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HMOs and Brain Development
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Human infants are unique in the animal world in that they are born without a fully developed brain. Brain development occurs after birth. Head circumference, considered a proxy for brain volume, increases at the phenotypic growth rate of 1.1 mm/day,1 growth by far exceeding that of any other organ in the body. Whether underdevelopment of the human brain at birth is due to a narrow birth canal caused by humans being bipedal or limitations of the mother’s metabolism is hotly debated,2 but it is beyond dispute that after birth human babies need optimal nutrition to support brain growth.

‘Such rapid brain growth places excep-
tionally high demands on the supply of
nutrients, with failure to meet overall
nutrient needs having significant con-
sequences for cognitive development,’ says Bing Wang, from Charles Sturt
University, New South Wales, Australia.

Although babies are born with neurons already formed, synaptic connections between these neurons are largely es-
blished after birth.3 Nutrients affect already formed, synaptic connections and neurodevelopmental outcomes,5 with long-term consequences for IQ and cognitive performances, memory functions, and learning and memory (from object recognition at maze tests) at one year than HMO free infants (the first two years).6

The mechanism for sialic acid exerting its beneficial effects on brain development is under investigation. Studies have demonstrated that the sialic acid lacto-
fucoses can cross the BBB via receptor mediated transcytosis.14 To my mind there’s no question sialic acid crosses the blood brain barrier,” says Wang.

Wang is the first to admit that her pro-
tected source of sialic acid was far
from ideal: ‘The problem is that sialic acid bound to HMOs has not been read-
ily available in sufficient quantities for
research,’ she explains.

Since 2FL is the most abundant HMO in the milk of most lactating women (and also one of the smallest comprising just three molecules) it has also been stud-
ied in relation to potential brain benefits. Much of the work has been undertaken by the R&D department of Abbott Nu-
trition in Granada, Spain, who in 2015
showed orally administering 2FL to rats improved long term potentiation and performance in learning behaviour.

In the current study, the team additionally showed supplementation increased expression of molecules involved in the storage of newly acquired memories, such as the postsynaptic density protein 95.7 In a second study, the team showed rats given oral 2FL supplements im-
mediately after birth had better learning and memory (from object recognition at maze tests) at one year than HMO free littermates, demonstrating that 2FL’s cognitive enhancing effects persist into adulthood.

One controversial issue is whether the HMOs (or metabolites from gut bacteria digestion of HMOs) directly influence the brain through the circula-
tion or whether the effect is mediated through the gut brain axis (a bidirection-
alm communication system enabling gut microbes to communicate with the brain). A recent study by Wang group strongly suggests that the gut brain axis is the mechanism underlying the beneficial effects of dietary 2FL. In the study, the team showed searing the vagus nerve in rats inhibited the beneficial effects of 2FL, tramiprosate (a long
term potentiation (LTP) and learning)21. From this finding the investigators concluded that the vagus nerve in the body that controls the heart, lungs and digestive system appears to be the main pathway under-
lying the effects of 2FL on CNS function.

Gut microbiota appears to play an important role in the axis. A recent study showed that in mice fed radiola-
belled 2FL (3C 2FL) there was no up-
take of 2FL in the brains of either mice with normal gut microbiota or those with sterile guts (a germ free mouse) demonstrating that dietary 2FL does not reach the brain. However, dietary 13C enrichment was found in the brains of mice with normal gut microbiota, but not in germ free mice. Such find-

ings suggest that the presence of gut bacteria plays a fundamental role in 2FL’s effects in the brain.

The effect, says Paul Forsythe, a researcher studying the gut brain axis, is likely to be mediated by the enteric nerv-
ous system, a mesh like system of neu-
rons enabling the gastrointestinal tract to operate independently of the brain. ‘My belief is that bacteria feeding 2FL make neurotransmitters or other signal-

ing molecules that influence the enteric nervous system,’ he explains. ‘HMOs, in turn, influ-
ences the vagal nerve that directly signals to the brain’ says Forsythe, from McMaster University, Canada.

Until recently, HMO availability acted as a bottle neck to performing clinical trials. Extracting HMOs from breast milk was both cumbersome and expensive due to limited access to raw materials. However, innovative technology using bacterial species (like Escherichia coli) to ferment milk proved the breakthrough opening the way for mass production. The bacteria, which have been genetically designed to catalyse specific reactions of adding the sugars, allow production of cost ef-

ective HMOs in kilogram to ton quantities. Using this fermentation technol-
ogy, Jennewein Biotechnologie GmbH, a company based in Germany, can now manufacture a range of HMOs, from which they can tailor the pk purposes.

For more information on Jennewein’s work and HMOs visit their website: https://www.jennewein.com
including 2’-Fucosyllactose, 3’-Fucosyllactose, 3’-Sialyllactose, 6’-Sialyllactose, Lacto-N-tetraose, Lacto-N-neotetraose, Lacto-N-turanose. Perhaps of greatest significance for brain researchers, like Bing Wang, is that Jennewein’s portfolio includes sialic acid HMOs (6’-Sialyllactose), at last enabling sialic acid products to be used in brain studies resembling those found in human breast milk.

The large scale production process is allowing Jennewein to undertake a clinical trial feeding babies an HMO mix containing the five most common HMOs in breast milk (2’FL, 3’FL, LNT, 3’SL and 6’SL), selected to allow formula to more closely resemble breast milk. If successful, the HMO mix will join formula products already on the market containing 2’FL that received FDA market approval for use in infant and toddler nutrition in 2015.

Ultimately, industry forecasters believe the HMO market will expand exponentially to include functional foods supplementing HMOs to combat a range of health conditions including neurodegeneration in the elderly. Evidence for a potential HMO role comes from a study reporting the sialic acid content of the human brain initially increases from infancy to adulthood (achieving maximum levels between 20 and 40 years), but then begins to decrease slowly at >60 years of age, with the most pronounced reduction occurring at >90 years of age. It would be really appealing to have compounds from human milk that could be used as a basis for drugs in the adult application space as they would be unlikely to have side effects,” says Bode.

References
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