May 27 Highlights

Direct access of drugs to the human brain after intranasal drug administration?

It has been suggested recently that intranasal drug delivery could be used to administer drugs directly to the CSF, bypassing the blood–brain barrier. Merkus et al. measured drug levels in patients with a CSF drain and found no evidence for such a direct pathway.

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The nose knows the answer is no

Commentary by Clifford B. Saper, MD, PhD

Like vampires rising from their graves at midnight, certain hypotheses seem to be regularly resurrected, despite what would seem to be adequate evidence to insure their demise. One of the most attractive of these ideas has been the concept that substances or microorganisms that enter the nose may have special access to the brain. In the early 1970s, Kristensson et al. examined whether viral particles might have direct access to the brain from the nose. They found that horseradish peroxidase in the nasal cavity was not able to reach the CSF, but could only be transported into the CNS via vesicular axonal transport after uptake by olfactory neurons.1 Subsequently, in the 1980s, it was hypothesized that aluminum might enter the CNS via the nose and cause toxicity that could lead to AD.2 After a run to reformulate aluminum chloride-containing deodorants, this route of access also proved to be nonexistent. The most recent reincarnation of this hypothesis came in a highly publicized article by Born et al. in *Nature Neuroscience* in 2002, claiming that the peptides melanoctrin and insulin entered the CSF rapidly after intranasal administration.3 As noted by Merkus et al. in this issue of *Neurology*, Born et al. lacked the control of administering the drug intravenously. The nasal epithelium contains a large absorptive area, and it was shown 20 years ago that neuropeptides such as DDAVP, when supplied intranasally, enter the CNS via vascular absorption, rather than directly from the nose.4 The new study by Merkus et al. nails the lid securely back on the coffin of the nose-to-CSF hypothesis, by showing that melatonin or vitamin B12 enter the CSF as quickly by IV as by intranasal administration. The nasal route has proven, once again, to be an excellent one for administering drugs into the venous, not the CSF, circulation.

References


Celiac neuropathy

Chin et al. report that 2.5% of the patients with neuropathy seen at their center have celiac disease. Most have a sensory neuropathy, with normal results on electrophysiologic studies. Gastrointestinal symptoms were absent or were preceded by neuropathic symptoms in approximately 50% of the patients.

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Antiganglioside antibodies in degenerative ataxias

Shill et al. investigated a possible link between autoimmunity and cerebellar degeneration. They examined 22 patients with sporadic and hereditary cerebellar degeneration and found 64% reactive for ganglioside antibodies.

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CNS presentation of T-cell lymphoma in celiac disease

Gobbi et al. diagnosed and molecularly confirmed, in a patient with treated celiac disease and new cognitive deficits, an enteropathy-associated T-cell lymphoma in the duodenum and CNS.

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Antigliadin antibodies in ataxia

Studying the prevalence of antigliadin antibodies, Abele et al. did not find differences among patients with sporadic ataxia, patients with hereditary ataxia, and normal controls. These data argue against gluten sensitivity as a causal factor for sporadic ataxia.

“We do not recommend routine screening for celiac disease for any given neurologic presentation.”

In the editorial accompanying these four articles, Cross and Golumbek review the immunopathogenesis of celiac disease, noting that it is common (0.5 to 1% of whites) and associated with T-cell infiltration in the gut and antigliadin antibodies in the blood. Both can be present without gastrointestinal symptoms. Ataxia, peripheral neuropathy, and many other neurologic diseases have been associated with celiac disease and with antigliadin antibodies. The finding of antigliadin antibodies in patients with hereditary ataxia argues against a pathogenetic role of celiac disease–related antibodies in ataxia. The editorialists note that “although gluten-sensitive enteropathy clearly improves with a gluten-free diet, it is not clear whether neurologic symptoms are prevented, stabilize, or improve.” They recommend that “to determine whether gluten sensitivity (with or without celiac disease) is causally related to the various neurologic syndromes, a controlled, randomized trial of gluten-free diet with compliance confirmed by reduction of antigliadin antibodies is needed (admittedly a challenging task).”

Clinical diagnosis of dementia with Lewy bodies (DLB)

Does the extent of superimposed AD neurofibrillary pathology affect the clinical characteristics—and thus the clinical diagnostic accuracy—of DLB? Merdes et al. found that subjects with DLB with high tangle load in the limbic and neocortical cortex are less likely to express the clinical features of DLB, making the recognition of DLB, and differentiation from AD, more difficult.

The accompanying editorial by Lippa and McKeith points out that while Merdes et al.’s low sensitivity for the diagnosis of DLB (49%) may reflect their failure to include fluctuation in their diagnostic schema, their finding of a high frequency of AD neurofibrillary pathology in DLB brains helps explain why clinicians experience difficulty diagnosing DLB. They stress that we still need a genetic- or bio-marker that can reliably distinguish AD from DLB and facilitate identifying patients for clinical studies including treatment trials.

Auditory comprehension of language in young children: Neural networks identified with fMRI

Ahmad et al. used MRI to identify the neural networks implicated in listening comprehension in 5- to 7-year-old children. They found regionally specific and lateralized activation along the left superior temporal sulcus. Regional organization underlying auditory language processing in young children is similar to that of adults.

The accompanying editorial by Anne Foundas notes that the age at which left hemispheric specialization for language occurs has not been established. The Ahmad et al. study suggests localization occurs as early as 5 years of age. Foundas points out that subsequent studies should follow language localization with longitudinal studies as well as address differences between boys and girls and differences between right- and left-handed subjects.
Cardiac benefit of idebenone in Friedreich ataxia (FRDA)

The Mariotti et al. 1-year randomized, placebo-controlled study of idebenone in 29 patients with FRDA showed a moderate reduction of cardiac hypertrophy with treatment. There was no improvement in neurologic signs.

Using new cardiac imaging techniques, Buyse et al. show that besides reducing cardiac hypertrophy, idebenone progressively improved cardiac function in FRDA.

The accompanying editorial by Filla and Moss reviews the pathogenesis of FRDA and notes that the cardiomyopathy of FRDA is frequent (80%) and often symptomatic. Evidence for mitochondrial dysfunction—iron accumulation, increased sensitivity to oxidative stress, and deficient respiratory chain complex activity—has prompted use of antioxidants such as coenzyme Q10 and idebenone, its short-chain analogue. Considering these two articles and earlier studies of idebenone, the authors conclude that despite these encouraging results, it is not yet clear that idebenone is of clinical benefit in FRDA cardiomyopathy. Longer duration trials, possibly with higher doses of idebenone, are needed.

Effect of frontotemporal dementia (FTD) on the painting of an accomplished artist

Chang Mell et al. found that progression of FTD was accompanied by evolution of the paintings of a 57-year-old woman into freer, more original work despite her loss of language skills.

Hemicrania horologica (clock-like hemicrania)

Granella and D’Andrea describe a patient with recurrent, strictly unilateral headache attacks, lasting 15 minutes, that occurred exactly every 60 minutes, day and night, for 3 years. Nonsteroidal anti-inflammatory agents reproducibly prevented attacks.