and acute phase response. IL-6 is produced by different cell types such as macrophages, endothelial cells, astrocytes, and neurons; its function in the inflammatory response is complex as it can support both pro-inflammatory and anti-inflammatory activity depending on the cellular and molecular environment (Scheller et al., 2011). In ischemic stroke, IL-6 is one of the main mediators of the neuroinflammatory response to ischemic brain injury. During ischemic brain injury, IL-6 levels become extremely elevated in the brain and cerebrospinal fluid as part of the immune response against neuronal injury (Cojocaru et al., 2009). This cytokine has both neuroprotective and destructive properties. The neuroprotective aspect includes the possibility of the expression of certain neurotrophic factors and an increase in neuronal survival (Feng et al., 2015).

IL-6 signaling is mainly mediated by the JAK/STAT3 pathway, where it activates STAT3, a transcription factor involved in both cellular repair and inflammatory activities; this process may contribute to the pathogenesis of IL-6-mediated ischemic stroke (Aliena-Valero et al., 2021; Zhong et al., 2021).

Although our patient's outcome was favorable, the literature reports cases of extensive ischemic strokes with poor prognoses. These findings should alert illicit substance users to the severity of their consumption and encourage healthcare providers to consider toxic causes when faced with acute vascular presentations in young patients.

5. Conclusion

Based on case studies and *in silico* approaches, this work highlights the complex interplay between the JAK/STAT3 pathway, ischemic stroke and external factors such as Δ^9-tetrahydrocannabinol (THC) and morphine. STAT3 appears as a key transcription factor involved in various physiological and pathological processes, including neuroinflammation and neuronal survival, with its dysregulation implicated in ischemic stroke. While THC shows the ability to activate and inhibit the JAK/STAT3 pathway, its dual function requires further *in vivo* and *in vitro* studies to understand its effect on ischemic stroke outcomes.

The results highlight the need for a deeper understanding of how external agents impact STAT3 and IL-6 signaling, which could lead to new therapeutic perspectives or reveal the risks associated with these agents. Future research should aim to verify these results *in silico* experimentally and to detail the mechanism of STAT3 and IL-6 modulation

by THC and morphine, discussing their therapeutic and pathological implications in ischemic stroke.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding authors.

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Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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