Mind-altering microbes

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On April 16, 2014, the Society for General Microbiology hosted a symposium on mind-altering microbes that was held in Liverpool, UK and was chaired by Drs. Rocky Cranenburgh and Karen Robinson. Three of the presentations given at the symposium on microbes involving humans and animals are the subject for minireviews in this issue of the *Journal of Neurovirology*.

In the animal kingdom, microbes have evolved to alter the “mind” and in some cases, more specifically, the behavior of their hosts in order to facilitate transmission to new hosts. In many cases, this has been an evolutionary process in which natural selection has served to select for mutations with enhanced biological fitness for completions of their life cycles. As examples, the minireview by Stilling et al. (2015) relates that the liver fluke *Dicrocoelium dendriticum* alters the behavior of ants to climb to the tips of blades of grass to be consumed by a ruminant host, whereas the Gordian worm *Paragordius tricuspidatus* drives grasshoppers towards water in order to enable reproduction of the worm. As discussed in the minireview on rabies (Jackson, 2015), the biological adaptation of rabies virus to alter its animal host’s behavior (the vector) in order to enhance transmission by biting another host at the time it secretes high-titer rabies virus in its saliva is truly diabolical. Our understanding of the neurobiological basis of the behavior changes in rabies is quite limited, largely due to a paucity of experimental studies because there are many barriers to working

in a natural model of rabies. Smart and Charlton (1992) have found experimental evidence of rabies virus infection affecting the serotonergic midbrain raphe nuclei that potentially explains aggressive behavior of experimentally infected skunks. Work from my own research laboratory has elucidated that rabies virus induces neuronal process degeneration in experimentally infected mice that affects dendrites and axons. In vitro studies indicate that oxidative stress plays a pathogenetic role in this process that is associated with mitochondrial dysfunction and increased activity of mitochondrial complex I. There is evidence that the rabies virus phosphoprotein interacts with complex I. Hence, we now have a better understanding how rabies virus infection can induce neuronal injury, at least in an experimental model, and produce behavioral changes in rabies vectors.

Host-microbiome interactions have recently received considerable attention, and in particular, the gut microbiome has been recognized to have a large potential influence on the nervous system, and this microbial interaction can be beneficial or detrimental to the host (Stilling et al. 2015). The benefits include guiding maturation of the host immune system. The minireviews of both Dobbs et al. (2015) and Stilling et al. (2015) focus on the role of the gut microbiome as an important player affecting the brain and also having a role in behavioral changes and neuropsychiatric disease.

Stilling et al. (2015) discuss how the host-associated microbiome affects host normal brain development and that developmental programming is particularly important during critical windows occurring early in life. Furthermore, the microbiome also interacts with the host genome and may act as an epigenetic modifier that can directly affect not only the host but can also be transmitted intergenerationally and exert an evolutionary effect on the host species. The influences of microbes on the nervous system may open up exciting future therapeutic avenues for neuropsychiatric diseases (Cryan and Dinan, 2012; Stilling et al. 2015).

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Dobbs et al. (2015) review the role of gut microbiome as an important driver of Parkinson's disease. In 1965, Strang (1965) reported that peptic ulceration is prodromal in Parkinson's disease. Persistence of *Helicobacter* at presentation with Parkinson's disease appears to protect against the small intestinal bacterial overgrowth, found in two-thirds (Dobbs et al. 2012). Moreover, a randomized controlled clinical trial showed that *H. pylori* eradication reduced the bradykinesia of Parkinson's disease; rigidity worsened, but there was overall clinical benefit (Dobbs et al. 2010). Morphological and neurochemical changes of Parkinson's disease are present throughout the enteric nervous system and may be the earliest manifestation (Dobbs et al. 2012; Dobbs et al. 2015). Changes in the gut microbiome could have important effects on the nervous system. Neuroinflammation in Parkinson's disease, which plays an important role in neuronal degeneration, appears to be mediated by systemic immune-inflammatory processes. There are biological gradients of circulating immune-inflammatory markers and leukocyte subset counts on measures of disease facets (Dobbs et al. 2012). Furthermore, there is evidence that disruption of the gut microbiome (dysbiosis) is an important driver of these processes (Dobbs et al. 2015). Successive courses of oral antimicrobials are associated with a cumulative increase in rigidity, and laxatives with its amelioration.

Microbes can potentially affect the nervous system in health, in infectious diseases, and in neurodegenerative diseases and even play an important role in evolutionary processes. We now recognize that the host gut microbiome can interact with the nervous system in many complex ways, and our understanding of the mechanisms is still in its infancy. Much more research will be needed to learn about the mechanisms

involved, and hopefully, this will lead to novel approaches to the therapy of neuropsychiatric diseases.

Conflict of interest The author declares that he has no competing interests.

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