7-1-2021

Neuron-glia crosstalk mediate the neurotoxic effects of ketamine via extracellular vesicles

Donald H. Penning
Henry Ford Health, dpennin2@hfhs.org

Simona Cazacu
Henry Ford Health, scazacu1@hfhs.org

V Jevtovic-Todorovic

Steven N. Kalkanis
Henry Ford Health, skalkan1@hfhs.org

Michael C. Lewis
Henry Ford Health, MLewis2@hfhs.org

See next page for additional authors

Recommended Citation

Penning DH, Cazacu S, Jevtovic-Todorovic V, Kalkanis S, Lewis M, and Brodie C. Neuron-glia crosstalk mediate the neurotoxic effects of ketamine via extracellular vesicles. GLIA 2021; 69(SUPPL 1):E302-E303.

Authors

Donald H. Penning, Simona Cazacu, V Jevtovic-Todorovic, Steven N. Kalkanis, Michael C. Lewis, and Chaya Brodie

Serapide, M.F.; Iraci, N. Glia-Derived Extracellular Vesicles in Parkinson's Disease. *J. Clin. Med.***2020**, *9*, 1941, doi:10.3390/jcm9061941.
4. Risiglione, P.; Leggio, L.; Cubisino, S.A.M.; Reina, S.; Paternò, G.; Marchetti, B.; Magrì, A.; Iraci, N.; Messina, A. High-resolution respirometry reveals mpp+ mitochondrial toxicity mechanism in a cellular model of parkinson's disease. *Int. J. Mol. Sci.***2020**, doi:10.3390/ijms21217809.

T09-042C

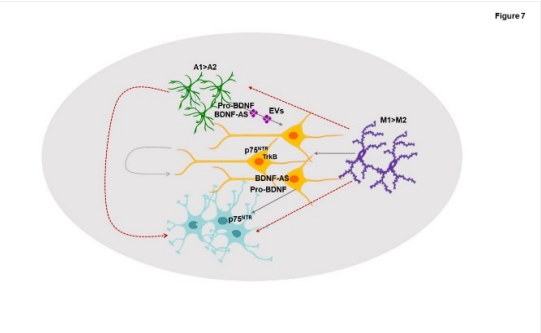
Neuron-glia crosstalk mediate the neurotoxic effects of ketamine via extracellular vesicles

D. H. Penning[1,2], S. Cazacu[2,1], V. Jevtovic-Todorovic[3], S. Kalkanis[2], M. Lewis[1], C. Brodie[4,2]

[1] *Henry Ford Health System, Anesthesiology, Detroit, USA*
[2] *Henry Ford Health System, Neurosurgery, Detroit, USA*
[3] *University of Colorado School of Medicine, Anesthesiology, Aurora, USA*
[4] *Bar-Ilan University, Faculty of Life Sciences, Ramat Gan, Israel*

Background: General anesthetics (GA) are associated with neurodevelopmental abnormalities including cell death, cognitive and behavioral changes. There is now powerful evidence for non-cell autonomous mechanisms in almost every pathological condition in the brain, especially relevant to glial cells, mainly astrocytes and microglia, that exhibit structural and functional contacts with neurons. These interactions were recently reported to occur via the secretion of extracellular vesicles (EVs). Here, we employed primary human neural cells to analyze ketamine effects focusing on the functions of glial cells and their polarization/differentiation state. We also explored the roles of extracellular vesicles (EVs) and different components of the BDNF pathway.
Methods: Ketamine effects were analyzed on human neuronal and glial cell proliferation and apoptosis and astrocytic (A1/A2) and microglial (M1/M2) cell activation were analyzed. The impact of the neuron-glial cell interactions in the neurotoxic effects of ketamine was analyzed using transwell co-cultures. The role of the brain-derived neurotrophic factor (BDNF) pathway, was analyzed using RT-PCR, ELISA western blot and gene silencing. EVs secreted by ketamine-treated cells were isolated, characterized and analyzed for their effects in neuron-glia cell interactions. Data were analyzed using analysis of variance or a Student's t test with correction for data sets with unequal variances.
Results: Ketamine induced neuronal and oligodendrocytic cell apoptosis and promoted the expression of pro-inflammatory astrocytes (A1) and microglia (M1) phenotypes. Astrocytes and microglia enhanced the neurotoxic effects of ketamine on neuronal cells, whereas neurons increased oligodendrocyte cell death. Ketamine modulated different components in the BDNF pathway: decreasing BDNF secretion in neurons and astrocytes while increasing the expression of p75 in neurons and oligodendrocytes. In addition, ketamine treatment increased the lncRNA BDNF-AS levels and the secretion of pro-BDNF secretion. We found an important role of EVs secreted by ketamine-treated astrocytes in neuronal cell death by delivering BDNF-AS.
Conclusions: Ketamine neurotoxicity involves both autonomous and non-cell autonomous mechanisms andomponents of the BDNF pathway expressed by neurons and glial cells represent major regulators of ketamine effects. We demonstrated for the first time a role of EVs as important mediators of ketamine effects by the delivery of specific non-coding RNAs. These results may contribute to a better understanding of cellular and molecular mechanisms underlying ketamine neurotoxic effects in humans and to the development of potential approaches to

decrease its neurodevelopmental impact.



Neuron-glia interactions, the BDNF pathway and extracellular vesicles in ketamine effects
The effects of ketamine on various components of the BDNF pathway, the interactions of neuron and glial cells and the role of EVs as mediators of these interactions are depicted in this diagram.

T09-043C

Neural-glia interactions mediate the loss of perisomatic inhibitory synapses in *Toxoplasma gondii* infection

G. L. Carrillo[1,2], V. Ballard[1], T. Glausen[3], Z. Boone[1,4], J. Teamer[1,5], C. Hinkson[1,6], E. Wohlfert[3], I. Blader[3], M. Fox[1,4,7]

[1] *Center for Neurobiology Research, Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, USA*
[2] *Translational Biology Medicine and Health, Virginia Tech, Roanoke, USA*
[3] *Department of Microbiology and Immunology, University at Buffalo, Buffalo, USA*
[4] *School of Neuroscience, Virginia Tech, Blacksburg, USA*
[5] *NeuroSURF, Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, USA*
[6] *Virginia Tech Carilion School of Medicine, Roanoke, USA*
[7] *Department of Biological Sciences, Virginia Tech, Blacksburg, USA*

Prolonged infection and inflammation within the brain can alter the connectivity and function of neuronal circuits. The intracellular protozoan parasite, *Toxoplasma gondii*, is one pathogen that can chronically infect the brain and lead to encephalitis and seizures. Currently, 1 in 3 humans are infected with *Toxoplasma gondii* worldwide, and these infections have been identified as a considerable risk factor for developing complex neurological and psychiatric disorders that arise from alterations in assembly and maintenance of synapses, such as schizophrenia. To directly assess changes in inhibitory synapses, we employed serial block face scanning electron microcopy and quantified perisomatic synapses in neocortex and hippocampus following parasitic infection. Ultrastructural analyses, in combination with genetic and immunohistochemical tools, revealed that persistent infection not only led to a significant loss of inhibitory perisomatic synapses, it also induced the ensheathment of neuronal somata and perisomatic nerve terminals by activated myeloid-derived cells (including microglia), suggesting they may displace or phagocytose synaptic elements in long-term infection. How might microglia contribute to inhibitory synapse loss in parasitic infection? One potential mechanism is the innate complement cascade, an immune