In The Name Of Allah

Opioids and Viral Infections

PhD Seminar
Department of Bacteriology and Virology

Presented by:
Pegah Khales

Supervisor:
Dr. Sarvari

Outline

- Introduction
  - Opioid classification
  - Opioid receptors
  - Opioid receptor signaling
- Opioids and immune function
- Opioid system effects on viral infections

Introduction

- Opioids and their receptors have the ability to alter immune function, which affects disease progression and outcome.

- In vitro and in vivo findings as well as observations in humans indicate that opioids and their receptors positively or negatively affect viral replication and virus-mediated pathology.

Opioid classification

Opiate and Opioid ?

- The term opiates include natural compounds obtained from opium poppy. (such as morphine, codeine and thebaine).

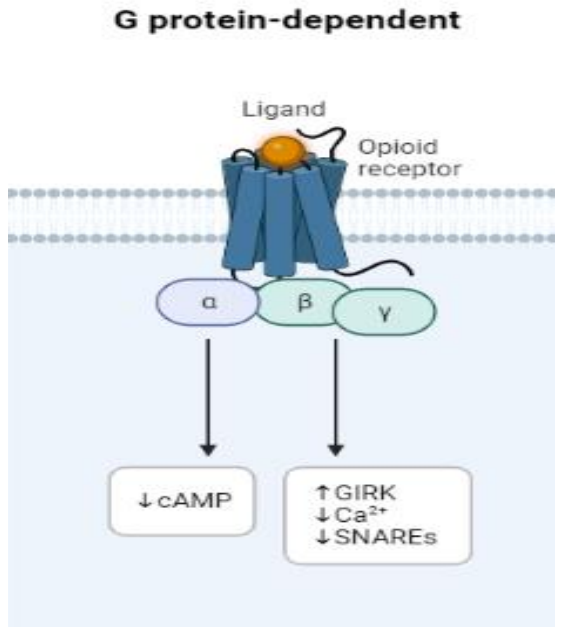
- Opioids are a group of endogenous and exogenous/synthetic compounds that function through activation of opioid receptors

Table 1 Synthetic representation of opioids classification

Opiates[a]	*Synthetic opioids*	*Semisynthetic opioids*	*Endogenous opioids*
Morphine ✓	Alfentanyl ✓	Buprenorphine[b]	Endorphins ✓
Codeine ✓	Fentanyl ✓	Hydrocodone[b]	Enkephalins
Thebaine	Meperidine	Oxycodone[b]	Dynorphins
	Methadone ✓	Oxymorphone[b]	
	Pentazocine	Hydromorphone[c]	
	Propoxyphene	Heroin[c] ✓	
	Sufentanyl		

[a]Definition: naturally occurring compounds derived from the active alkaloids of the opium poppy.
[b]from thebaine.
[c]from morphine.

Opioid receptors

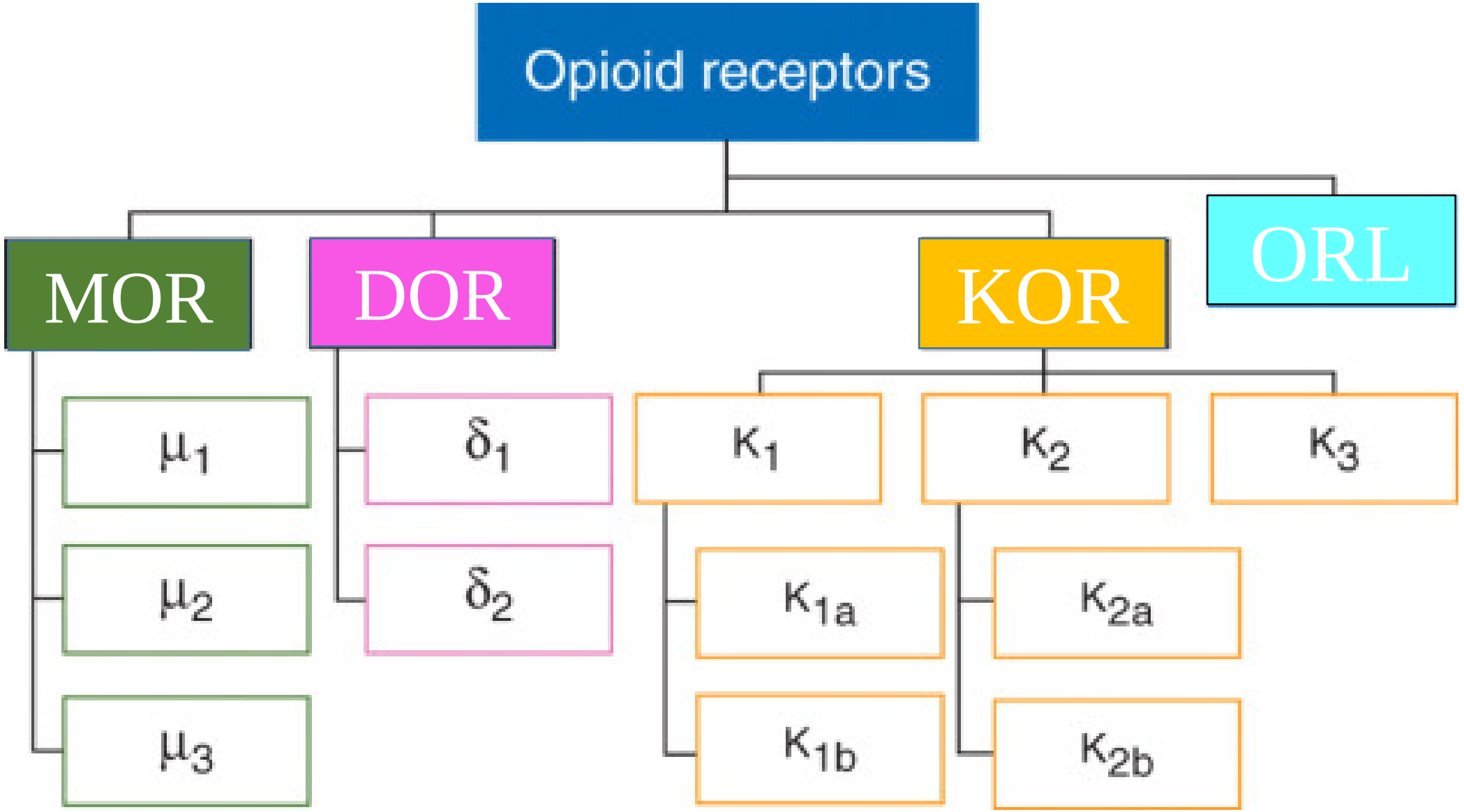


Opioid receptors have been isolated, cloned, and classified as:

1) μ-opioid receptors (MORs)
2) δ-opioid receptors (DORs)
3) κ-opioid receptors (KORs)
4) opioid-like or nociceptin/orphanin receptors (ORL)

➢ OPRM1: Opioid Receptor Mu1

Receptors	Gene
(μ1, μ2, μ3)	➢ OPRM1
(δ1, δ2)	OPRD1
(κ1, κ2, κ3)	OPRK1
N/OFQ	OPRL1


Opioid receptors
MOR
DOR
KOR
ORL
μ1
μ2
μ3
δ1
δ2
κ1
κ2
κ3
κ1a
κ1b
κ2a
κ2b

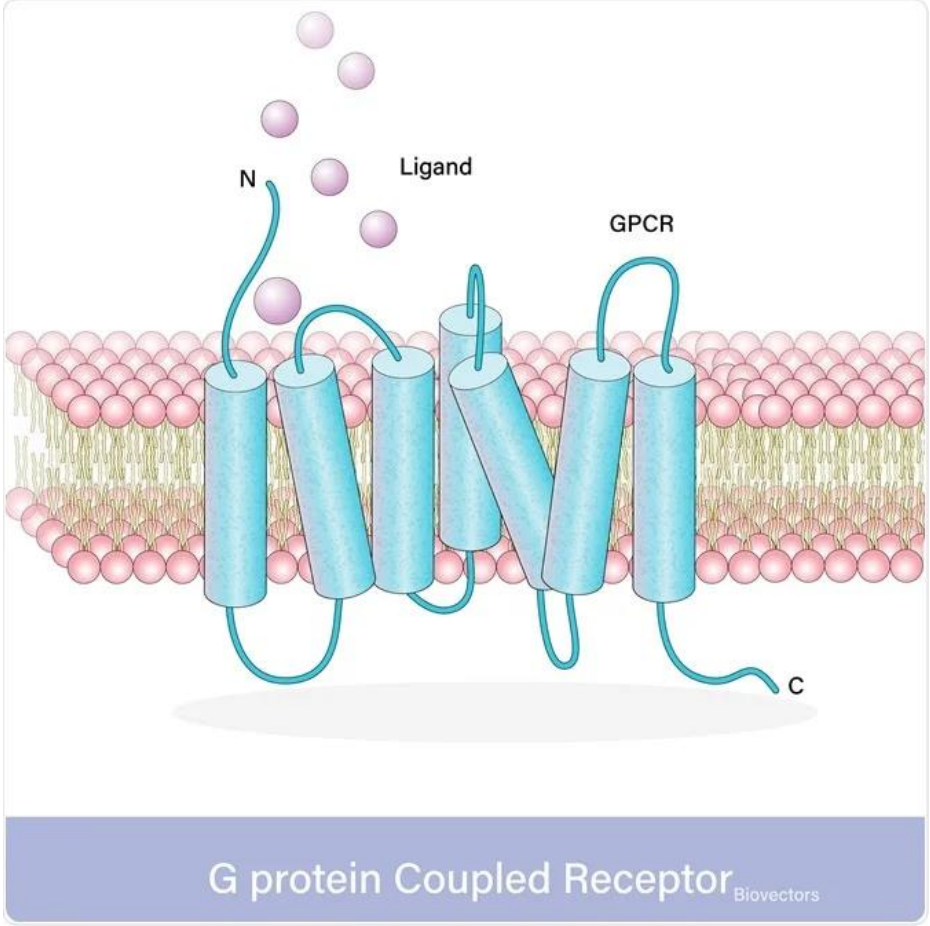
Opioid Receptors

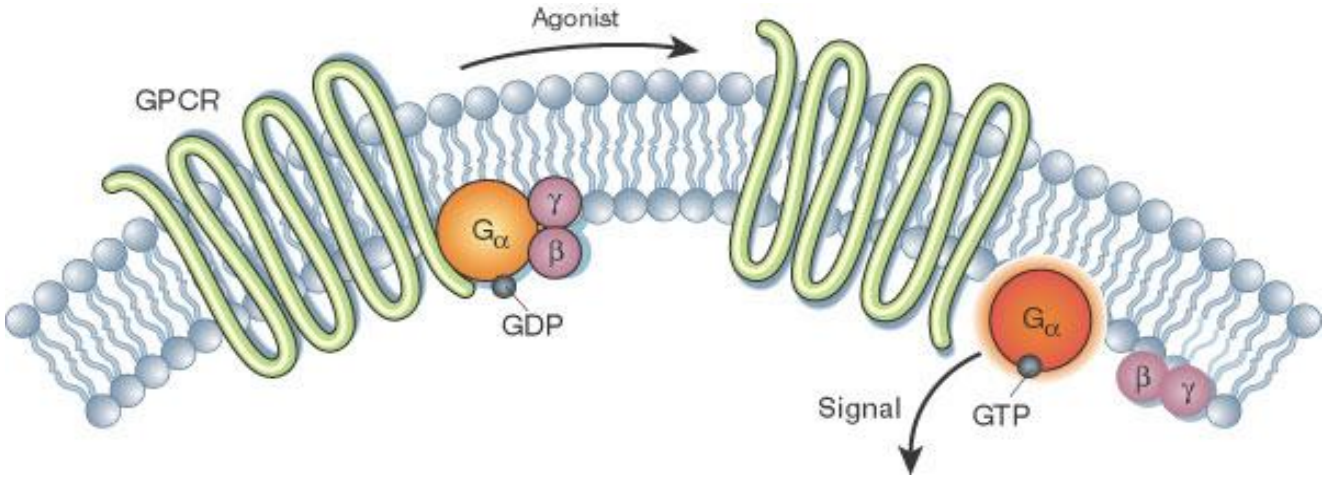
Type of receptor	Location	Effects
μ (Mu)	•Brain stem •Lymbic system •Dorsal horn of spinal cord	•Sedation •Analgesia •Euphoria •Respiratory depression •Constipation •Miosis •Itching
K (Kappa)	•Central cortex •Hippocampus •Mid brain	•Psychomimetic effects: dysphoria •Analgesia
δ (delta)	•Brain •Spinal cord	•Spinal analgesia •Respiratory depression

✓ The Mu receptor is the main receptor for opioid agonists used in pain management.

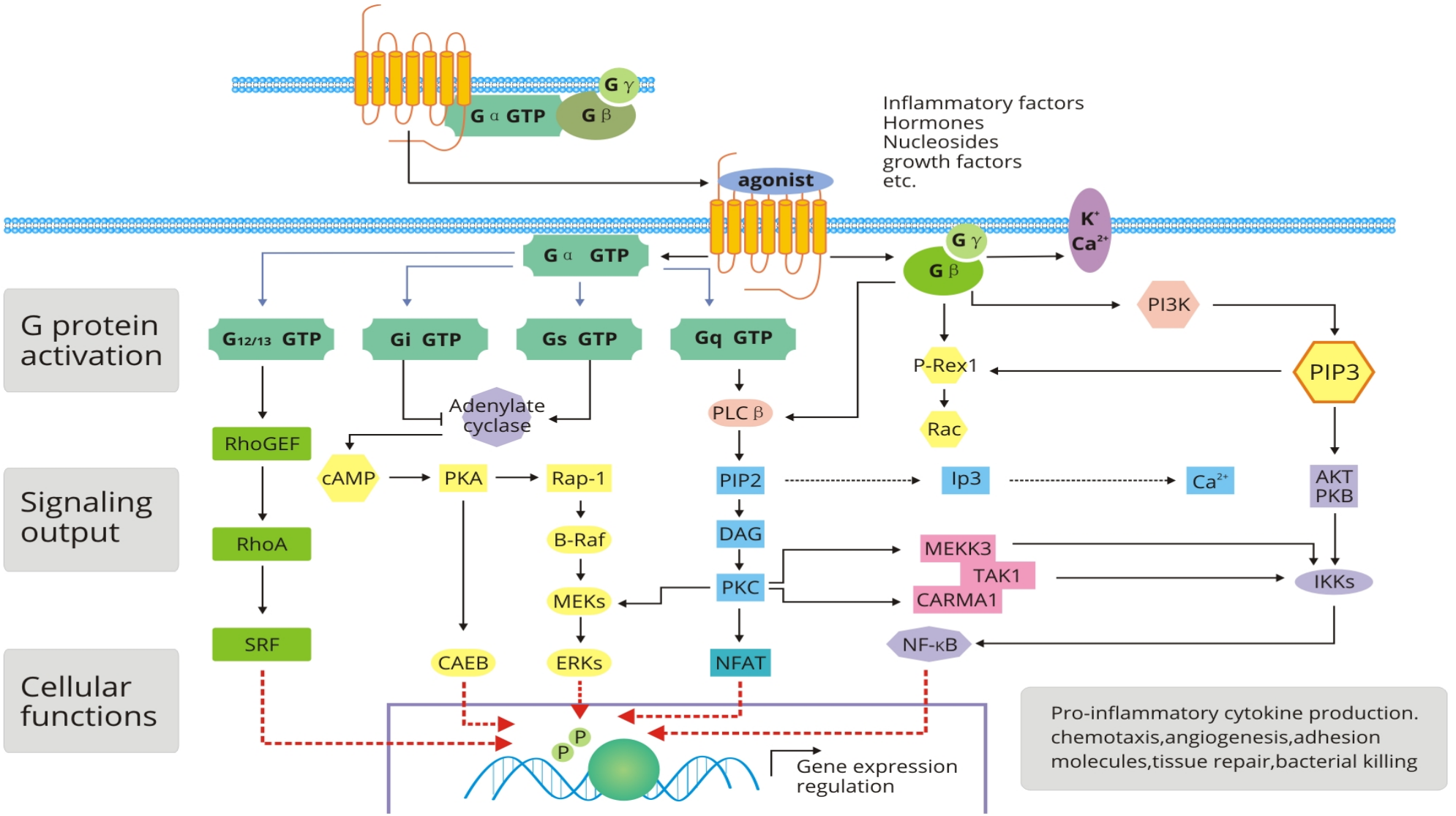
Opioid receptors

- Opioid Receptors are G protein-coupled receptors.
- They mediate the human body's response to most hormones, neurotransmitters, drugs.
- All GPCRs consists of seven transmembrane spanning proteins that couple to intracellular G proteins.





G protein-coupled receptor signaling pathway

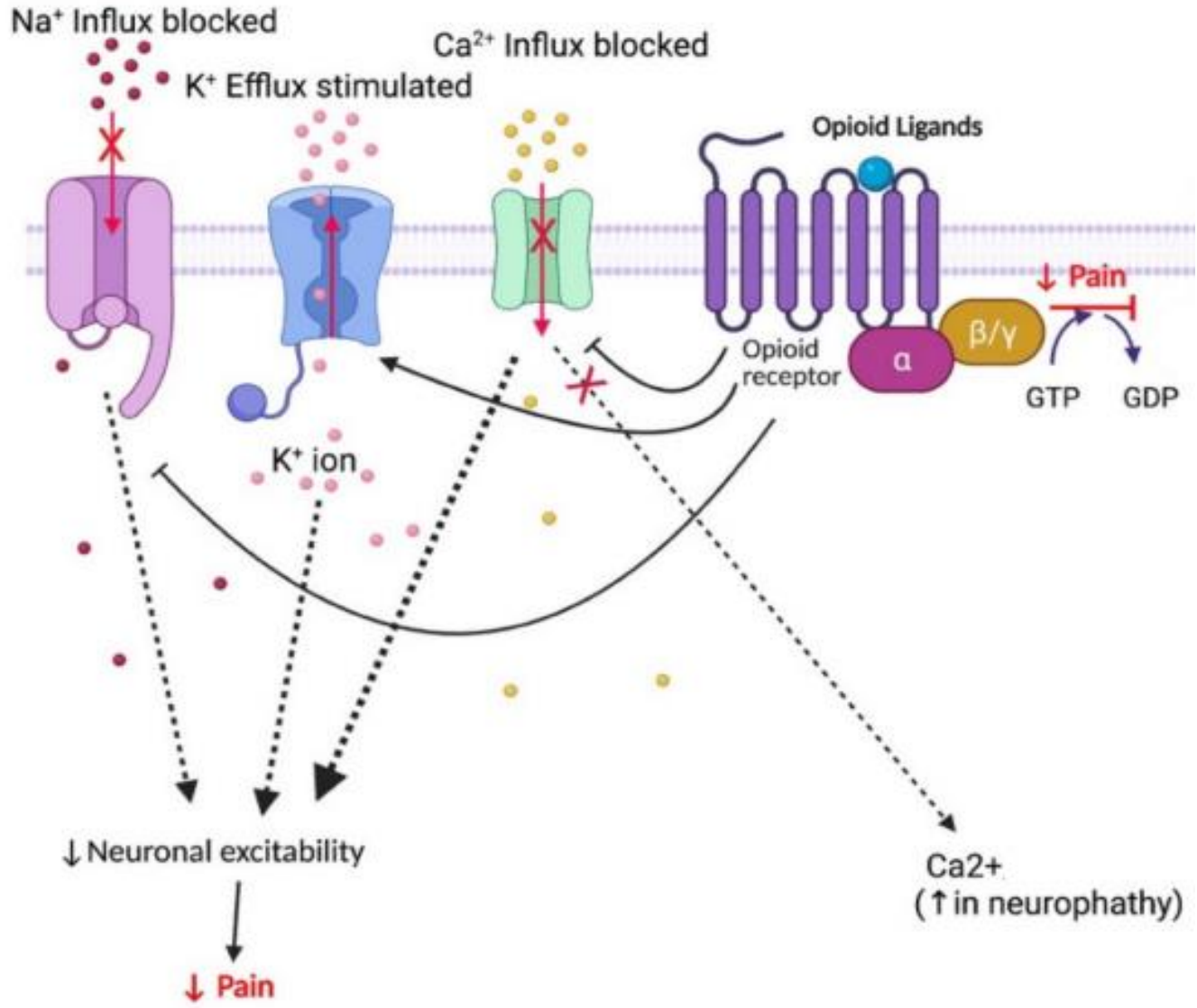


https://www.cusabio.com/pathway/G-protein-coupled-receptor-signaling-pathway.html

Opioid receptor signaling

- Following activation of the opioid receptors, adenylyl cyclase is inhibited, which activates K+ channels and diminishes the conductance of voltage-sensitive Ca2+ channels.

- All these effects lead to activation or inhibition of several downstream signals that contribute to the intrinsic effects of opioids.



Opioids and immune function

- Opioid receptors are abundantly expressed on various immune cells. (lymphocytes, macrophages, neutrophils, and monocytes, ...)

- Opioids, opioid receptors, and opioid signaling pathways together form a system (opioid system) which modulates immune function.

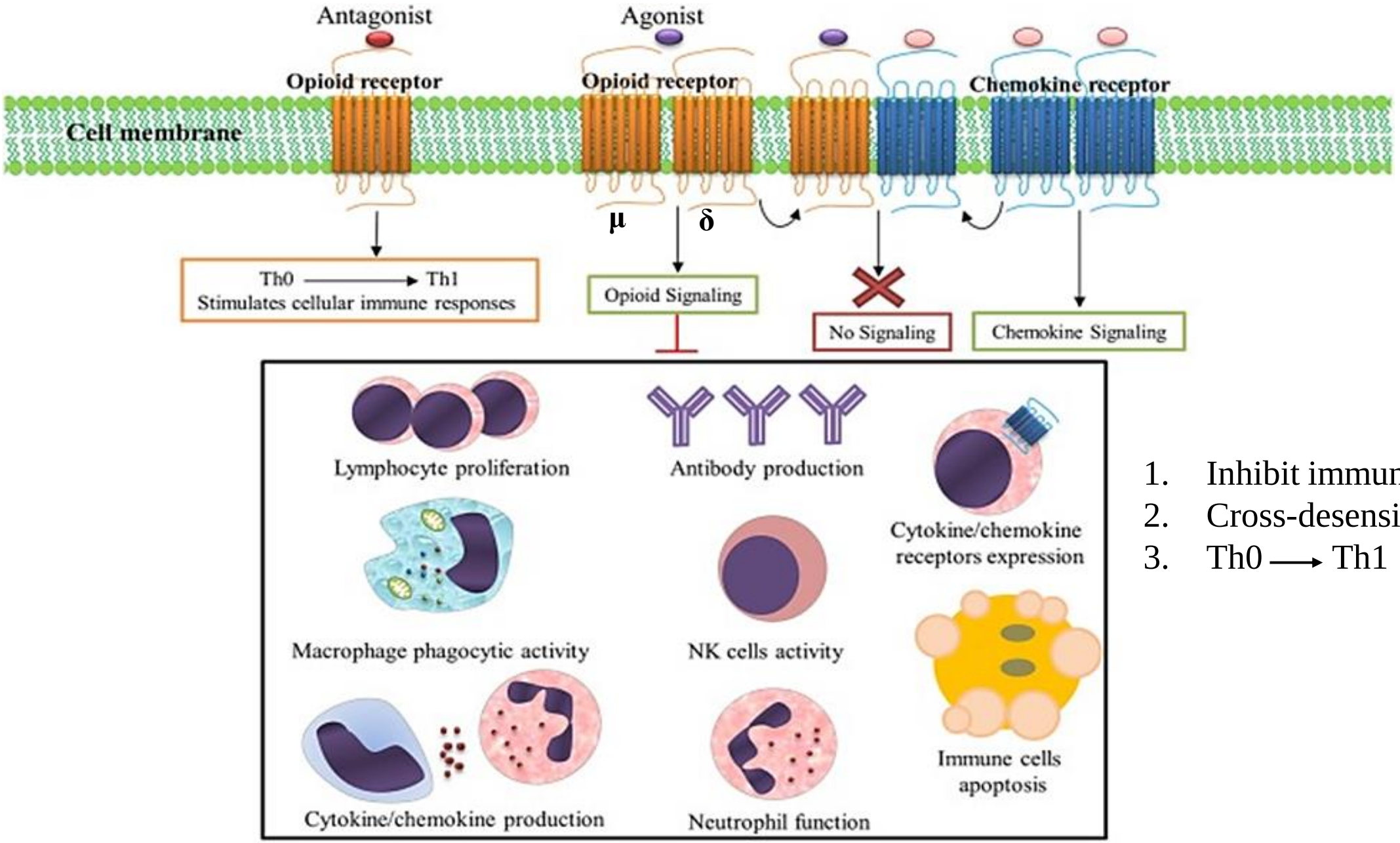
Opioids suppress immune responses.

Possible mechanisms include:

- Impaired function of natural killer cells, T cells, B cells, neutrophils, dendritic cells, and macrophages.
- Altered expression of cytokines and chemokines.

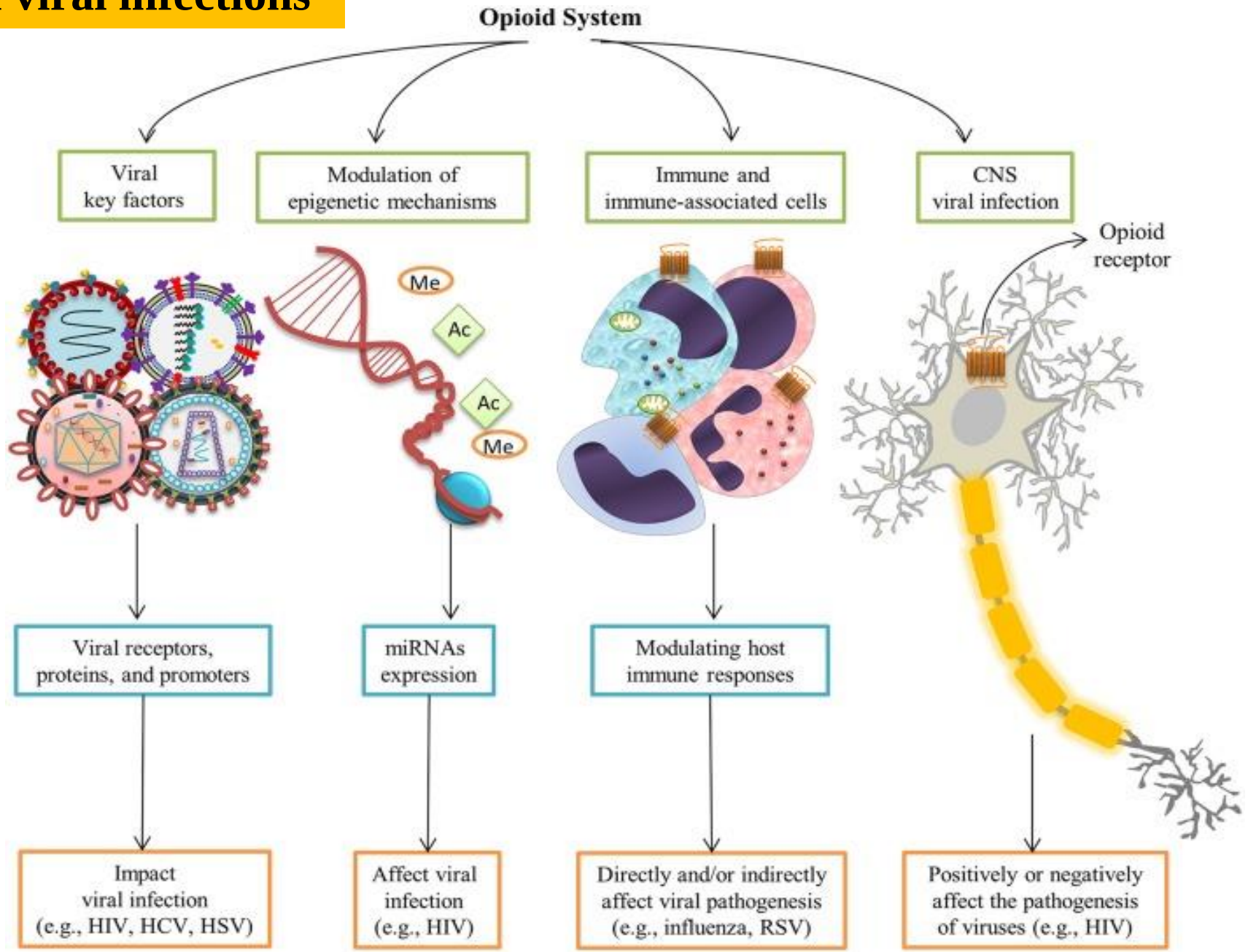
→ Decreased ability to control pathogens and limit their clearance.

Opioids and immune function

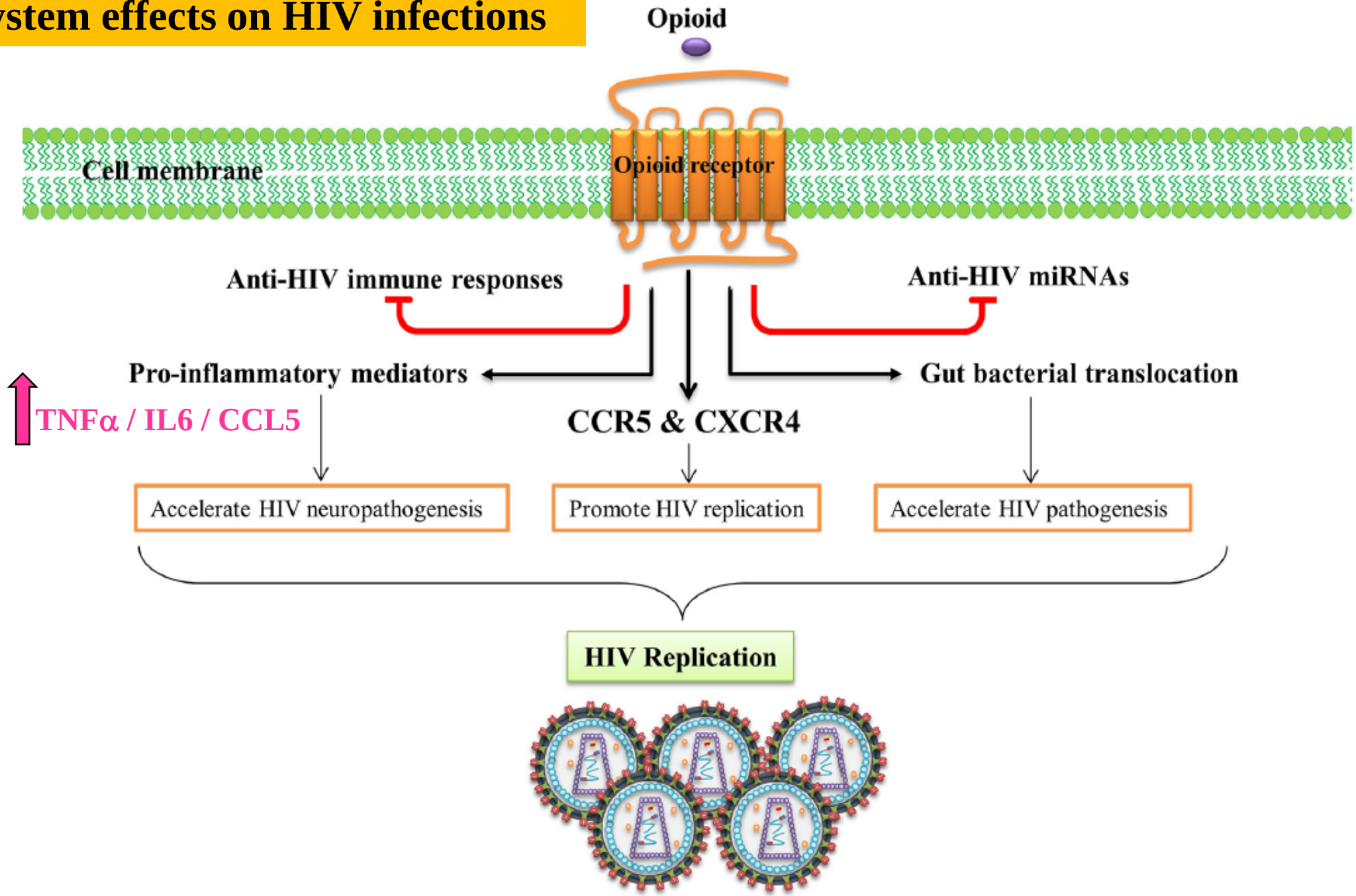


1. Inhibit immune system
2. Cross-desensitization
3. Th0 ⟶ Th1

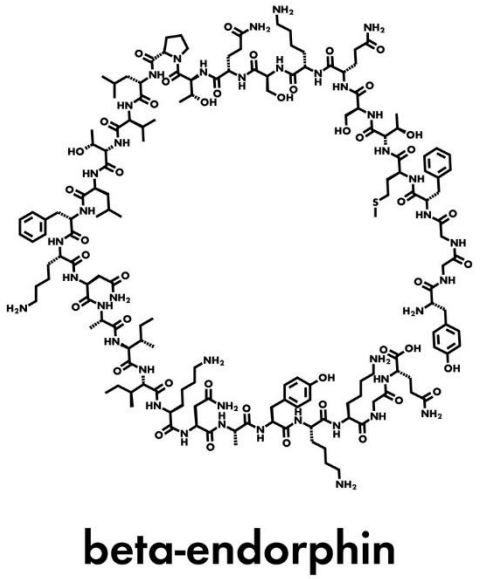
Opioid system effects on viral infections



Opioid system effects on HIV infections



Opioid system effects on HIV infections



Endogenous opioid peptides enhance HIV expression.

β-endorphin

- Enhances: 1.viral protein production and 2.long terminal repeat (LTR) activation in microglia
- Increases HIV expression in mixed glial/neuronal cell cultures

Opioid system effects on HIV infections

Morphine

- Triggers viral reactivation in latently-infected lymphocytes
- Inhibits the expression of IFNs and IFN-inducible genes
- Inhibits regulators of the JAK–STAT signaling pathway
- Decreases expression of anti-HIV microRNAs
- Attenuates the inhibitory effect of antiretroviral therapies on HIV replication
- Synergizes with HIV proteins to alter cell cycle regulation, and exacerbate neurotoxicity and neuroinflammation

Opioid system effects on HIV infections

Heroin

- Triggers HIV reactivation in latently-infected lymphocytes in vitro
- Suppresses IFNs
- Enhances HIV expression in macrophages
- Inhibits several anti-HIV microRNAs
- Expresses lower levels of host restriction factors such as TRIM5α, TRIM22 and ABOBEC3G

Opioid system effects on HIV infections

Cocaine

- Associates with higher HIV RNA levels and greater CD4+ T cell decline
- Enhances HIV expression in PBMCs, macrophages, CD4+ T cells, dendritic cells, microglia and astrocytes
- Enhances HIV neuro invasion by remodeling microvascular endothelial cells in the brain

Opioid system effects on HIV infections

Methamphetamine

- Associates with higher HIV viral loads and lower CD4+ T cell counts
- Enhances expression of chemokine co-receptors
- Dysregulates signal transduction pathways
- Inhibits TLR9

Opioid system effects on HIV infections

Alcohol

- Increased risk of infection and transmission
- Reduces viral suppression
- Increases viral resistance to antiretroviral therapies
- Associates with immunosuppression that increases the risk of opportunistic infections and disease progressions
- Alters the microbiome and affects gut permeability
- Increased HIV replication in the presence of alcohol in various cell types

Opioid system effects on HIV infections

Tobacco/Nicotine

Cigarette smoke exposure is associated with increased HIV replication, lower CD4+ T cell counts, immune activation, oxidative stress, and decreased response to antiretroviral therapy

Nicotine enhances HIV replication in macrophages, T lymphocytes and microglia

Ranjit et al. observed a 3 to 4 fold increase in HIV replication in macrophages exposed to benzopyrene (a major carcinogen found in cigarettes)

Opioid system effects on HIV infections

HIV

MORs activation up-regulates the CCR5 and CXCR4 expression----------Steele et al., 2003

Opioids impair the anti-HIV activity of immune system----------Wang X. et al., 2005

Opioids induce the pro-inflammatory mediators expression----------El-Hage et al., 2006

Morphine activated the HIV LTR in human neuroblastoma cells----------Squinto et al., 2009

Morphine increased HIV replication in neural progenitor cells----------Balinang et al., 2017

Opioids inhibit the anti-HIV miRNAs expression----------Wang et al., 2011

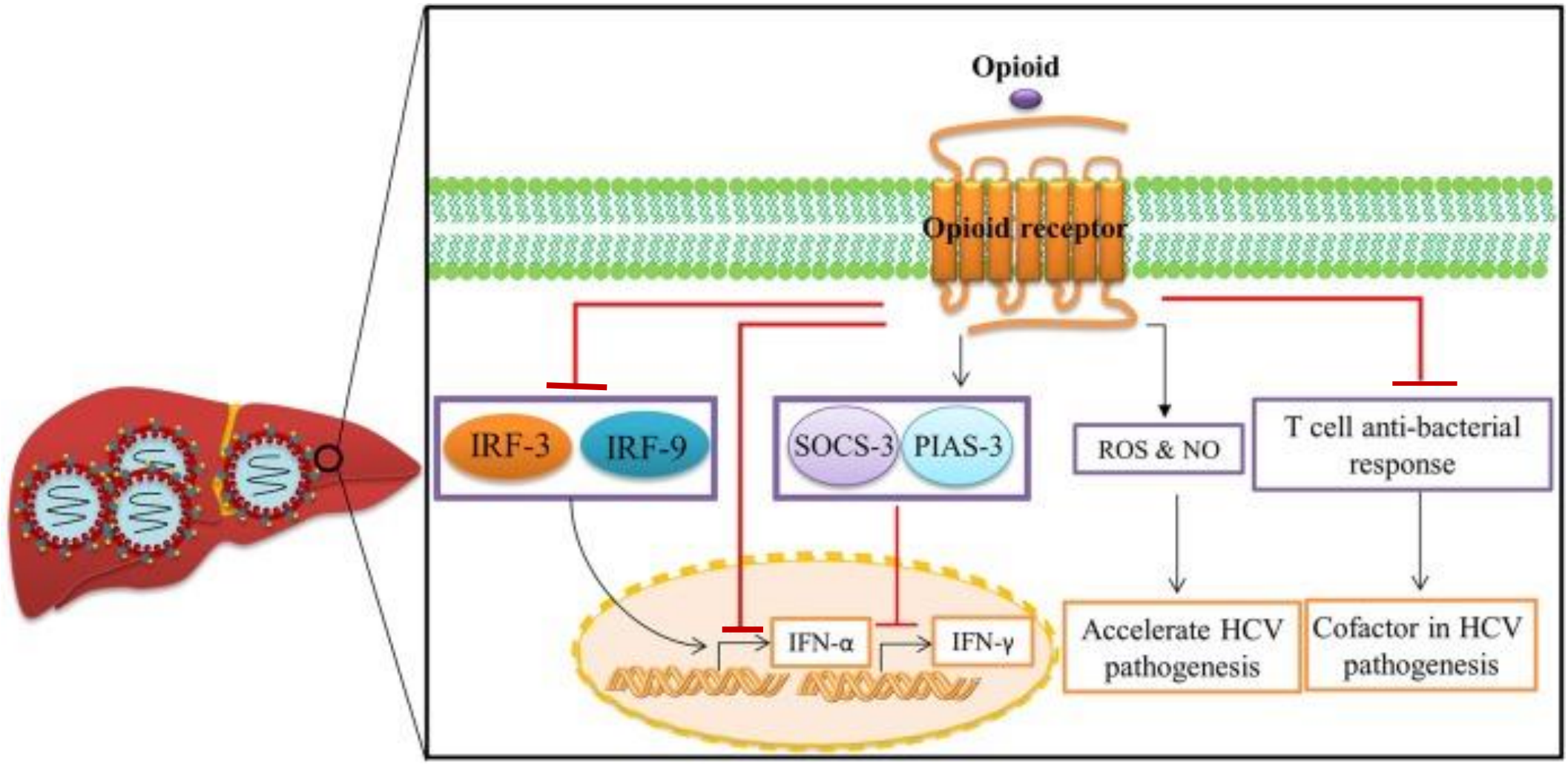
Opioid system reactivate the HIV latently infection----------Prottengeier et al., 2014

Opioid system disrupts the gut homeostasis----------Meng et al., 2015

Fentanyl enhanced expression of the CCR5 and CXCR4 Expression--------Krishnan et al., 2023

Opioid system effects on HCV infections

IRF: Interferon regulatory factors
SOCS-3: suppressor of cytokine signaling 3
PIAS3: protein inhibition of activated STAT3

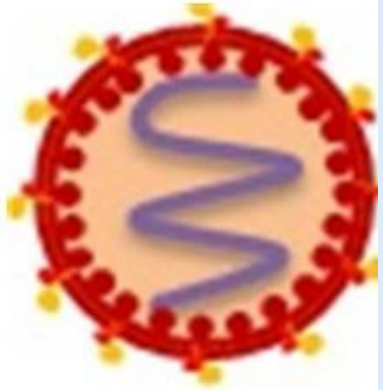


Alcohol and Viral Hepatitis

- Contributes to liver injury and progression to cirrhosis, leading to increased morbidity and mortality
- Increased viral replication following the exposure of permissive cells to alcohol
- Increased HBsAg levels in HepG2 cells in the presence of ethanol
- Upregulates the microRNA-122 that facilitates HCV replication

Opioid system effects on HCV infections

HCV



Morphine compromises anti-HCV effect of recombinant IFN-α----------Li et al., 2003

Opioid system synergize the alcohol acceleration of HCV expression----------Zhang et al., 2003

Morphine withdrawal inhibits expression of endogenous IFN-α----------Wang C.-Q. et al., 2005

Met-enkephalin as a marker in hepatocellular damage in chronic HCV----------Ciesla et al., 2006

Met-enkephalin enhances replication of HCV----------Bergasa and Boyella, 2008

Methamphetamine inhibits hepatic IFN-α expression----------L.Ye et al., 2008

Opioids impair CD56+ T cell-mediated innate immune function----------Ye et al., 2010

Morphine induces hepatic pro-inflammatory cytokine and free radicals----------El- Hage et al., 2011

Opioid dependence therapy associates with lower incidence of HCV----------Tsui et al., 2014

Fentanyl increases replication of HCV and HBV in hepatocytes----------L. Kong et al., 2021

Mechanism of virus-opioid interactions

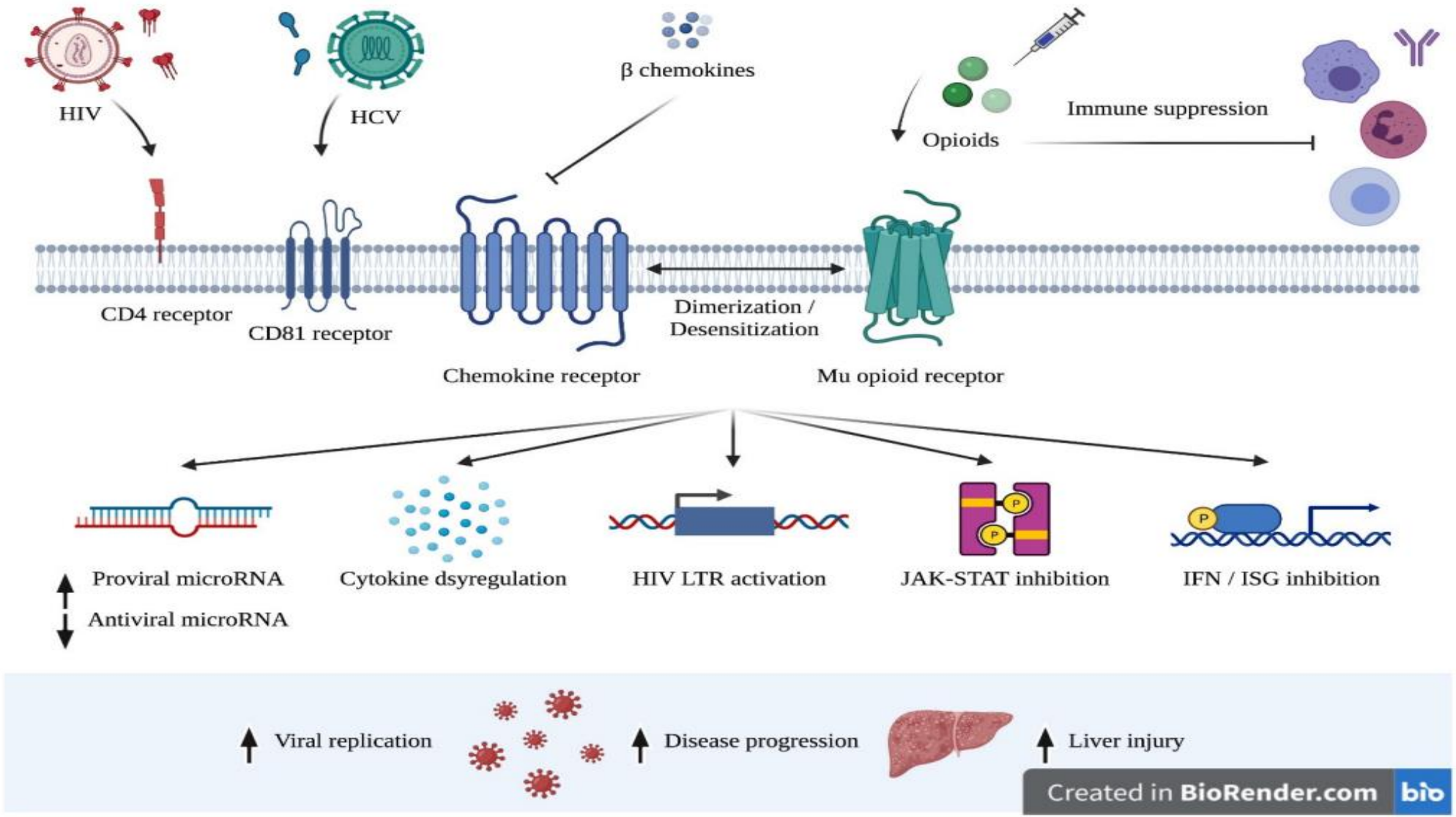
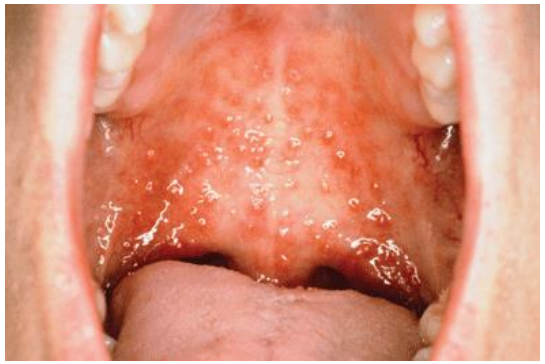


Figure 1. Mechanisms of virus–drug interactions that lead to increased viral replication and accelerated disease progression for HIV and HCV, and/or liver injury.

Opioid system effects on HSV infections



ELSEVIER

Journal of Neuroimmunology 172 (2006) 9 – 17

Journal of Neuroimmunology

www.elsevier.com/locate/jneuroim

Acute morphine exposure potentiates the development of HSV-1-induced encephalitis

Daniel T. Lioy [a,1], Patricia A. Sheridan [b,1], Sean D. Hurley [c], James R. Walton [d], Amy M. Martin [d], John A. Olschowka [c], Jan A. Moynihan [d,*]

[a] *Department of Microbiology and Immunology, 575 Elmwood Ave., University of Rochester, Rochester, NY 14621, United States*
[b] *Interdepartmental Program in Neuroscience, 575 Elmwood Ave., University of Rochester, Rochester, NY 14621, United States*
[c] *Department of Neurobiology and Anatomy, 575 Elmwood Ave., University of Rochester, Rochester, NY 14621, United States*
[d] *Department of Psychiatry, 575 Elmwood Ave., University of Rochester, Rochester, NY 14621, United States*

Received 8 August 2005; accepted 12 October 2005

- Herpes simplex viruses causing variety of diseases such as oral and genital lesions, encephalitis and neonatal infections.
- Morphine, a widely used opioid, is known to alter HSV infection, and because of it´s immunosuppressive effects, it has been demonstrated that reactivates latent HSV.
- Morphine administration potentiates the development of encephalitis in HSV-1 infected mice **(Lioy et al., 2006).** In this regard morphine exposure decreases integrity of the blood-brain barrier (BBB) and might explain its potential role for involvement of BBB in the development of encephalitis in morphine-treated. mice

Opioid system effects on HSV infections

ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect
Microbial Pathogenesis 43 (2007) 217–223

MICROBIAL PATHOGENESIS
www.elsevier.com/locate/micpath

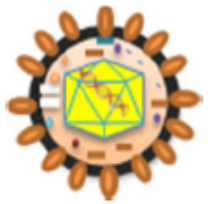
Naloxone, an opioid receptor antagonist, enhances induction of protective immunity against HSV-1 infection in BALB/c mice

Abbas Jamali[a], Mehdi Mahdavi[b], Shahram Shahabi[c,*], Zuhair M. Hassan[b], Farzaneh Sabahi[a], Mohammad Javan[d], Mohammad Jazayeri Farsani[a], Masoud Parsania[e], Taravat Bamdad[a]

[a]*Department of Virology, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran*
[b]*Department of Immunology, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran*
[c]*Department of Microbiology, Immunology and Genetics, Faculty of Medicine, Urmia University of Medical Sciences, Road of Nazloo, Urmia, Iran*
[d]*Department of Physiology, School of Medical Sciences, Tarbiat Modares University, Tehran, Iran*
[e]*Tehran Medical Unit, Islamic Azad University, Tehran, Iran*

Received 11 January 2007; accepted 11 May 2007
Available online 31 July 2007

HSV



Morphine alters innate immune responses against HSV-1	Sheridan and Moynihan, 2005
Morphine diminishes protective innate immune defense against HSV-1	Jamali et al., 2007a
Morphine reduced CTL responses, lymphocyte proliferation, and IFN-γ	Mojadadi et al., 2009
Withdrawal from morphine reduces protective immunity against HSV-1	Jamali et al., 2012
Endogenous opioids could suppress protective immunity against HSV-1	Jamali et al., 2007b
Morphine treatment reduces HSV-1 mortality in infected mice	Alonzo and Carr, 1999
Morphine treatment reduces HSV-1 pathogenesis in infected mice	Weeks et al., 2001
High incidence of HSV in patients given epidural morphine	Gieraerts et al., 1987
Epidural morphine reactivates oral herpes in the obstetric population	Crone et al., 1990
Morphine potentiates development of encephalitis in HSV-1 infected mice	Lioy et al., 2006
Attenuated hippocampal dynorphin causes seizures in HSV-1 infected rats	Solbrig et al., 2006
MORs activation by loperamide suppress mechanical allodynia in mice with herpetic pain	Sasaki et al., 2007
MORs activation by morphine suppress mechanical allodynia in mice with herpetic pain	Sasaki et al., 2008

Opioid system effects on HSV infections

Iranian Journal of Virology 2010;4(3&4): 1-6

Original Article

Effects of Morphine on Replication of Herpes Simplex Virus Type 1&2

Monavari SH[1*], Shamsi-Shahrabadi M[1]

1. Department of Virology and Antimicrobial resistance research center, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Abstract

Background and Aims: Several drugs are being used in treatment of HSV infection in human but still introducing an effective safe drug is desirable.

Methods: We investigated the inhibitory effect of morphine on replication of HSV in vitro.

Results: The results indicated that a concentration of up to 200 ug/ml morphine had a limited effect on Vero cell viability. At this concentration the growth of HSV was inhibited considerably and after the third passage in presence of morphine it was completely diminished. Presence of viral antigens in infected cells in presence of morphine by IF staining showed that after the first passage a small number of infected cells contained viral proteins and at the third passage no cells with viral antigen was observed.

Conclusion: This was confirmed by page and immunobloting techniques. Electron microscopy observation in cellular section indicated that there was no virus present in treated cells as compared with control untreated infected cells.

Keywords: Herpes simplex virus; morphine; Cytotoxicity

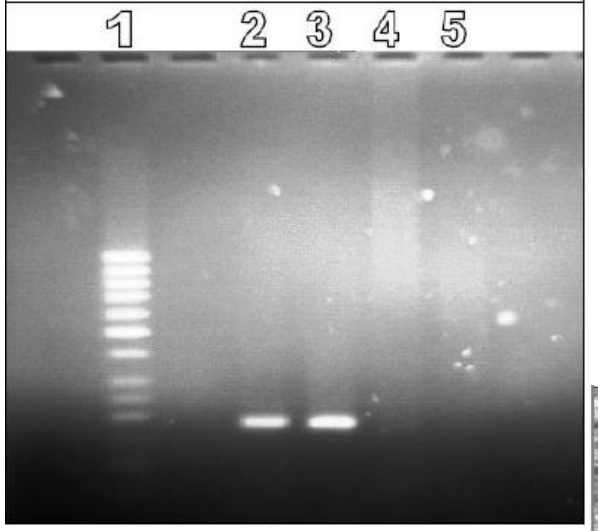


Fig. 4. Effect of Morphine on Viral DNA synthesis Lane-2: Positive control, Lane-3: first passage, Lane-4: third passage, lane-5: Negative control respectively.

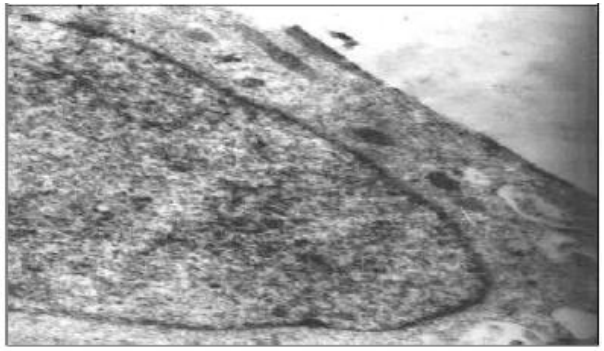


Fig. 6a. Electron micrograph of morphine treated infected cells showing no HSV-2 virus particles.

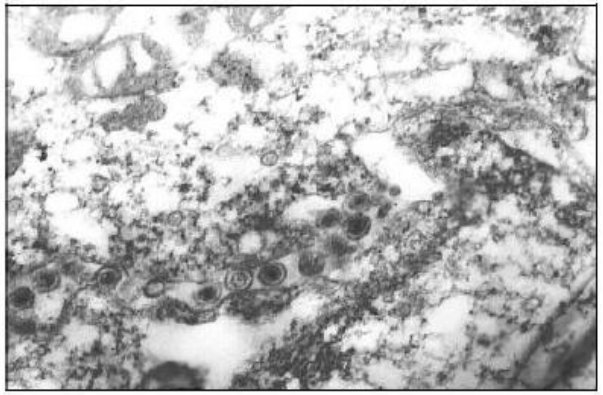
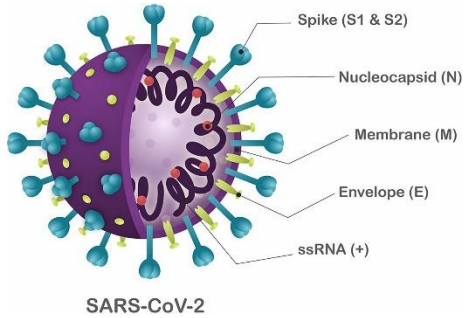


Fig. 6b. Electron micrograph of morphine treated infected cells in presence of Naloxone showing HSV-2 virus particles.

Opioid system effects on SARS-CoV-2 infections



Positive points of opioids use:

1. Occurrence of analgesia to facilitate intubation.
2. Optimize ventilation.
3. Promoting suitable pain relief.
4. Preventing the activation of the sympathetic nervous system.
5. In viral infections where the host inflammatory response is pathogenic (known as immunopathogenic), activation of opioid receptors is beneficial for control of immunopathology.
6. Reduces disease-induced morbidity and mortality by inhibition of cytokine storm and hyperinflammatory response.

Negative points of opioids use:

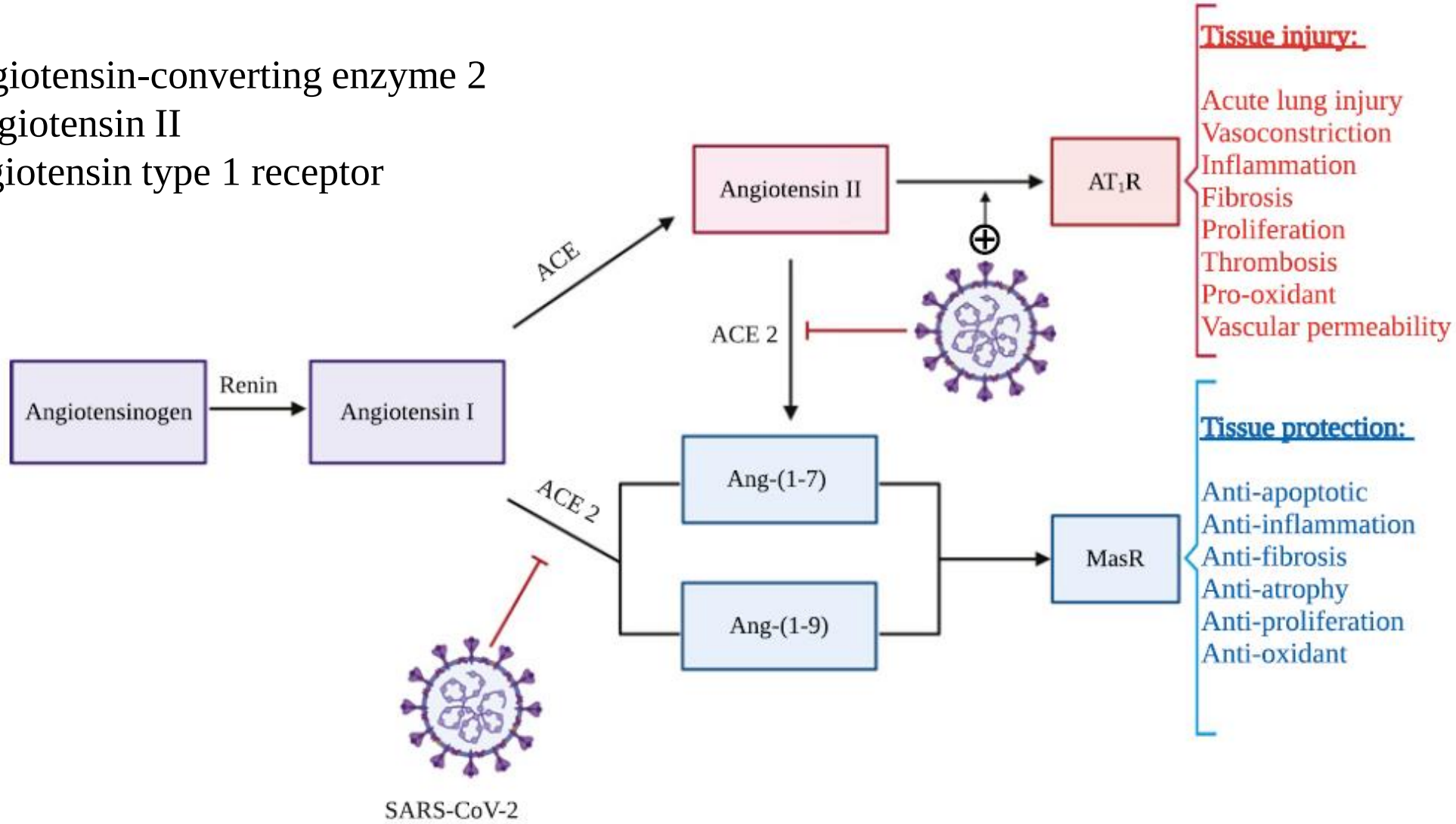
1. Associated with increased chest wall rigidity, which lead to the respiratory depression.
2. Increase hypercapnia, leading to slow and irregular breathing, which in severe cases can progress to fatal apnea.
3. Chronic use can trigger opioid tolerance.
4. Present side effects such as diarrhea, hyperalgesia, dysphoria and dependence processes.
5. Their prolonged use might be associated to suppression of the proliferation of lymphocytes B and T and induction of immune cell apoptosis.

Characteristics of the main opioids used in patients affected by the COVID-19. Adapted from Ammar et al., 2020.

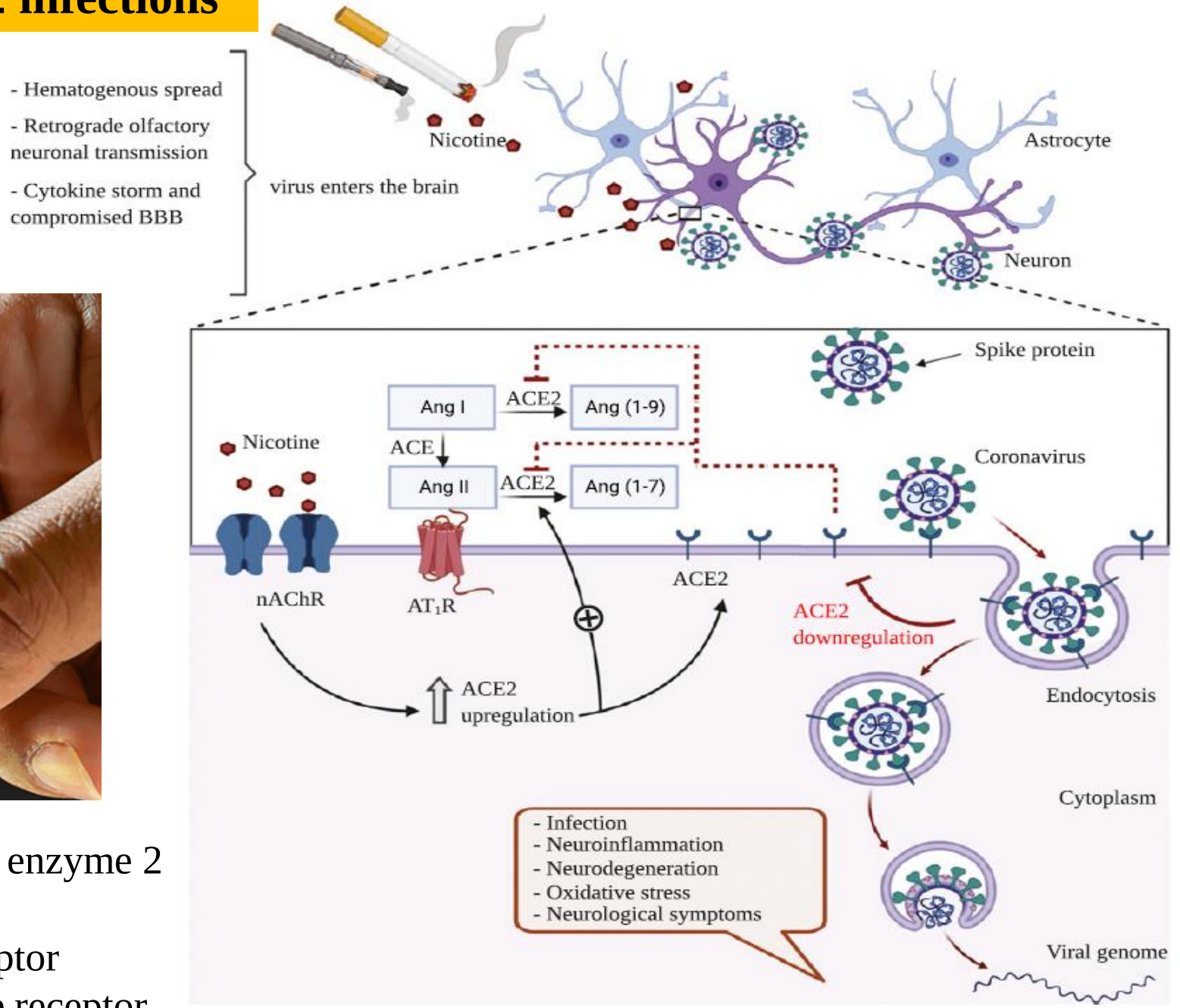
Medication	Mechanism of action	Pharmacokinetics	Adverse events	Place in therapy
Fentanyl	Mu-opioid receptor agonist	Onset: immediate Duration: 3-60 min Elimination: 2-4 h	Chest wall rigidity with rapid infusion	First-line therapy
Morphine	Mu-opioid receptor agonist	Onset: 5-10 min Duration: 3-5 h Elimination: 3-4 h	Hypotension and bradycardia	First-line therapy
Hydromorphone	Mu-opioid receptor agonist	Onset: 15-30 min Duration: 3-4 h Elimination: 2-3 h	Hypotension	First-line therapy
Sufentanil	Mu-opioid receptor agonist	Onset: 1-3 min Duration: 2 h	Bradyarrhythmia and hypotension	Alternative therapy
Alfentanil	Mu-opioid receptor agonist	Onset: 5 min Duration: 30-60 min	Hypotension	Alternative therapy
Methadone	Mu-opioid receptor agonist	Onset: 10-20 min Duration: 12-48 h	QTc prolongation	Opioid conservation and adjuvant therapy

Mechanism of SARS-CoV-2 pathogenesis

ACE2: Angiotensin-converting enzyme 2
Ang-II: Angiotensin II
AT1R: Angiotensin type 1 receptor

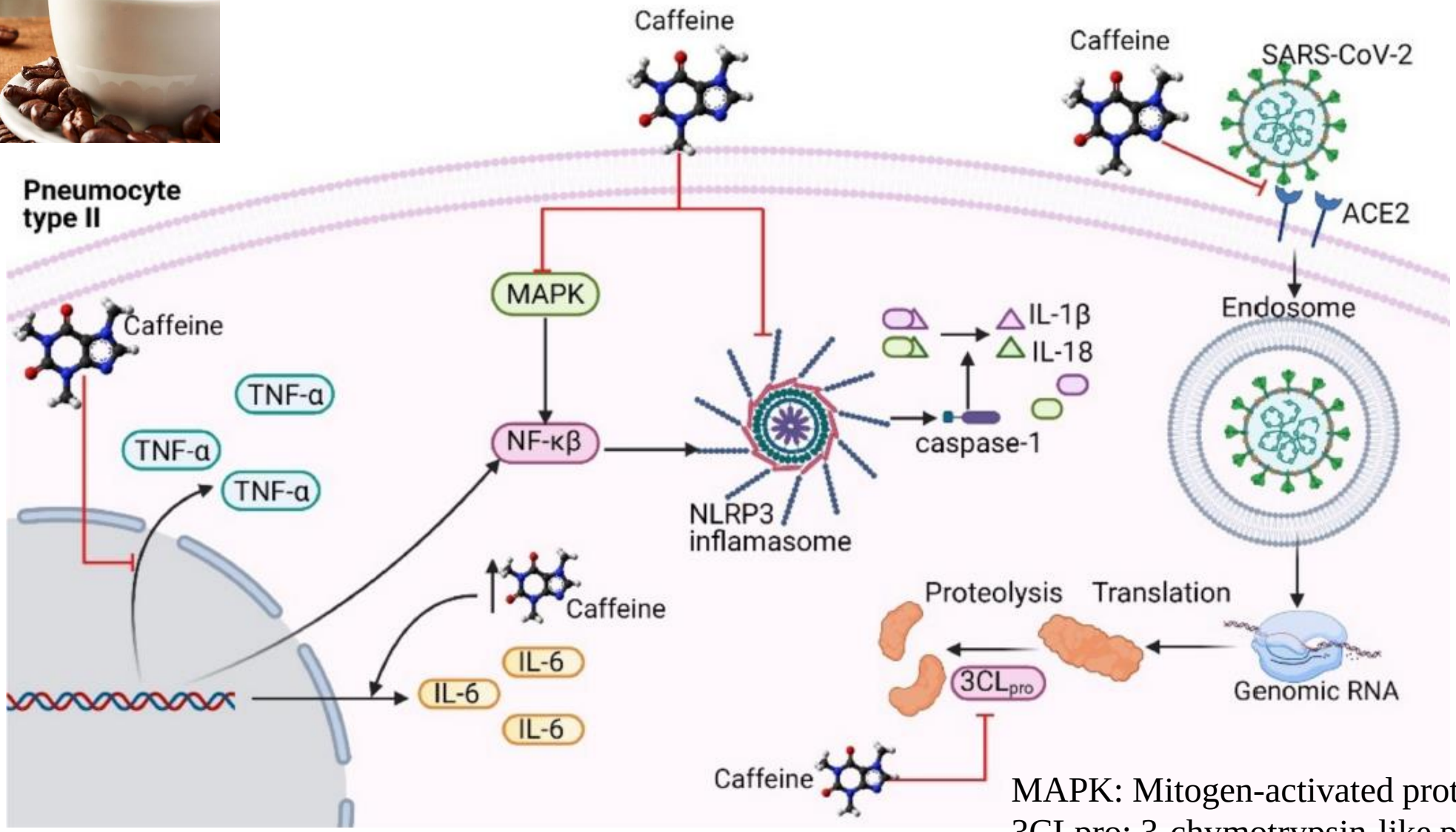


Nicotine effects on SARS-CoV-2 infections



ACE2: Angiotensin-converting enzyme 2
Ang-II: Angiotensin II
AT1R: Angiotensin type 1 receptor
nAChR: nicotinic acetylcholine receptor

Caffeine effects on SARS-CoV-2 infections



MAPK: Mitogen-activated protein kinase
3CLpro: 3-chymotrypsin-like protease
NLRP3: Inflammasome NOD-like receptor 3

Opioids in COVID-19: Two Sides of a Coin

Camila Vantini Capasso Palamim [1,2†‡], Matheus Negri Boschiero [1,2†‡], Aléthea Guimarães Faria [1,2], Felipe Eduardo Valencise [1,2†‡] and Fernando Augusto Lima Marson [1,2†‡]*

[1]*Laboratory of Cell and Molecular Tumor Biology and Bioactive Compounds, São Francisco University, Bragança Paulista, Brazil,*
[2]*Laboratory of Human and Medical Genetics, São Francisco University, Bragança Paulista, Brazil*

Introduction: The treatment of most severe COVID-19 patients included the large-scale use of sedatives and analgesics–possibly in higher doses than usual–which was reported in the literature. The use of drugs that decrease mortality is necessary and opioids are important agents in procedures such as orotracheal intubation. However, these drugs seem to have been overestimated in the COVID-19 pandemic. We performed a review of the PubMed-Medline database to evaluate the use of opioids during this period. The following descriptors were used to enhance the search for papers: "Opioids", "COVID-19," "COVID-19 pandemic," "SARS-CoV-2," "Opioid use disorder," "Opioid dependence" and the names of the drugs used. We also evaluated the distribution of COVID-19 patients in Brazil and the applicability of opioids in our country during the COVID-19 pandemic.

Opioids/cannabinoids as a potential therapeutic approach in COVID-19 patients

Alireza Tahamtan, Masoumeh Tavakoli-Yaraki & Vahid Salimi

To cite this article: Alireza Tahamtan, Masoumeh Tavakoli-Yaraki & Vahid Salimi (2020) Opioids/cannabinoids as a potential therapeutic approach in COVID-19 patients, Expert Review of Respiratory Medicine, 14:10, 965-967, DOI: 10.1080/17476348.2020.1787836

To link to this article: https://doi.org/10.1080/17476348.2020.1787836

The Role of Smoking and Nicotine in the Transmission and Pathogenesis of COVID-19

Ali Ehsan Sifat, Saeideh Nozohouri, Heidi Villalba, Bhuvaneshwar Vaidya, and Thomas J. Abbruscato

Department of Pharmaceutical Sciences, School of Pharmacy, Texas Tech University Health Sciences Center, Amarillo, Texas

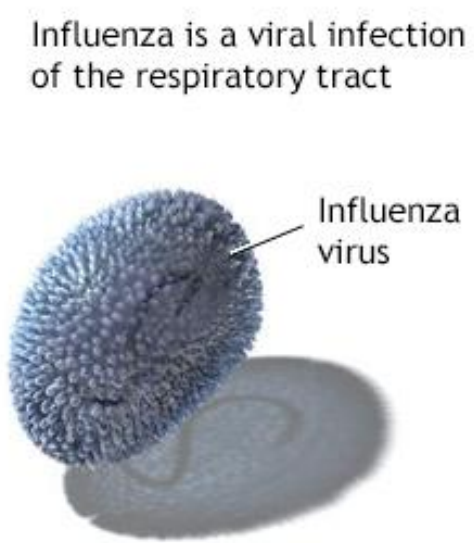
Received June 16, 2020; accepted September 30, 2020

Review

Possible Beneficial Actions of Caffeine in SARS-CoV-2

Bianca S. Romero-Martínez [1], Luis M. Montaño [1], Héctor Solís-Chagoyán [2], Bettina Sommer [3], Gemma Lizbeth Ramírez-Salinas [4], Gloria E. Pérez-Figueroa [5] and Edgar Flores-Soto [1,*]

Opioid system effects on Influenza infections



- Influenza causes viral respiratory tract diseases ranging from mild upper respiratory infection to severe pneumonia.
- When airway epithelial cells are infected by the influenza virus, infiltration of various immune cells occurs, causing immunopathogenesis.
- Opioids alter immune function, so affect the immunopathogenesis of influenza in the pulmonary tract.

Opioid system effects on influenza infections

Morphine

- Impairs the inflammatory response to influenza infection in the lung
- lowering the percentage of polymorphonuclear cells in the bronchoalveolar lavage fluid (BALF)
- The influenza virus cleared slowly from the lungs of morphine-treated rats compared to non-treated

Opioid system effects on Influenza infections

Addiction Biology
SSA SOCIETY FOR THE STUDY OF ADDICTION
ORIGINAL ARTICLE
doi:10.1111/adb.12305

Methadone enhances human influenza A virus replication

Yun-Hsiang Chen[1,2], Kuang-Lun Wu[1], Ming-Ta Tsai[1], Wei-Hsien Chien[3], Mao-Liang Chen[4] & Yun Wang[1]

Center for Neuropsychiatric Research, National Health Research Institutes, Taiwan[1], Department of Life Science, Fu Jen Catholic University, Taiwan[2], Department of Occupational Therapy, Fu Jen Catholic University, Taiwan[3] and Department of Research, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan[4]

ELSEVIER
Available online at www.sciencedirect.com
SCIENCE DIRECT®
Brain, Behavior, and Immunity 19 (2005) 153–164
BRAIN, BEHAVIOR, and IMMUNITY
www.elsevier.com/locate/ybrbi

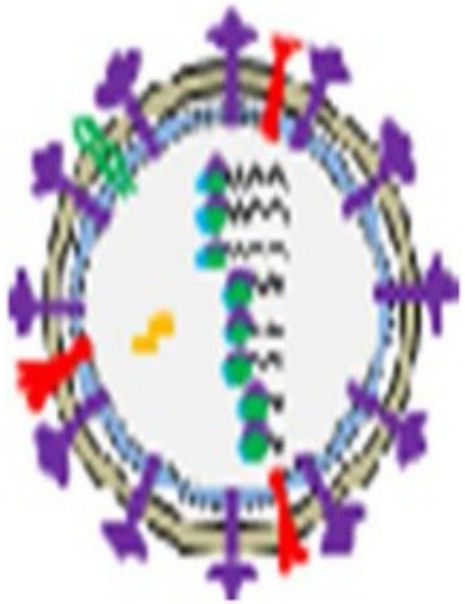
Stress-induced modulation of NK activity during influenza viral infection: role of glucocorticoids and opioids

Raymond J. Tseng[a], David A. Padgett[a,b,c], Firdaus S. Dhabhar[a,b,c], Harald Engler[a], John F. Sheridan[a,b,c,*]

[a] *Department of Oral Biology, Ohio State University College of Dentistry, Columbus, OH, USA*
[b] *Institute for Behavioral Medicine Research, Ohio State University Medical Center, Columbus, OH, USA*
[c] *Department of Molecular Virology, Immunology and Medical Genetics, Ohio State University College of Medicine, Columbus, OH, USA*

Received 17 June 2004; received in revised form 12 July 2004; accepted 12 July 2004
Available online 9 September 2004

Influenza



Morphine impairs the inflammatory response to influenza in the lungs — Hu et al., 2011

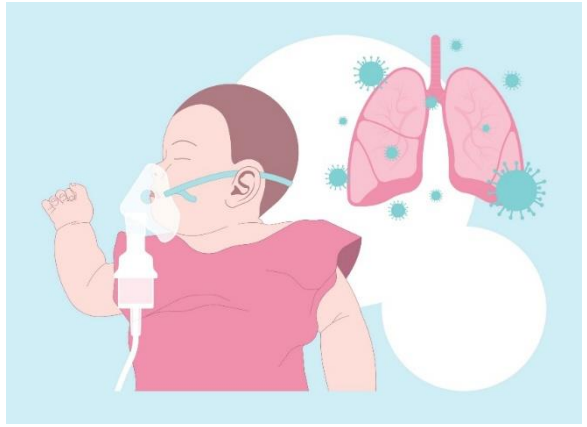
Morphine treated rates slowly clear virus from their lungs — Coussons-Read et al., 1998

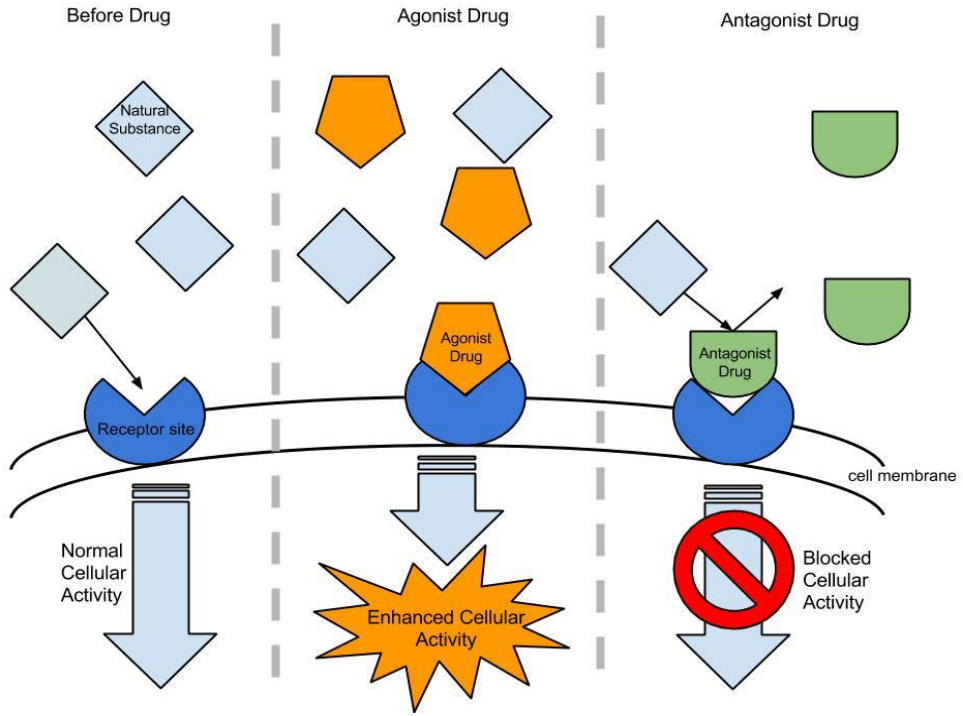
Opioid system modulate NK cell cytotoxicity during influenza infection — Tseng et al., 2005

Opioids could increase risk of pneumonia after influenza as a consequent of immune suppression — Dublin et al., 2011

Exposure to methadone significantly increased H1N1 viral replication — Chen et al., 2015

Opioid system effects on Respiratory Syncytial Virus





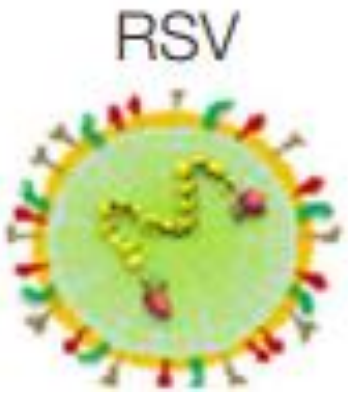
- RSV infections such as influenza causes infiltration of immune cells into the lung tissue and obstruction of the airways that can lead to shortness of breath, bronchiolitis, pneumonia, and even death.
- Opioids are frequently used during mechanical ventilation of severe RSV infection.
- Activation of opioid receptors using μ, κ and δ agonists reduced neutrophil influx.

Opioid system effects on RSV infections

Respiratory Syncytial Virus

Symptoms of RSV infection usually include:

- Runny nose
- Decrease in appetite
- Coughing
- Sneezing
- Fever
- Wheezing



Opioid Receptors Control Viral Replication in the Airways*

Vahid Salimi, PhD[1]; Marije P. Hennus, MD[2]; Talat Mokhtari-Azad, PhD[1]; Fazel Shokri, PhD[3]; Riny Janssen, PhD[4]; Hennie M. Hodemaekers, BAppSc[4]; Tomasz P. Rygiel, PhD[5]; Frank E. J. Coenjaerts, PhD[6]; Linde Meyaard, PhD[5]; Louis Bont, MD, PhD[2,5]

Objective: Opioids are frequently used during mechanical ventilation for severe viral infection in infancy. Opioid receptors have immunomodulatory properties, but nothing is known about their antiviral effects. We therefore aimed to investigate the role of opioid receptors in virus-induced airway inflammation.

Patients and Interventions: Two single nucleotide polymorphisms in *OPRM1* and *OPRD1* were genotyped in 465 infants with severe respiratory syncytial virus infection and 930 control subjects. Subsequently, the mechanism by which opioid receptors affect clinical outcome in respiratory syncytial virus bronchiolitis was studied in BALB/c mice. Animals were injected daily with nalmefene, a nonselective opioid receptor antagonist, and infected by intranasal inoculation of respiratory syncytial virus 24 hrs after the first dose of nalmefene. The potential therapeutic effect of pharmaceutical opioids was studied using μ (DAMGO), κ (U50488), and δ (DPDPE) opioid receptor agonists 48 hrs after infection.

Measurements and Main Results: In our human study, the A118G single nucleotide polymorphism rs1799971 was associated with respiratory syncytial virus disease severity ($p = 0.015$). In mice, nalmefene treatment increased viral titers and was associated with more pronounced weight loss. Increased viral replication was associated with increased levels of cytokines and chemokines in the bronchoalveolar lavage fluid, enhanced bronchoalveolar cellular influx, and exaggerated lung pathology. Pharmaceutical opioids, in particular DPDPE, did not affect viral replication. They did induce a decreased influx of neutrophils, but an increased influx of lymphocytes and monocytes into the bronchoalveolar lumen during respiratory syncytial virus infection.

Conclusions: Using a human study and an experimental model, we show that opioid receptor signaling has a potential beneficial role in the outcome of respiratory viral disease. We show that opioid receptor signaling is required to control respiratory syncytial virus replication and thereby to control disease severity. However, we also show that caution is required before using pharmaceutical opioids as anti-inflammatory or antiviral treatment of patients with viral respiratory infection. (*Crit Care Med* 2013; 41:205–214)

Key Words: mechanical ventilation; nalmefene; opioid agonists; respiratory syncytial virus; single nucleotide polymorphism; viral replication

*See also p. 361.

[1] Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
[2] Department of Pediatric Intensive Care, Wilhelmina Children's Hospital Utrecht, University Medical Center Utrecht, Utrecht, The Netherlands.
[3] Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
[4] Laboratory for Health Protection Research, National Institute for Public Health and the Environment, Bilthoven, The Netherlands.
[5] Department of Immunology, University Medical Center Utrecht, Utrecht, The Netherlands.
[6] Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, The Netherlands.

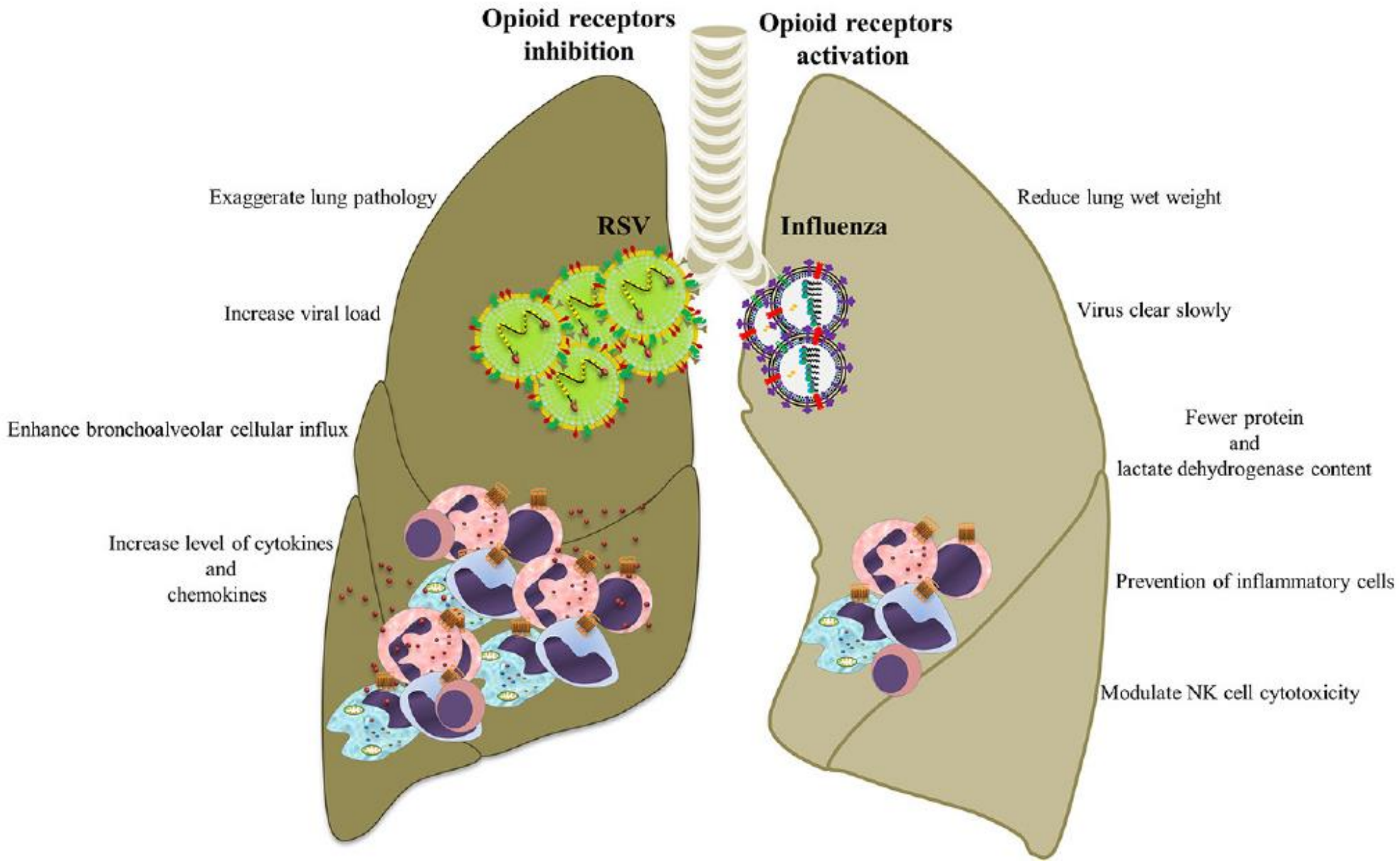
Respiratory syncytial virus (RSV) infection is the most common disease during infancy with a wide spectrum of respiratory manifestations, ranging from common cold-like symptoms to serious lower respiratory tract illnesses such as pneumonia and bronchiolitis (1, 2). Severely ill children requiring mechanical ventilation are often treated with exogenous opioids such as morphine for sedative purposes as well as to alleviate pain (3).

Exogenous (e.g., morphine) and endogenous (e.g., β-endorphine) opioids interact with their corresponding receptors named by μ (MOR), κ (KOR), and δ (DOR), which are, respectively, encoded by the *OPRM1*, *OPRK1*, and *OPRD1*

The A118G single nucleotide polymorphism rs1799971 associated with RSV disease severity — Salimi et al., 2013

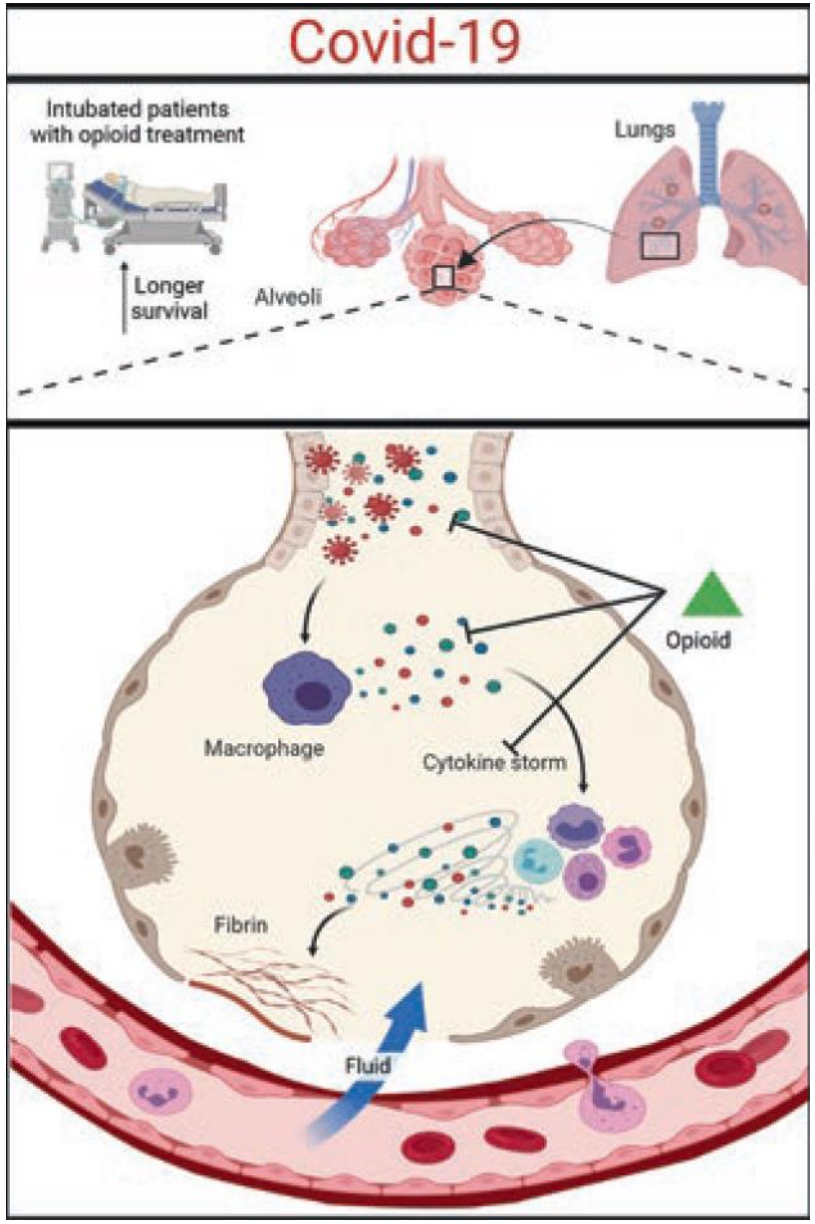
Opioid system control RSV replication in the lung and consequently control virus immunopathogenesis — Salimi et al., 2013

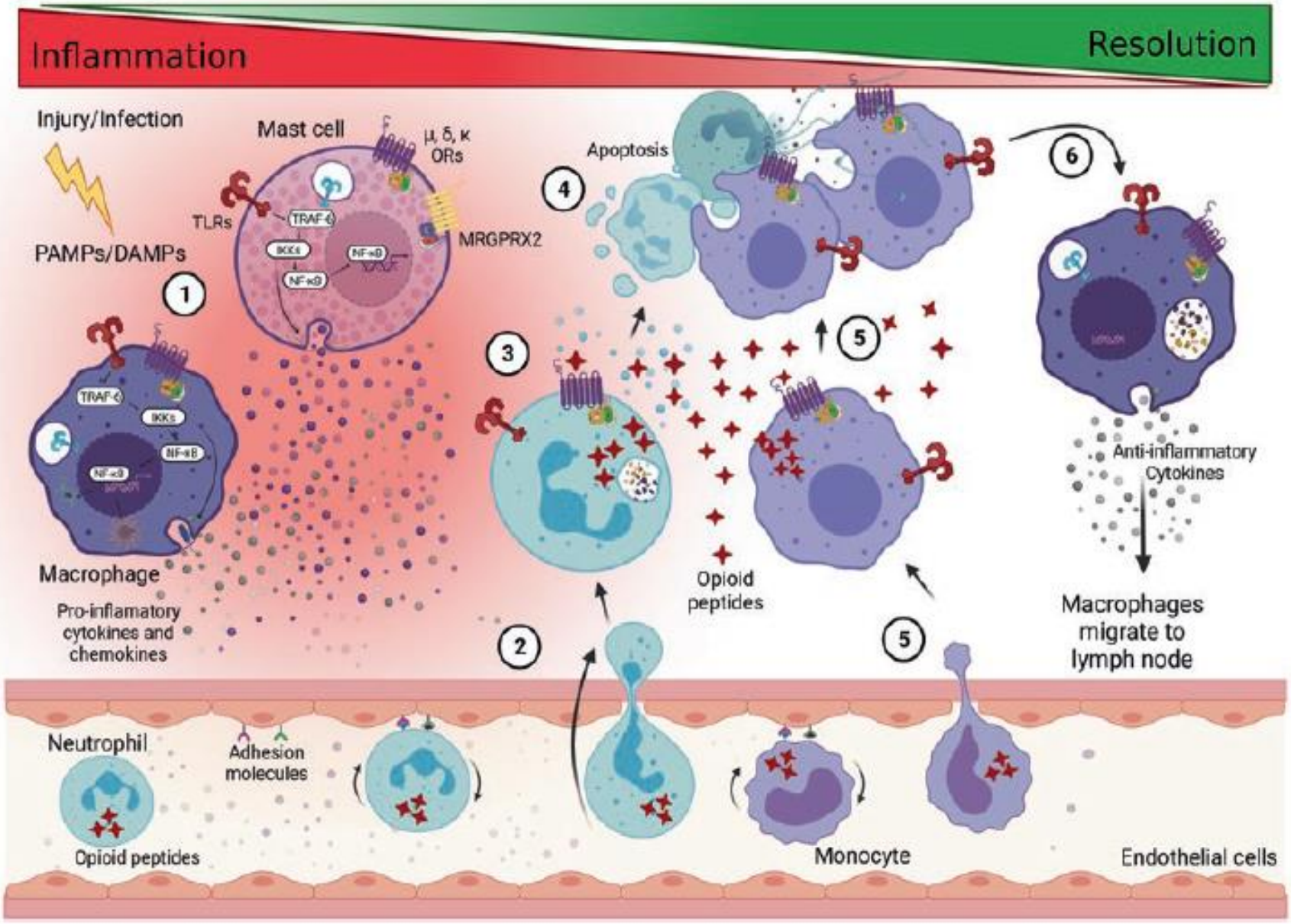
Opioid system effects on Influenza & RSV infections



Opioids and immunopathogenesis

1. SARS-Cov2
2. Influenza



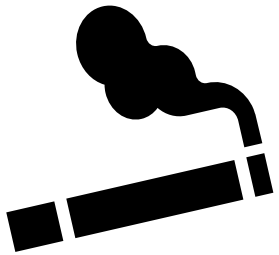


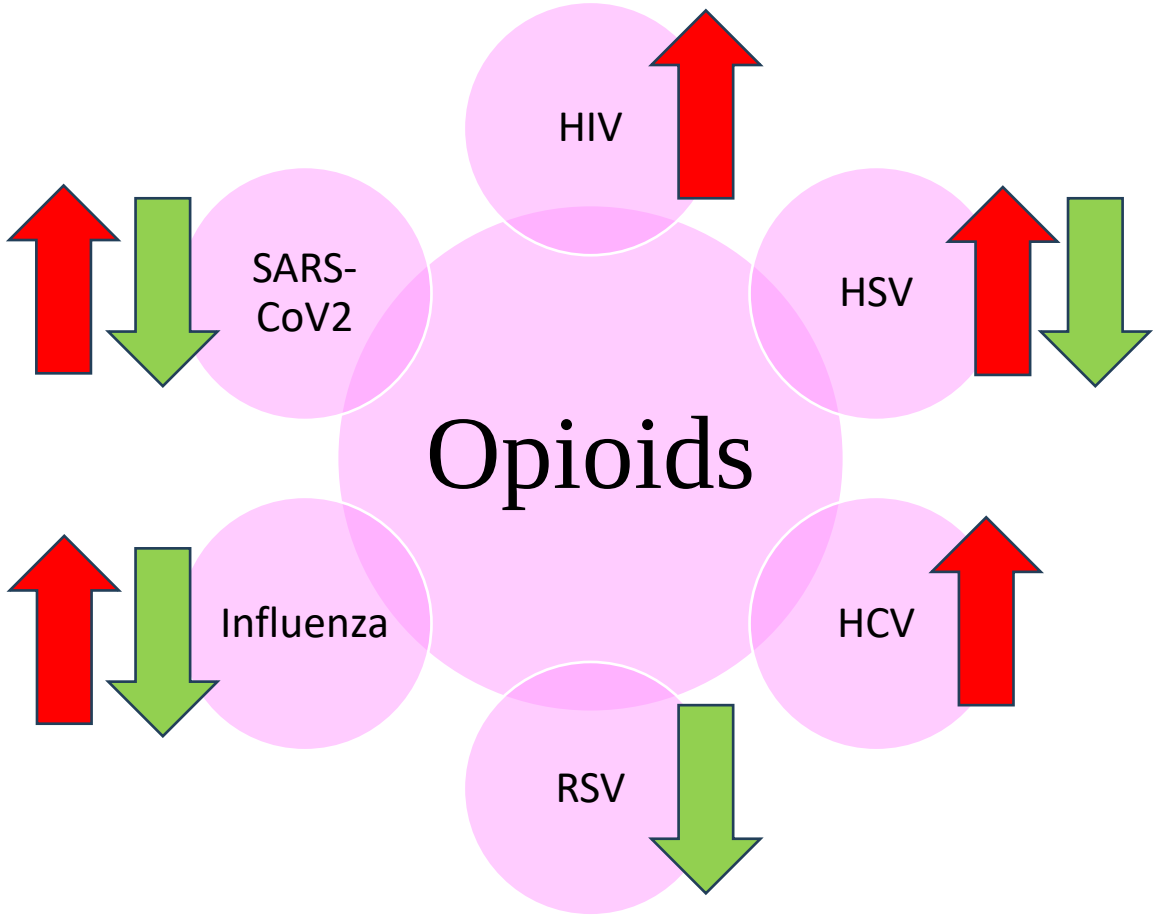
Conclusion

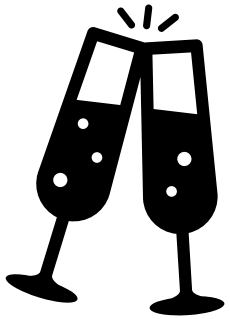
- In vivo and in vitro models indicating that opioid systems effect viral replication and virus-mediated pathology.
- The diverse effects of the opioid system on viral infection imply involvement of different mechanisms.
- In the majority of viruses, opioid system enhances viral pathogenesis by modulation of immune responses.
- Blockage of opioid receptors can potentially be applied for viral control.
- Activation of opioid receptors is beneficial for controlling viral pathogenesis in those viral infections where host immune responses are pathogenic.
- Viruses and opioid system and molecular mechanisms is an important tool for understanding the effect of opioids, mechanisms of action, and development of therapeutic strategies.

Conclusion

Opioid system effects on viral infections:







References

1. Tahamtan A, Tavakoli-Yaraki M, Mokhtari-Azad T, Teymoori-Rad M, Bont L, Shokri F, et al. Opioids and Viral Infections: A Double-Edged Sword. Front Microbiol. 2016;7:970.
2. Wang X, Tan N, Douglas SD, Zhang T, Wang Y-J, Ho W-Z. Morphine inhibits CD8+ T cell-mediated, noncytolytic, anti-HIV activity in latently infected immune cells. Journal of leukocyte biology. 2005;78(3):772-6.
3. Tsui JI, Evans JL, Lum PJ, Hahn JA, Page K. Opioid agonist therapy is associated with lower incidence of hepatitis C virus infection in young adult persons who inject drugs. JAMA internal medicine. 2014;174(12):1974.
4. Milloy MJ, Marshall B, Kerr T, Richardson L, Hogg R, Guillemi S, Montaner JS, Wood E. High-intensity cannabis use associated with lower plasma human immunodeficiency virus-1 RNA viral load among recently infected people who use injection drugs. Drug and alcohol review. 2015 Mar;34(2):135-40.
5. Salehi Z, Motlagh Ghoochani BF, Hasani Nourian Y, Jamalkandi SA, Ghanei M. The controversial effect of smoking and nicotine in SARS-CoV-2 infection. Allergy, Asthma & Clinical Immunology. 2023 Jun 1;19(1):49.
6. Stein C. Opioid receptors. Annual review of medicine. 2016;67:433-51.
7. Sifat AE, Nozohouri S, Villalba H, Vaidya B, Abbruscato TJ. The Role of Smoking and Nicotine in the Transmission and Pathogenesis of COVID-19. Journal of Pharmacology and Experimental Therapeutics. 2020 Dec 1;375(3):498-509.
8. Steele AD, Henderson EE, Rogers TJ. μ-opioid modulation of HIV-1 coreceptor expressionand HIV-1 replication. Virology. 2003;309(1):99-107.
9. Pello OM, Martínez-Muñoz L, Parrillas V, Serrano A, Rodríguez-Frade JM, Toro MJ, Lucas P, Monterrubio M, Martínez-A C, Mellado M. Ligand stabilization of CXCR4/δ-opioid receptor heterodimers reveals a mechanism for immune response regulation. European journal of immunology. 2008 Feb;38(2):537-49.

References

10. Chen YH, Wu KL, Tsai MT, Chien WH, Chen ML, Wang Y. Methadone enhances human influenza A virus replication. Addiction Biology. 2017 Jan;22(1):257-71.

11. Tseng RJ, Padgett DA, Dhabhar FS, Engler H, Sheridan JF. Stress-induced modulation of NK activity during influenza viral infection: role of glucocorticoids and opioids. Brain, behavior, and immunity. 2005 Mar 1;19(2):153-64.

12. Salimi V, Hennus MP, Mokhtari-Azad T, Shokri F, Janssen R, Hodemaekers HM, Rygiel TP, Coenjaerts FE, Meyaard L, Bont L. Opioid receptors control viral replication in the airways. Critical care medicine. 2013 Jan 1;41(1):205-14.

13. Jamali A, Mahdavi M, Shahabi S, Hassan ZM, Sabahi F, Javan M, Farsani MJ, Parsania M, Bamdad T. Naloxone, an opioid receptor antagonist, enhances induction of protective immunity against HSV-1 infection in BALB/c mice. Microbial pathogenesis. 2007 Nov 1;43(5-6):217-23.

14. Lioy DT, Sheridan PA, Hurley SD, Walton JR, Martin AM, Olschowka JA, Moynihan JA. Acute morphine exposure potentiates the development of HSV-1-induced encephalitis. Journal of neuroimmunology. 2006 Mar 1;172(1-2):9-17.

15. Monavari SH, Shahrabadi MS. Effects of morphine on replication of herpes simplex virus type 1 and 2. African Journal of Biotechnology. 2010;9(20).

16. Romero-Martinez BS, Montano LM, Solis-Chagoyan H, Sommer B, Ramirez-Salinas GL, Perez-Figueroa GE, Flores-Soto E. Possible beneficial actions of caffeine in SARS-CoV-2. International Journal of Molecular Sciences. 2021 May 22;22(11):5460.

17. Paul AK, Smith CM, Rahmatullah M, Nissapatorn V, Wilairatana P, Spetea M, Gueven N, Dietis N. Opioid analgesia and opioid-induced adverse effects: A review. Pharmaceuticals. 2021 Oct 27;14(11):1091.

Thanks for your kindly attention