Undergraduate Journal of Experimental Microbiology and Immunology (UJEMI) Vol. 8:1-5

UJEMI PERSPECTIVES

Potential Pathophysiological Mechanisms Explaining the Association Between Viral Infections and Depression

Rachel Leong

Department of Microbiology and Immunology, University of British Columbia, Vancouver, British Columbia, Canada

SUMMARY Depression, a common neuropsychiatric disorder, affects millions worldwide and causes immense economic and health burdens. With the COVID-19 pandemic in our recent history, more attention needs to be turned to reducing fallout from the pandemic such as depression. Various viruses, most notably SARS-CoV-2, HIV, and HHV-6B, have been associated with depression. This suggests a complex interplay between viral infections and mental health. Social and psychological factors, exacerbated by events like the COVID-19 pandemic, further contribute to depressive symptoms. Proposed pathophysiological mechanisms include neuroinflammation, monoamine dysregulation, hypothalamic-pituitary-adrenal axis activation and more, underscoring the multifaceted nature of depression's etiology. Specifically, inflammation, mediated by cytokine storms following viral infections, contributes to neuroinflammation and subsequent depressive symptoms. While treatments targeting viral infections and depression exist independently, integrated approaches remain limited. Promising avenues include antiviral medications with antidepressant properties or vice versa, and lifestyle interventions addressing stress and inflammation. Understanding the intricate relationship between viral infections and depression holds potential for mitigating the global burden of depression through targeted interventions.

INTRODUCTION

Depression is one of the most common neuropsychiatric disorders characterized by long-term recurrent depressed mood, despair, pessimism, anxiety and even suicidal tendencies (1). The World Health Organization estimates that, worldwide, 5% of adults suffer from depression (2). Approximately 12 billion work days are lost in the US every year to depression and anxiety, causing an economic burden of $1 trillion USD (2). Depression is associated with an increased risk of cardiovascular and respiratory disease, cancer, and diabetes (2). Factors contributing to depression include interpersonal issues, developmental events, personality or cognitive dispositions, biological and environmental factors and more (3). As with any worldwide issue, a clearer understanding of the mechanisms precipitating depression would allow for the identification of modifiable factors at the individual, population, and global levels.

The impact of the COVID-19 pandemic continues to manifest itself in the mental health problems it caused or exacerbated. These consequences are not restricted to the COVID-19 pandemic alone. Historically, viral outbreaks have been associated with increased frequencies of neuropsychiatric, neurodegenerative, and neurobehavioural disorders (4). Certain stealth adapted viruses cause persistent systemic infections commonly infecting the brain, including major mood and cognitive disorders (5). Specifically, herpes simplex virus (HSV)-related encephalitis is associated with affective disorders while Borna disease virus (BDV) is associated with neurodevelopmental abnormalities and psychiatric disorders like schizophrenia (6). Of note, there is also a substantial body of literature linking various viruses to depression.

The mechanisms connecting prior viral infections with depression remain largely unclear. The current work synthesizes the extant knowledge on the pathophysiological mechanisms of viral infections and depression. The various viruses that have been implicated with depression will be delineated. Non-biological causes and all proposed pathophysiological

Published Online: September 2024

Citation: Leong. 2024. Potential pathophysiological mechanisms explaining the association between viral infections and depression. UJEMI Perspectives 8:1-5

Editor: François Jean (Ph.D.), University of British Columbia

Address correspondence to:
https://jemi.microbiology.ubc.ca/

mechanisms from the literature will be summarized. Specifically, an in-depth synthesis on inflammation as the link between viruses and depression will be described. Finally, the most promising treatment and management strategies that could simultaneously target viral infections and depression will be highlighted. Identifying pathophysiological mediators between viral infections and depression means potential for targeting these mediators to reduce the global burden of depression.

PROPOSED RESEARCH QUESTIONS

What are the various viral infections associated with depression? Depression is linked to various viruses. These include common viruses such as influenza A, chronic viruses like HIV/AIDS, sexually transmitted infections like human herpes simplex virus (HSV), *Chlamydia trachomatis* and *Trichomonas vaginalis* (7, 8). In particular, the odds of depression were increased in patients infected with HSV-2 or cytomegalovirus (9). Multiple studies on patients infected with asymptomatic and symptomatic human T-cell lymphotropic virus-1 (HTLV-1) reported that patients experienced more depression than controls (10, 11). Depression has also consistently been reported in patients with hepatitis C virus (HCV), at a much higher prevalence than in the general population (12). Patients with chronic HIV develop neurological disturbances that may negatively impact their quality of life and adherence to antiretroviral therapy protocols (13). The latent phase of human herpesvirus 6B (HHV-6B) is involved in depression onset (14). Lastly, a meta-analysis taking 28 studies into account corroborated the association of HSV-1 and *Chlamydia trachomatis* with depression, as well as Borna disease virus (BDV), varicella zoster virus (VZV), and Epstein-Barr virus (EBV) (15).

What are other social and psychological factors that could explain the association between viral infection and depression? Psychological symptoms, including depression, likely have complex and multifactorial causes including environmental, psychological and biological causes (16). Certain social and psychological factors, especially made relevant after a pandemic, include social quarantine, economic problems, stress and malnutrition (17). On a macroscopic scale, the COVID-19 pandemic modified economic, social and political structures as well as impacted daily routines (18). This contributes to poorer diets, increased sedentary behaviour and increased stress (18). Specifically, the impact of social quarantine manifests itself in increased social media usage and loneliness, which are consistently associated with psychological symptoms (19). Additionally, sleep disturbances and anxiety symptoms are common experiences in relation to pandemics or severe viral infections (20). These and other psychosocial factors likely interact with viral mechanisms to create a depressive mood (13). Concomitantly, this is a reciprocal relationship in which depressive symptoms and related stress reduce the protective immune response. Depressive symptoms were found to be related to C-reactive protein, a biomarker indicative of coronary burden and pathogen burden for viruses such as cytomegalovirus, HSV, and EPV in patients with acute coronary syndromes (21).

What are the proposed pathophysiological mechanisms that could mediate the relationship between viral infections and depression? There are many hypotheses as to the pathophysiological mechanisms between viral infections and depression. Viruses are known to cause chronic increases in proinflammatory cytokine levels by activating microglia and astrocytes (13, 17). Cytokines are involved in neuropathological processes, such as in hepatitis patients in which the use of cytokine treatment caused psychiatric side effects (22). A second mechanism is the monoamine theory, in which patients have insufficient or polymorphic variants of the genes for monoamine neuromediators which may lead to depression (22). Certain viruses such as HIV may decrease this monoaminergic function or induce neurotoxicity in dopaminergic neurons (13). Additionally, viruses may reduce brain-derived neurotrophic factors or cause other neuroplasticity/neurogenesis defects (13, 18). Such disturbances of normal neurogenesis have been extensively associated with depression (22). Furthermore, activation of the hypothalamic-pituitary-adrenal (HPA) axis is associated with viral infections and can also be due to inflammatory cytokines (17, 23). For example, expression of SITH-1, a protein specific to HHV-6B latent infection, was associated with

hyperactivation of the HPA axis and depressive symptoms in mice (14). This same protein was found significantly higher in antibody titers of depressed patients compared to controls (14). Other proposed mechanisms include mitochondrial disorders, damage to the hippocampus, induced autoimmunity, antibody formation against virus antigens, and virus-induced damage to non-brain tissues (5, 17).

Specifically, how does inflammation and the purinergic system contribute to depression following a viral infection? While there is substantial evidence for the relationships between inflammation, depression and certain viruses (e.g., HIV), few clinical studies have been performed that elucidate their exact interactions (24). A proposed pathway explaining these relationships begins with viral neuroinvasion (particularly respiratory viruses such as SARS-CoV-2) which trigger a cytokine storm (Figure 1) (23). Activated cytokines include interferons, which then activate interferon-induced genes like the indoleamine-pyrrole 2,3-dioxygenase-1 (IDO-1) enzyme (23, 25, 26). IDO-1 is an intracellular monomeric enzyme that causes a reduction in tryptophan by instead breaking down one of its metabolites, kynurenine (26). The kynurenine pathway in turn releases toxic metabolites which then increase glial activation (25). Glial cells affect the transmission of proteins, neurotransmitters and cytokines which lead to neuroinflammation, toxicity, neuronal death and decreases in serotonin levels (1, 23). This eventually leads to depression (Figure 1). Impacts on glial cells have specifically been found for SARS-CoV-2, BDV-1, Zika virus B, HIV, and HHV-6B (1, 27). In particular, upon SARS-CoV-2 neuroinvasion, an additional mechanism includes the increase of local angiotensin II as mediated by the down-regulation of angiotensin converting enzyme-2 (25). Angiotensin II then increases kynurenine metabolites and continues down the purinergic pathway (8, 17, 23, 25, 26).

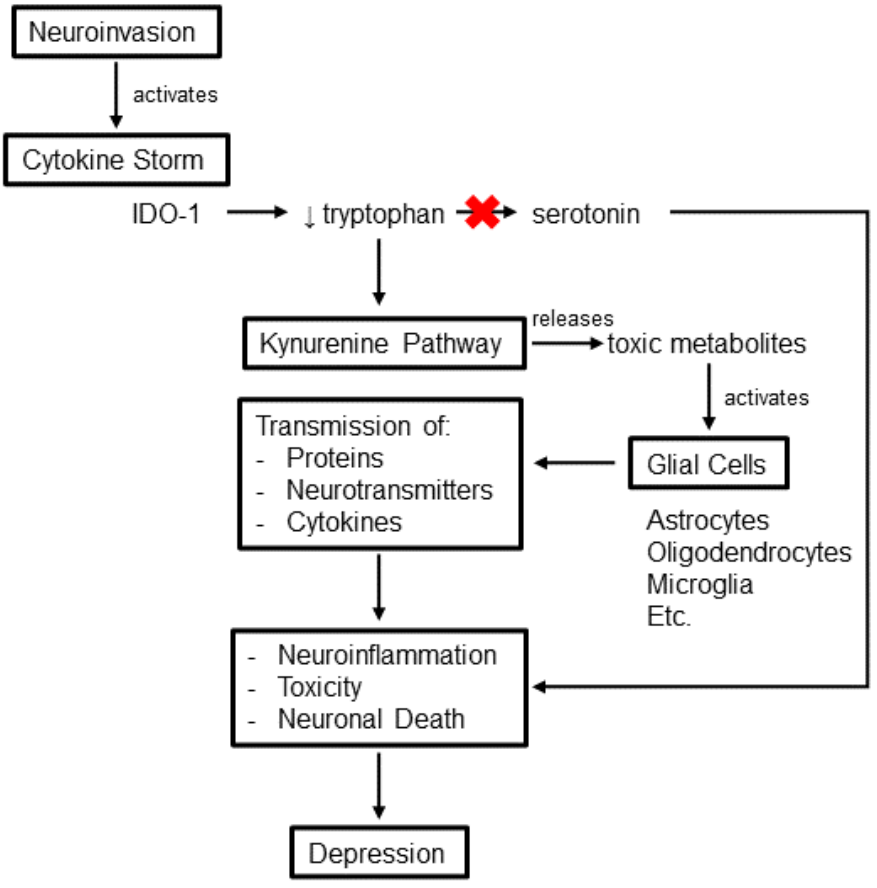

FIG. 1 The inflammation and purinergic pathway linking viruses and depression.

What is the current state of evidence on the treatment or management of viral infections and associated depression? While there is a large body of evidence for treating or managing viral infections and depression separately, there is less on simultaneous management of these

associated afflictions. One randomized controlled trial tested amantadine, often used to treat dyskinesia and influenza, as an antidepressant and antiviral medication for patients with BDV-1 (28). Researchers found that amantadine was effective as an antidepressant and antiviral, showing reduced suicidal behaviours and decreases in cumulative infection measures over time (28). Lifestyle management strategies for viral infections and their associated depression would include controlling stress levels, preventing the cytokine storm with anti-inflammatory drugs, and proper nutrition (17). Chlorpromazine is normally used in psychiatric care but has been suggested to have antiviral properties, however these findings have not been translated into clinical trials for antiviral treatment (29).

CONCLUSION

There is likely a pathophysiological mechanism linking prior infections with viruses and the subsequent development of depression. The purinergic system is the most well-studied pathway explaining this link. More research on the pathophysiological mechanisms of depression as caused by viruses could eventually translate into the reduction of the global depression burden.

ACKNOWLEDGEMENTS

I would like to thank Dr. Marc Horwitz for the invaluable guidance and support throughout the construction of this manuscript.

REFERENCES

1. **Yu X, Wang S, Wu W, Chang H, Shan P, Yang L, Zhang W, Wang X**. 2023. Exploring new mechanism of depression from the effects of virus on nerve cells. *Cells* **12**:1767.
2. World Health Organization. 2023. Depressive disorder (depression). World Health Organization.
3. **Khalsa S-R, McCarthy KS, Sharpless BA, Barrett MS, Barber JP**. 2011. Beliefs about the causes of depression and treatment preferences. *J Clin Psychol* **67**:539–549.
4. **Aytaç HM, Pehlivan S**. 2020. Viral pandemics as possible psycho-immunological causes of psychiatric symptoms: from past to present. *J Adv Res Health Sci* **3**:92–98.
5. Martin WJ. 2015. Stealth adapted viruses: a bridge between molecular virology and clinical psychiatry. *Open J Psychiatry* **05**:311–319.
6. **Taieb O, Baleyte JM, Mazet P, Fillet AM**. 2001. Borna disease virus and psychiatry. *Eur Psychiatry* **16**:3–10.
7. **Coughlin SS**. 2012. Anxiety and depression: linkages with viral diseases. *Public Health Rev* **34**:7.
8. **Doyle C, Swain WA, Swain Ewald HA, Ewald PW**. 2019. Inflammation, infection and depression: an evolutionary perspective. *Evol Hum Sci* **1**:e14.
9. **Gale SD, Berrett AN, Erickson LD, Brown BL, Hedges DW**. 2018. Association between virus exposure and depression in US adults. *Psychiatry Res* **261**:73–79.
10. **Rocha-Filho PAS, Goncalves LR**. 2018. Depression and anxiety disorders among patients with human T-cell lymphotropic virus type-1: a cross-sectional study with a comparison group. *Rev Soc Bras Med Trop* **51**:357–360.
11. **Stumpf BP, Carneiro-Proietti AB, Proietti FA, Rocha FL, INTERDISCIPLINARY HTLV RESEARCH GROUP (GIPH)**. 2008. Higher rate of major depression among blood donor candidates infected with human t-cell lymphotropic virus type 1. *Int J Psychiatry Med* **38**:345–355.
12. **Adinolfi LE, Nevola R, Rinaldi L, Romano C, Giordano M**. 2017. Chronic hepatitis c virus infection and depression. *Clin Liver Dis* **21**:517–534.
13. **Del Guerra FB, Fonseca JLI, Figueiredo VM, Ziff EB, Konkiewitz EC**. 2013. Human immunodeficiency virus-associated depression: contributions of immuno-inflammatory, monoaminergic, neurodegenerative, and neurotrophic pathways. *J Neurovirol* **19**:314–327.
14. **Kobayashi N, Oka N, Takahashi M, Shimada K, Ishii A, Tatebayashi Y, Shigeta M, Yanagisawa H, Kondo K**. 2020. Human herpesvirus 6B greatly increases risk of depression by activating hypothalamic-pituitary -adrenal axis during latent phase of infection. *iScience* **23**:101187.
15. **Wang X, Zhang L, Lei Y, Liu X, Zhou X, Liu Y, Wang M, Yang L, Zhang L, Fan S, Xie P**. 2014. Meta-analysis of infectious agents and depression. *Sci Rep* **4**:4530.
16. **Thye AY-K, Law JW-F, Tan LT-H, Pusparajah P, Ser H-L, Thurairajasingam S, Letchumanan V, Lee L-H**. 2022. Psychological symptoms in COVID-19 patients: insights into pathophysiology and risk factors of long COVID-19. *Biology* **11**:61.
17. **Mohammadkhanizadeh A, Nikbakht F**. 2021. Investigating the potential mechanisms of depression induced-by COVID-19 infection in patients. *J Clin Neurosci* **91**:283–287.
18. **Perlmutter A**. 2021. Immunological interfaces: the COVID-19 pandemic and depression. *Front Neurol* **12**:657004.

19. **Bellapigna C, Kalibatseva Z**. 2023. Psychosocial risk factors associated with social anxiety, depressive and disordered eating symptoms during COVID-19. *AIMS Public Health* **10**:18–34.
20. **Zulkifli NA, Guan NC, Zainal NZ, Ling TS**. 2021. Psychosocial factors associated with depression and anxiety during COVID-19 pandemic among outpatients with depression. *Alpha Psychiatry* **22**:185–193.
21. **Miller GE, Freedland KE, Duntley S, Carney RM.** 2005. Relation of depressive symptoms to C-reactive protein and pathogen burden (cytomegalovirus, herpes simplex virus, Epstein-Barr virus) in patients with earlier acute coronary syndromes. *Am J Cardiol* **95**:317–321.
22. **Shadrina M, Bondarenko EA, Slominsky PA**. 2018. Genetics factors in major depression disease. *Front Psychiatry* **9**:334.
23. **Mingoti MED, Bertollo AG, Simões JLB, Francisco GR, Bagatini MD, Ignácio ZM**. 2022. COVID-19, oxidative stress, and neuroinflammation in the depression route. *J Mol Neurosci* **72**:1166–1181.
24. **Mudra Rakshasa-Loots A, Whalley HC, Vera JH, Cox SR**. 2022. Neuroinflammation in HIV-associated depression: evidence and future perspectives. *Mol Psychiatry* **27**:3619–3632.
25. **Bouças AP, Rheinheimer J, Lagopoulos J**. 2022. Why severe COVID-19 patients are at greater risk of developing depression: a molecular perspective. *The Neuroscientist* **28**:11–19.
26. **Karimi Z, Chenari M, Rezaie F, Karimi S, Parhizgari N, Mokhtari-Azad T.** 2022. Proposed pathway linking respiratory infections with depression. *Clin Psychopharmacol Neurosci* **20**:199–210.
27. **Wong AC, Devason AS, Umana IC, Cox TO, Dohnalová L, Litichevskiy L, Perla J, Lundgren P, Etwebi Z, Izzo LT, Kim J, Tetlak M, Descamps HC, Park SL, Wisser S, McKnight AD, Pardy RD, Kim J, Blank N, Patel S, Thum K, Mason S, Beltra J-C, Michieletto MF, Ngiow SF, Miller BM, Liou MJ, Madhu B, Dmitrieva-Posocco O, Huber AS, Hewins P, Petucci C, Chu CP, Baraniecki-Zwil G, Giron LB, Baxter AE, Greenplate AR, Kearns C, Montone K, Litzky LA, Feldman M, Henao-Mejia J, Striepen B, Ramage H, Jurado KA, Wellen KE, O'Doherty U, Abdel-Mohsen M, Landay AL, Keshavarzian A, Henrich TJ, Deeks SG, Peluso MJ, Meyer NJ, Wherry EJ, Abramoff BA, Cherry S, Thaiss CA, Levy M**. 2023. Serotonin reduction in post-acute sequelae of viral infection. *Cell* **186**:4851-4867.e20.
28. **Dietrich DE, Bode L, Spannhuth CW, Hecker H, Ludwig H, Emrich HM**. 2020. Antiviral treatment perspective against Borna disease virus 1 infection in major depression: a double-blind placebo-controlled randomized clinical trial. *BMC Pharmacol Toxicol* **21**:12.
29. **Stip E**. 2020. Psychiatry and COVID-19: the role of chlorpromazine. *Can J Psychiatry* **65**:739–740.