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Analysing of The Effects of an Interleukin – 1 Receptor Antagonist and a RNA Polymerase Inhibitor on Neurodegeneration in the Hippocampal Cell Line

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Research Article

History

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ABSTRACT

Objective: The aim of the present study is to investigate the anti-neurodegenerative effects of favipiravir, a RNA polymerase inhibitor, and anakinra, an interleukin-1 receptor antagonist, on glutamate-induced cytotoxicity. Due to their heightened sensitivity to glutamate, the hippocampal HT22 cell line were used.

Methods: Five groups of cells were established to examine the effects of anakinra and favipiravir on glutamate-induced cytotoxicity. The control group received no treatment. The group induced with glutamate received 10 mM of glutamate for 24 hours. The anakinra group was exposed to different concentrations (1,10,25,50,100 µg) of anakinra for 24 hours. The favipiravir group was exposed to different concentrations (1,10,25,50,100 µg) of favipiravir for 24 hours. The anakinra+glutamate group was pre-treated with anakinra at various concentrations (1,10,25,50,100 µg) for 1 hour and then exposed to 10 mM of glutamate for 24 hours. The favipiravir+glutamate group was pre-treated with favipiravir at various concentrations (1,10,25,50,100 µg) for 1 hour and then exposed to 10 mM of glutamate for 24 hours. Effective doses were subsequently determined, and combinations of anakinra+favipiravir+glutamate were applied.

Results: Viability was not affected by the application of different doses of favipiravir alone ($p < 0.01$ compared to the control group). It was observed that the group treated with 100 µg anakinra showed higher viability compared to other groups ($p < 0.01$ compared to glutamate). Viability was not affected by the application of different doses of anakinra alone ($p< 0.01$ compared to the control group). However, anakinra was observed to prevent the cytotoxicity induced by glutamate when applied at 100 µg, exhibiting a protective effect against neurodegeneration at this dose. In the group where anakinra and favipiravir were combined and applied with glutamate, anakinra showed a protective effect against glutamate toxicity, but the combination of anakinra and favipiravir did not alter this effect.

Conclusion: More extensive animal and human studies are required to determine the clinical implications of these findings.

Keywords: Neurodegeneration, Hippocampal cell line, interleukin-1 receptor antagonist, RNA polymerase inhibitor.

İnterlökin - 1 Reseptör Antagonisti Ve RNA Polimeraz İnhibitörünün Hipokampal Hücre Hattında Nörodejenerasyon Üzerine Etkilerinin İncelenmesi

Araştırma Makalesi

Süreç

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ÖZET

Amaç: Bu çalışmada bir RNA polimeraz inhibitörü; favipravirin ve İnterlökin-1 reseptörü antagonisti anakinranın, hipokampal hücrelerde glutamatla oluşturulacak sitotoksisite üzerine anti-nörodejeneratif etkilerinin araştırılması amaçlandı. Glutamata olan aşırı duyarlılığı nedeniyle HT22 hücre hattı kullanıldı.

Yöntem: Kontrol, glutamat (10 mM), anakinra (1,10,25,50,100 µg), favipravir (1,10,25,50,100 µg) ve anakinra+favipravir hücre grupları oluşturuldu Kontrol grubuna herhangi bir tedavi uygulanmadı. Glutamat ile indüklenen grubun hücrelerine 24 saat boyunca 10 mM glutamat verildi. Anakinra grubundaki hücrelere 24 saat boyunca çeşitli konsantrasyonlarda (1,10, 25, 50, 100 µg) anakinra verildi. Favipravir grubundaki hücrelere 24 saat boyunca çeşitli konsantrasyonlarda (1,10,25,50,100 µg) favipravir verildi. Anakinra+glutamat grubundaki hücreler, 1 saat boyunca farklı konsantrasyonlarda (1,10,25,50,100 µg) anakinra ile ön işleme tabi tutuldu ve ardından 24 saat boyunca 10 mM glutamat uygulandı. Favipiravir+glutamat grubundaki hücreler, 1 saat boyunca farklı konsantrasyonlarda (1, 10, 25, 50,100 µg) favipiravir ile ön işleme tabi tutuldu ve ardından 24 saat boyunca 10 mM glutamat uygulandı. Ardından etkili dozlar belirlenerek anakinra+favipiavir+glutamattan oluşan kombinasyonları uygulandı.

Bulgular: Yalnızca favipravirin farklı dozlarının uygulanmasınında viabilite üzerinde herhangi bir etkisi gözlenmedi ($p< 0.01$ kontrole göre). 100 µg anakinra uygulanan grupta hücre canlılığının diğer gruplara göre daha fazla olduğu gözlendi ($p<0.01$ glutamata göre). Anakinranın farklı dozlarının uygulanmasınında viabilite üzerinde herhangi bir etkisi gözlenmedi ($p< 0.01$ kontrole göre). Sitotoksisitenin anakinra 100 µg uygulamasıyla önlendiği gözlendi. Anakinranın bu dozda nörodejenerasyon üzerine koruyucu etkisi izlendi. Anakinra+favipravir+glutamat kombine uygulanan grupta ise anakinranın glutamat toksisitesine karşı koruyucu fakat anakinra+favipravir kombinasyonu bu etkiyi değiştirmediği gözlendi.

Sonuç: Ancak bu etkinin klinik açıdan önemi için daha detaylı hayvan ve insan çalışmalarına gereksinim vardır.

Anahtar Kelimeler: Nörödejenerasyon, Hipokampal hücre hattı, interlökin-1 reseptör antagonisti, RNA polimeraz inhibitörü.

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Introduction

It is important to investigate the pathogenesis of neurodegenerative diseases (NDD) and target cytokines and molecules to develop new treatment strategies. To achieve this aim, in vitro disease models, especially cell culture models can be utilized. Cell culture studies can be carried out in normal tissues or NDD models.

Glutamate is the primary excitatory neurotransmitter of the central nervous system involved in various neurophysiological functions. Disturbance of its homeostasis can have deleterious effects on neurons, which may result in cell death.[1] Called excitotoxicity, this pathological process can induce degeneration of neurons following excessive excitation of glutamate on specific ionotropic receptors. Activation of these receptors can lead to a neuronal Ca^2 influx that can mediate excitotoxicity through a series of events including activation of various enzymes in free radical production, mitochondrial dysfunction and normal cell development and functions and damage cell membranes, cytoskeleton and DNA.[2] Interestingly, excitotoxicity has been reported to be involved in several neurodegenerative diseases such as Alzheimer's disease (AD) and multiple sclerosis.[3] In vitro and in vivo studies have shown that excessive amounts of excitatory amino acids like glutamate and their analogues cause neurodegeneration.

It is known that glutamate produces acute and chronic neurodegenerative conditions and initiate cell death. Therefore, a healthy glutamate signal transmission is crucial for protection of neurons. The phenomenon of excitotoxicity, i.e. cell necrosis resulting from activation of excessive glutamate on the surface receptors, has been associated with various pathological conditions of the nervous system including seizures, ischemia, anoxia, hypoglycemia and inflammation.[4] Since the introduction of the concept of excitotoxicity, the fundamental dogma has been that glutamate-related cell damage or death results from activation of excitatory amino acid (EAA) receptors and these effects can be blocked by the use of competitive or noncompetitive l-glutamate receptor inhibitors.[4] Neurotoxicity secondary to exposure of neurons to high extracellular glutamate concentrations can occur via two different neuronal damage and death mechanisms. A short exposure to glutamate (5-15 minutes) leads to neuronal swelling, the breakdown of the cells and the release of lactate dehydrogenase depending on extracellular Na^+ and Cl^- concentrations.[4] This information about excitotoxic cell death is significant with respect to the role of glutamate in ischemic or hypoglycemic neuronal damage.

Glutamate reuptake is essential for the regulation of physiological extracellular glutamate concentrations and it is primarily mediated by high-affinity sodium-dependent transmitters. At least five different glutamate transmitters expressed on neuronal or glial cells (GLT-1, GLAST, EAAC1, EAAT4 and EAAT5) are well characterized [5] and up to 90% of the total glutamate reuptake is achieved in the adult central nervous system.[5] Disruption of GLT-1 expression in a few neurological diseases has been reported to be related to a change in glutamate uptake.[6]

Due to its oversensitivity to glutamate, the hippocampal HT22 cell line is used to model NDDs.[3,7,8,9] There have been several studies on glutamate-induced cytotoxicity in cell lines.[3,8,10,11]

Anakinra, an interleukin-1 receptor antagonist, is used for the prevention of inflammation in many autoinflammatory diseases. In the present study, possible effects of anakinra on inflammation and neurodegeneration in NDDs were examined. Besides, the HT22 cell line was utilized to examine the anti-inflammatory and/or anti-neurodegenerative effects of favipiravir, a RNA polymerase inhibitor. In addition to glutamate-induced cytotoxicity, cell viability was investigated.

Material and Methods

All steps of the study were completed in accordance with ethical principles. Ethical approval for the study was obtained from Sivas Cumhuriyet University Ethical Board of Non-Interventional Clinical Research (approval date: 20 Oct., 2021; approval number: 2021-10/39). The study was supported by Sivas Cumhuriyet University Scientific Research Projects Coordination Unit (the project number: T-984).

HT22 (SCC129) cell line was obtained from Merck ® cell collection and cultured in Dulbecco's modified eagle medium (DMEM) (Thermo Fisher Scientific, Altrincham, UK) containing 10% fetal bovine serum (FBS) (Sigma-Aldrich Co., St Louis, MO, USA), 1% penicillin/streptomycin (Sigma Aldrich Co., St Louis, MO, USA) and 1% L-glutamine. It was incubated under appropriate conditions (at 37 °C and atmosphere humidified with 5% CO2). The cells were passaged when they reached 80%-90% density. After passaging three times, the cells were seeded in a 96-well plate with a cell density of 1-104 in each well.

Anakinra, favipiravir and glutamate (Sigma-Aldrich Co., St Louis, MO, ABD) were dissolved in DMEM and stock solutions were formed before processing.

Cell groups were created to examine the effects of anakinra and favipiravir on glutamate-induced cytotoxicity. The control group did not receive any treatment. The cells of the glutamate-induced group were administered 10mM glutamate for 24 hours. The cells in the anakinra group were administered anakinra at various concentrations (1,10, 25, 50 and 100 µM) for 24 hours. The cells in the favipiravir group were administered favipiravir at various concentrations (1, 10, 25, 50 and 100 µM) for 24 hours. The cells in the anakinra + glutamate group were pretreated with anakinra at various concentrations (1, 10, 25, 50 and 100 µM) for one hour and then were administered 10mM glutamate for 24 hours. The cells in the favipiravir + glutamate group were pretreated with favipiravir at various concentrations for one hour and then administered 10 mM glutamate for 24 hours. After that, effective doses were determined and anakinra + favipiravir + glutamate combinations were administered.

Cell viability was evaluated by using the XTT test (Roche Diagnostic, MA, USA). Initially, HT22 cells were seeded in 96-well plates at the density of 1X104 cells in 100 µL DMEM per well and incubated for 24 hours. Glutamate-induced cytotoxicity was achieved as described before. Following 24-hours incubation, 96-well plate was removed and the wells were washed with phosphate-buffered saline. Then 100 µL DMEM without phenol red and 50 µL XTT were added to the wells and the plates were kept at 37 °C for 4 hours. Absorbance values were determined by using an ELISA microplate reader (Thermo Fisher Scientific, Altrincham, UK) at 450 nm. All the experiments were conducted three times and cell viability was expressed in percentages of live

cells and compared with that of the control group (untreated cells). Cell viability in the control group was considered as 100%.

All the measurements were performed three times. Statistical analyses of obtained data were made with Statistical Package Program for Social Sciences 23.0. Shapiro Wilk test was utilized to determine whether the data were evenly distributed. Mean and standard deviation were determined for descriptive statistics. One-way ANOVA was adopted to determine differences in the normally distributed data and Kruskal-Wallis and Mann-Whitney U test were utilized for the data without a normal distribution. Statistical significance was set at $p<0,05$.

Results

After glutamate-induced excitotoxicity in the hippocampal HT22 cell line, the effects of different concentrations of anakinra alone, favipiravir alone and the combinations of anakinra and favipiravir on cell viability were examined (Figure 1, Figure 2, Figure 3). Percentages of viable cells in the hippocampal HT22 cell line administered anakinra alone, favipiravir alone and the combination of anakinra and favipiravir were compared with those in the control cell line.

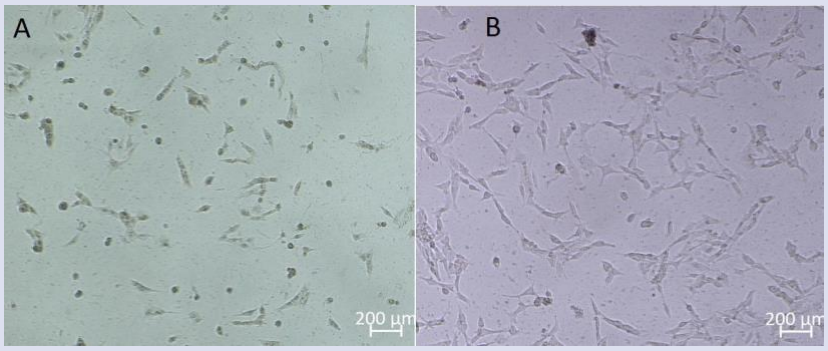

Figure 1. Microscopic Views of the Hippocampal HT22 Cell Line Morphology after Glutamate-Induced Excitotoxicity in Glutamate Group (A) and Control Group (B)

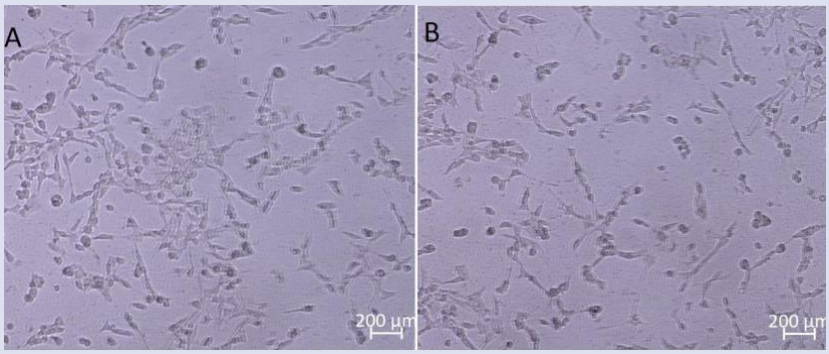

Figure 2. Microscopic Views of the Hippocampal HT22 Cell Line Morphology after Glutamate-Induced Excitotoxicity in Anakinra 100 µg-administered Group (A) and Favipiravir 100 µg-administered Group (B)

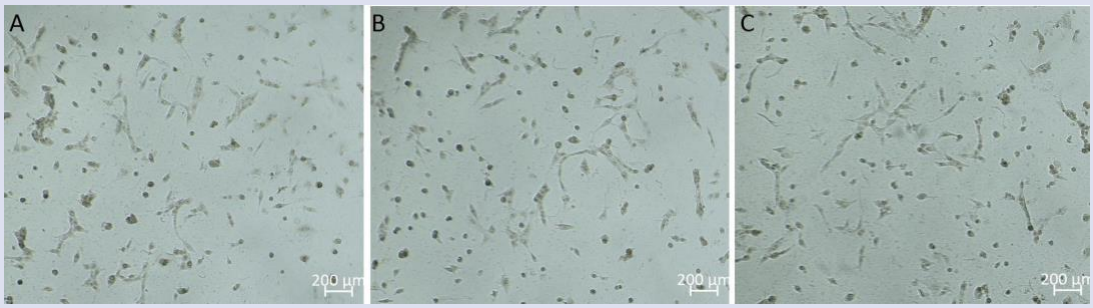

Figure 3. Microscopic Views of the Hippocampal HT22 Cell Line Morphology after Glutamate-Induced Excitotoxicity in Anakinra 100 µg and Glutamate-Administered Group (A), Favipiravir 100 µg and Glutamate-Administered Group (B) and Anakinra 100 µg, Glutamate and Favipiravir 100 µg-Administered Group (C)

When the effects of 100, 50, 25, 10 and 1 µM concentrations of anakinra on cell viability in the HT22 cell line after 10mM glutamate administration were evaluated, the cell viability was found to be significantly higher in the group administered anakinra 100 µM than in the other groups ($p < 0.01$ compared to glutamate). In other words, administration of different doses of anakinra alone did not have an effect on cell viability ($p< 0.01$ compared to the control group) (Figure 4).

Favipiravir at the doses of 100, 50, 25, 10 and 1 µM did not have an effect on cell viability after the administration of 10 mM glutamate to the HT22 cell line. In other words, different doses of favipiravir did not have an effect on cell viability ($p< 0.01$ compared to the control group) (Figure 5)

In the group administered a combination of anakinra, favipiravir and glutamate, anakinra 100 µM combined with favipiravir 100, 50, 25, 10 and 1 100 µM and glutamate 10 M was protective against glutamate toxicity, but the combination of anakinra and favipiravir did not change this effect (Figure 6).

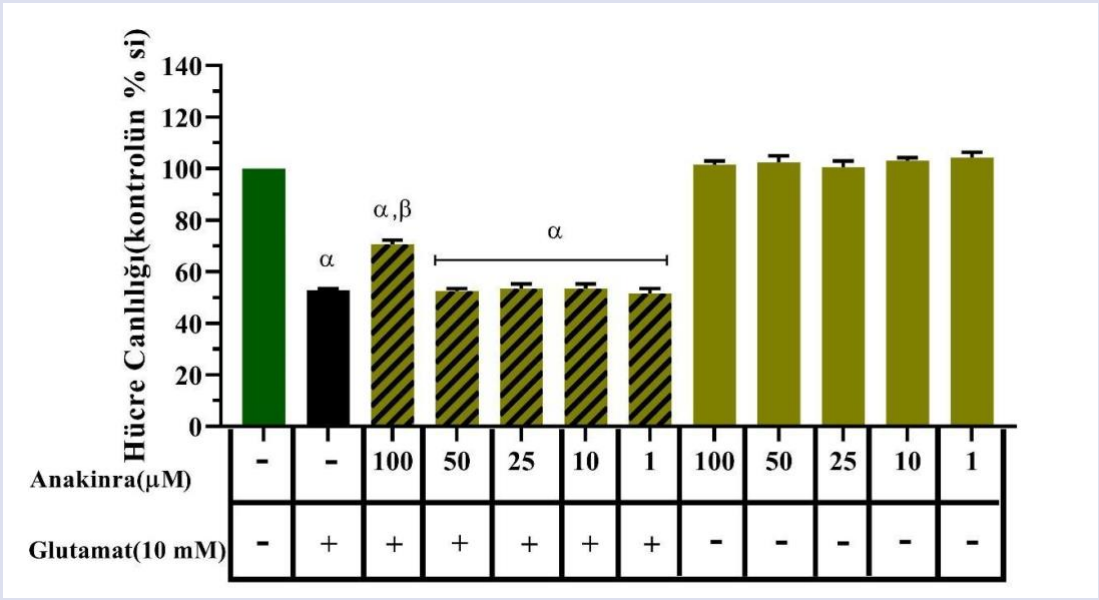

Figure 4. The Effect of Different Doses of Anakinra on Cell Viability in the HT22 Cell Line after Glutamate-Induced Excitotoxicity ($p < 0.01$ compared to glutamate) ($p< 0.01$ compared to the control group)

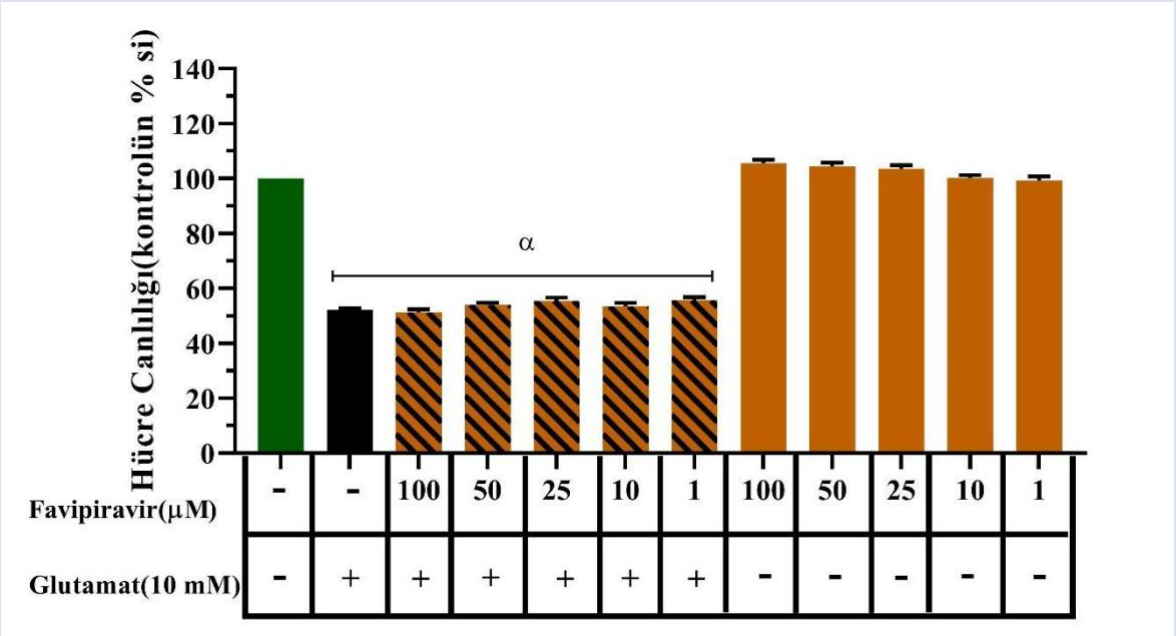

Figure 5. The Effect of Different Doses of Favipiravir on Cell Viability after Glutamate-Induced Excitotoxicity in the HT22 Cell Line ($p< 0.01$ compared to the control group)

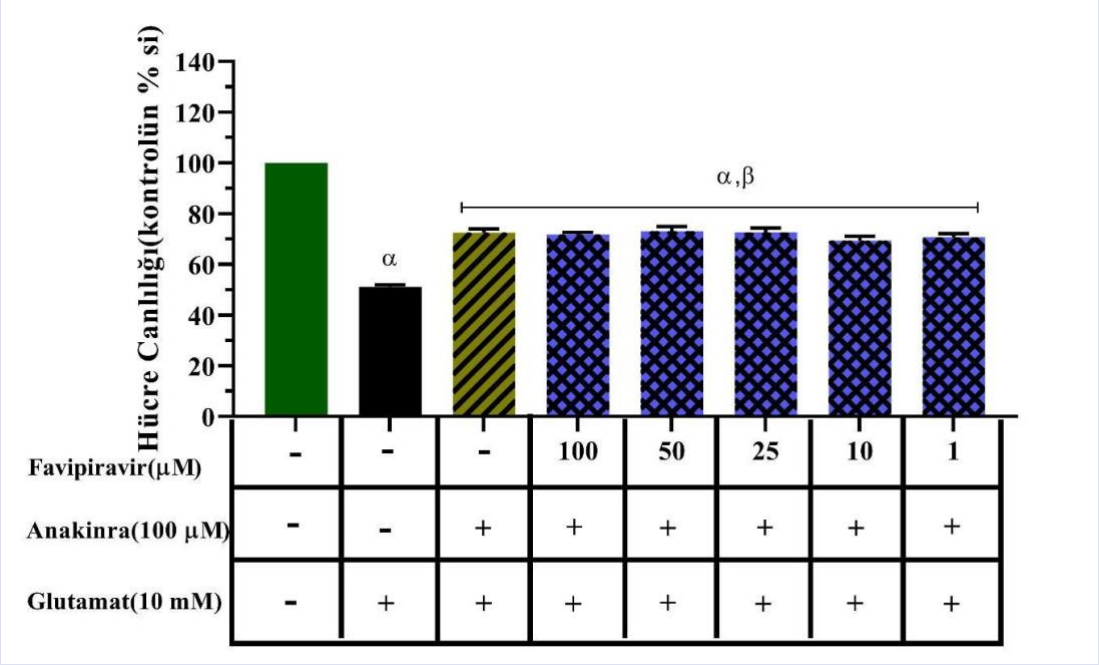

Figure 6. The Effect of the Combination of Anakinra and Favipiravir on Glutamate-Induced Excitotoxicity in the HT22 Cell Line

α; p< 0.01 compared to the control group
β; p< 0.01 compared to glutamate

Discussion

Hippocampal cells are sensitive to glutamate toxicity and suitable for in vitro neurodegeneration modelling. The present study aimed to examine the effects of anakinra and favipiravir individually and in combination at different concentrations on cell viability in glutamate-induced excitotoxicity in the hippocampal HT22 cell line.

High doses of favipiravir were used for the treatment of COVID-19 and anakinra, an anti-inflammatory drug approved by the Turkish Ministry of Health, is used to treat the patients developing respiratory failure when oxygen saturation decreases in cases of cytokine storms. Following COVID-19 infection, brain fog, which may also include many cognitive dysfunctions like forgetfulness, decreased attention and recalling and memory problems, appears. It is not known whether brain fog results from an inflammation involving glial cells, microglia and astrocytes affected by a cytokine storm and neurodegeneration accompanied by inflammation or neurodegeneration related to toxicity caused by high doses of drugs used individually or in combination. To our knowledge, none of the prior studies have focused on this issue.

NDDs include a group of diseases encountered and diagnosed at an increasing frequency today. Among the primary NDDs are AD, amyotrophic lateral sclerosis, Huntington's disease and Parkinson's disease.[12,13] Frontotemporal dementia and spinocerebellar ataxias have also been considered as NDDs in some reports.[14] While some of these diseases can be characterized by memory and cognition disorders, others can present as difficulties in moving, speaking and breathing.[14] In vivo studies performed to understand cellular and molecular etiopathogenesis of these diseases can cause financial problems and waste of time and require trained workforce and sophisticated laboratory equipment. Therefore, in vitro studies on NDDs have become more important.

Experimental studies on NDDs have used rats, fruit flies, nematode worms and yeast cultures.[14] Besides, there have been studies using pluripotent stem cells recently.[14] Several studies have shown that protein aggregates are transmitted from neuron to neuron and have a role in the pathogenesis of NDDs. Moreover, recent studies have revealed that excessive activation of microglia and release of reactive oxygen radicals in addition to environmental toxins and endogenous proteins play a role in the development of NDDs.[15,16]

Several animal studies have attempted to showcase functional, neurochemical and anatomic differences between NDDs by employing positron emission tomography (PET) and magnetic resonance imaging.[17] Furthermore, various rat models have been utilized to perform preclinic imaging and examine neurovascular components by means of PET and single-photon emission computed tomography (SPECT).[18] However, these examinations are costly and impose additional temporal and environmental burdens such as laboratories. There are less costly and more molecular studies to replace them. For instance, a study by Woerman has shown transmission of florescent-labelled α-synuclein fibrils from one neuron to another in a primary rat cell culture.[19]

TREM2 variants, which play a role in the pathogenesis of NDDs, have also been studied. TREM2 receptors are expressed on various immune cells.[20] The effect of

interleukin-1 (IL-1), a proinflammatory cytokine, was investigated in a rat AD model.[21] It was suggested that increased hippocampal IL-1 levels can have a relation with memory problems in AD.[21]

In the current study, the effect of different doses of anakinra on cell viability in glutamate-induced excitotoxicity in the HT22 hippocampal cells was examined. The cell viability was higher in the group administered anakinra 100 µM than in the groups administered lower doses of anakinra ($p< 0.01$, compared to glutamate). Administration of anakinra at lower doses did not have an effect on cell viability.

Anakinra, an interleukin-1 antagonist, is used to treat many inflammatory diseases now.[22] It is important to suppress both apoptosis, natural part of aging and not recognized in daily life, and the inflammation developing in neuronal cells for various reasons.

Cliteur et al. utilized recombinant human IL-1ra (anakinra) to prevent microglial activation, inflammation and brain damage in patients with spontaneous intracerebral hemorrhage during the second phase of their randomized clinical study.[23] They divided the patients into three groups: the first group received a high dose of anakinra (500mg/day), the second group received a low dose of anakinra (100mg/day) and the third group received standard treatment. They found that the high dose of anakinra could cross the blood-brain barrier and could be useful in prevention of secondary neuroinflammation.[23] Consistent with their findings, the present study showed that high doses of anakinra protected HT22 hippocampal cell viability better. Anakinra was also employed for the treatment of cytokine storms that developed in COVID-19 infection.[24] It is known that anakinra is effective in inflammatory conditions presenting as intracellular caspase activation and the development of inflammasome complex.[25]

It was proposed that abnormal microRNA (miRNA) levels can be related to the pathogenesis of many NDDs (26). Especially miR-9-5p, miR-21-5p, miR-29, miR-132-3p, miR-124-3p, miR-146a-5p, miR-155-5p, and miR-223-3p were associated with the disease pathogenesis.[26] Also, genetic mutations in the progranulin gene played a role in the loss of functions in familial frontotemporal dementia.[27]

Proinflammatory mechanisms have been reported to be involved even in the early stages of AD.[28] Especially the role of cytokines like TNF-α and IL-1β has been underscored. Effects of these cytokines on synaptic plasticity have been shown in rat AD amyloidosis models.[28] Mcc950, anakinra -an IL-1 receptor antagonist- and etanercept -an anti-TNF-α agent- were utilized as an NLRP3 inflammasome inhibitor.[28] It has been reported that IL-1 blockage through anakinra could be effective in prevention of amyloidosis by inhibiting extracellular transthyretin accumulation and apoptosis in neurodegenerative diseases, especially AD.[25]

It is stated in the literature that accumulation of transthyretin and amyloid fibrils plays a role in the pathogenesis of familial amyloidotic polyneuropathy (FAP).[29] IL-1 blockage with anakinra has been shown to prevent transthyretin accumulation and toxicity in an experimental FAP model -V30M FAP rat model.[29] Several studies have also focused on the genetic regulation of macroautophagy in NDD models.[30,31] In some animal models of NDD, creatinine has been shown to be neuroprotective.[32] In vitro microfluidic models have been considered important to gain insight into the pathogenesis of NDDs.[33]

Favipiravir was used particularly for the antiviral treatment of SARS-CoV-2 infection.[34] Favipiravir, a nucleoside analogue originating from prasine carboxamide, inhibits viral polymerase.[34] However, further in vitro and in vivo studies are needed to elucidate the effects of anakinra and favipiravir on neuroinflammation and neurodegeneration.

Conclusion

None of the doses of favipiravir utilized in the present study had an effect on cell viability in the HT22 cell line following glutamate administration. Regarding the effect of all the doses of anakinra utilized in this study, anakinra 100 µM was more effective in cell viability in the HT22 cell line after glutamate administration than other doses of anakinra ($\beta < 0.01$ compared to glutamate). In other words, only administration of anakinra at different doses (1 µM, 10 µM, 25 µM and 50 µM) had no effect on cell viability. However, anakinra 100 µM was observed to prevent cytotoxicity produced by glutamate in the HT22 cell line. It was protective against neurodegeneration. In the group administered the combination of anakinra, favipiravir and glutamate, at the doses of anakinra 100 µM and favipiravir 100 µM, 50 µM, 25 µM, 10 µM and 1 µM and glutamate 10 mM, anakinra was protective against glutamate toxicity, but the combination of anakinra and favipiravir did not alter this effect. In conclusion, high doses of anakinra were observed to be protective against excitotoxicity induced by glutamate in the HT22 cell line.

Conflicts of interest

There are no conflicts of interest in this work.

Acknowledgements

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Authors' contributions

MS: concept, design, supervision, resources, materials, data collection, analyses, literature review, reporting. AKF: analyses, literature review, reporting, critical examination, other.

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