

Potential impact of *Helicobacter pylori*-related human β -defensin-1 on hepatic encephalopathy and neurodegeneration

Jannis Kountouras^a, Christos Zavos^a,
Stergios A. Polyzos^a, Georgia Deretzi^b

Aristotle University of Thessaloniki, Ippokration Hospital;
Papageorgiou General Hospital, Thessaloniki, Macedonia, Greece

Kaltsa *et al* [1] reported that human β defensin-1 (hBD-1) is upregulated in cirrhotic patients and might serve as a biomarker of bacterial translocation involved in the pathogenesis of complications including hepatic encephalopathy (HE); dysbiosis of gastrointestinal microbiota, even salivary and gastric *Helicobacter pylori* (*Hp*) and multiple non-*Hp* organisms, is associated with systemic inflammation and complications including HE [1-3].

Hp infection (*Hp*-I), strongly associated with viral-related cirrhosis, is more common in cirrhotic patients with HE. *Hp* may be involved in HE and post-HE persistent cognitive dysfunction pathophysiology by releasing proinflammatory and vasoactive substances involved, through blood-brain barrier (BBB) disruption, in brain pathologies; *Hp* might access the brain via the oral-nasal-olfactory pathway or by circulating monocytes (infected with *Hp* due to defective autophagy) through disrupted BBB, leading to neurodegeneration [4-6]. Likewise, human defensins might also contribute to *Hp*-related brain pathophysiology by modulating innate and adaptive immune system responses [7].

Hp-I induces hBD-1 mRNA expression [8], but develops resistance against hBD-1 [9]. Moreover, *Hp* might be further involved in the BBB breakdown, by releasing defensins, particularly those that display unique distribution at BBB sites. *Hp* can activate granulocytes and induce defensin release from granulocytes; consequently, defensins, secreted by activated granulocytes, penetrate the BBB, gain access to the brain, thereby possibly contributing to neurodegeneration [9]. In the brain, HBD-1 expression acts as activator and modulator of innate and adaptive immunity within microglia and astrocytes, cerebral cells critical to the brain neuroinflammatory responses. HBD-1 mRNA expression is significantly increased in the choroid plexus and hippocampus of the neurodegenerative brain; HBD-1 might be of considerable importance early in the neurodegenerative process [9]. Finally, serum sCD14 levels, mentioned by the authors [1], are associated with genetic variants in both CD14 promoter and *Hp*-I and consequently with certain disease or diseases outcomes [10]. However, further studies are needed to elucidate the aforementioned considerations.

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Departments of ^aMedicine, Second Medical Clinic, Aristotle University of Thessaloniki, Ippokration Hospital (Jannis Kountouras, Christos Zavos, Stergios A. Polyzos); ^bNeurology, Multiple Sclerosis Unit, Papageorgiou General Hospital (Georgia Deretzi), Thessaloniki, Macedonia, Greece

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Correspondence to: Jannis Kountouras, MD, PhD, Professor of Medicine, 8 Fanariou St, Byzantio, 551 33 Thessaloniki, Macedonia, Greece, Tel: +30 2310 892238, Fax: +30 2310 892744, e-mail: jannis@auth.gr

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The role of stomach in neurological disorders: 1000 years historical background

Arman Zargaran^{a,b}, Hossein Rezaeizadeh^c

Tehran University of Medical Sciences, Tehran; Shiraz University of Medical Sciences, Shiraz, Iran

We read with great interest the published paper by J. Kountouras *et al* in the *Annals of Gastroenterology* [1]. The role of stomach and the rest of the gastrointestinal system in neurological disorders will be further clarified in the years to come. Theories like the “gut-brain” axis shed light on this relation [2], however, it seems that physicians in the past centuries believed in the role of stomach in neurological disorders.

Avicenna (980-1037 AD) (Fig. 1) was a great Persian physician who influenced the progress of medical sciences 1000 years ago. His medical encyclopedia, the *Canon of Medicine*, was one of the main medical textbooks in the western and eastern universities at least until the 17th century AD [3]. Avicenna believed that the stomach interacts with other organs causing various types of disorders including neurological diseases. He stated that, in many cases, neurological symptoms have gastrointestinal origins, meaning that gastrointestinal disorders affect the neural system causing symptoms. He wrote in the *Canon of Medicine*: “stomach [meaning the gastrointestinal tract] is involved in many head disorders”.



Figure 1 Avicenna's statue in Hamadan (west Iran), where Avicenna's tomb is located

Moreover, he stated that “gastrointestinal disorders can cause neurological diseases but not *vice versa*”. Avicenna believed flatulence affects other organs especially neurological disorders. Furthermore, he noted that other organs such as the bladder and the uterus, apart from the gastrointestinal system, could interact with the neural system and cause neurological diseases. He explained a brief differential diagnosis for them in his *Canon of Medicine* [4].

Avicenna's words have thus proven valid in clinical practice, and his idea on the relationship between the gut and the brain shaped 1000 years ago, now called “gut-brain theory”, merits historical value.

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^aDepartment of Traditional Pharmacy, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran (Arman Zargaran);

^bResearch Office for the History of Persian Medicine, Shiraz University of Medical Sciences, Shiraz (Arman Zargaran); ^cDepartment of Traditional Medicine, School of Traditional Medicine, Tehran University of Medical Sciences, Tehran (Hosein Rezaeizadeh), Iran

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Correspondence to: Hosein Rezaeizadeh, Department of Traditional Medicine, School of Traditional Medicine, Vafamanesh str., Heravi Sq. 1417653761, Iran, e-mail: rezaeizadeh@sina.tums.ac.ir

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