Restoring the function of the glutamate-nitric oxide-cGMP pathway by treatments acting on different brain targets restores cognitive function in rats with minimal hepatic encephalopathy

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Abstract

Chronic liver disease (e.g. cirrhosis) affects brain function. There is a high incidence of mild cognitive impairment and psychomotor slowing in patients with cirrhosis. This condition, known as minimal hepatic encephalopathy (MHE) affects more than 2 million people in the European Union and has serious health, social and economic consequences. There are no effective treatments for MHE.

Rat models of MHE reproduce cognitive and motor alterations seen in patients, showing reduced performance in different types of cognitive tests, including learning a conditional discrimination task in a Y maze. We have shown that reduced ability to learn the Y maze task is due to reduced function of the glutamate-nitric oxide (NO)-cGMP pathway in cerebellum, assessed in vivo by microdialysis. This results in reduced formation of cGMP in response to activation of NMDA receptors and impairment of learning ability. We have found that both hyperammonemia and neuroinflammation contribute to impair this pathway. The effect is mediated by enhanced tonic activation of NMDA and GABAA receptors and of MAP-kinase p38. Based on this mechanistic studies, we have designed and tested new therapeutic strategies acting on specific targets in the brain, which have successfully restored the function of the glutamate-NO-cGMP pathway in vivo and learning ability in rats with MHE. This can be achieved by therapeutic treatments using:

a) phosphodiesterase 5 inhibitors (sildenafil, zaprinast), that increase cGMP levels by reducing its degradation
b) extracellular cGMP
c) antagonists of type A GABA receptors (bicuculline)
d) neurosteroids that modulate GABAergic tone (pregnenolone sulfate)
e) inhibitors of cyclooxygenase (ibuprofen) which reduce neuroinflammation
f) inhibitors of MAP-kinase p38 (SB239063), that reduce microglial activation and neuroinflammation
g) Translation of some of these treatments to clinical practice would improve cognitive function, quality of life and life span of patients with cirrhosis and MHE and reduce health systems costs.

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Modeling and simulation the conduit connecting translational medicine with portfolio management

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Abstract

Translational medicine science and the volume of information generated in this field have grown exponentially in the last decade and continue to grow faster every day. This has generated a huge amount of data. The application of