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Previews

Hints of a Therapeutic Vaccine for Alzheimer's?

In this issue of *Neuron*, Hock et al. report the cognitive functions of a small number of Alzheimer's disease patients that participated in a clinical trial of immunization with β-amyloid. Patients with serum antibodies against β-amyloid plaques showed a diminished cognitive decline and slowed disease progression. Dangerous meningoencephalitis was present in some patients, as has been previously reported.

Many mechanistic insights into the etiology and pathogenesis of Alzheimer's disease have been gained in recent years. As with other polygenic disorders, a minority of cases appear directly linked to specific gene mutations, and it has been hoped that the biological insights gained from those cases can be leveraged to address the sporadic cases, which are the majority. A central idea that has emerged in this fashion has been that dysfunctional processing of the amyloid precursor protein APP drives disease pathology in familial Alzheimer's disease (FAD) and perhaps even late-onset Alzheimer's disease (LOAD). In this issue of *Neuron*, Hock et al. (2003) report a significant reduction of the cognitive decline in patients with Alzheimer's disease who participated in an immunization protocol involving aggregated Aβ42. These results provide support for the proposal that this β-amyloid peptide is a key driver of pathology in Alzheimer's disease. There is the suggestion, as well, that if safety issues can be addressed, a vaccine approach will prove to have important therapeutic value.

A very strong note of caution must be sounded, however, about the therapeutic implications. These patients comprised the Zurich cohort of the larger ELAN/Wyeth-Ayerst AN1792(QS-21) Phase IIA multicenter trial. That trial received widespread press coverage when all study dosing was halted in January of 2002 because 17 of the 300 study patients who were immunized developed aseptic meningoencephalitis (Schenk, 2002). This response has not been successfully treated in all cases. Thus, while there are hopes that it can be mitigated or eliminated, this potentially fatal side effect remains an overriding concern.

The study reported by Hock et al. is very small. A total of 30 patients were included in this particular cohort, less than 10% of the number involved in the full multicenter trial of which this cohort was a part. Only 6 of the 30 patients received placebo. With a small sample, the chances of false positive results increase and there is a greater likelihood that some systematic error will bias the results. For example, the patient sample could be biased by personal history, medical history, or genotype. Thus, while the results are statistically significant, it will be important to confirm that they hold up with a much larger sample size. In this sense the results should be regarded as preliminary.

The patients in this double-blind study received either preaggregated synthetic Aβ42 with the saponin QS-21 as an adjuvant to stimulate a vigorous immune response or placebo in two injections separated by 1 month. The β-amyloid/placebo status of the patients is still unknown to the authors. What was assayed was the antibody production of the patients. Serum samples were taken from the patients before and 12 months after treatment, and β-amyloid immunoreactivity was assayed on fixed brains from a mouse model of AD that produces β-amyloid plaques. This test is called the tissue amyloid plaque immunoreactivity (TAPIR) assay.

Patients who produced antibodies in the TAPIR assay showed less cognitive decline over the course of 1 year than those who did not produce antibodies. This correlation was found for several standard tests, including the Mini Mental State Examination (which combines assays of several aspects of cognitive status, including orientation, attention, recall, language, and the ability to follow simple commands), Disability Assessment for Dementia (which assays basic self-care and instrumental activities of daily living), and the visual delayed recall test from the Wechsler Memory Scale. Thus, the clinical benefits appear to cover a wide spectrum of cognitive functions that are attacked in Alzheimer's disease, from memory to daily self-care.

In the evaluation of the clinical significance, the authors are presenting data on prevention of disease progression or even disease arrest by using the MMSE scores. A normal decline in MMSE score over 1 year in an Alzheimer population is around 3 points and in clinical trials with cholinergic drugs somewhat lower (Aguero-Torres et al., 1998). In the present report by Hock et al., patients without immune response (9 patients) worsened significantly by -6.3 ± 4.0 points on the MMSE scale after 1 year. This decline is larger than typical, which again points to the need to confirm the findings when the data from the larger study are analyzed. The authors also point out that their TAPIR assay appears to produce a tighter correlation with cognitive efficacy than ELISA. They raise the possibility that a functional immune response is related to the development of conformation-specific antibodies. It is unclear at this point if TAPIR will be compatible with modified ELISA assays.

Since it is likely that many of the AD cases in this cohort suffered from LOAD (given age and severity), it appears possible that the treatment may be effective in sporadic AD cases, which are the majority. Thus, even in those cases where mutant β-amyloid is not an obvious culprit, antibody production against it appears to have beneficial effect. On the other hand, since there is no clear sign that the treatment actually reverses cognitive deficits within 1 year, it may be that there is residual damage, whether from tau pathology, synapse or neuron degeneration, or otherwise, that may be irreversible, at least by attacking β-amyloid.

The effects of antibody production are impressive and the findings presented are important in providing further evidence for the validity of the prevailing working hypothesis, the Amyloid Cascade Hypothesis. So far, the

findings are of great interest from a scientific perspective, but they are also clearly important from a clinical and societal perspective. Even though the meningoencephalitis side effect remains a problem, this article shows that the concept of vaccination is alive.

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Selected Reading

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Learning Is Bitter and Sweet in Ventral Striatum

The ventral striatum (VS) plays a key role in motivationally guided learning. Setlow et al. show that VS neurons encode the significance of cues associated with both aversive and rewarding outcomes and that this neural linkage develops over time in a fashion roughly paralleling the expression of learned behavior. Subpopulations of VS neurons may contribute distinct signals to the learning process, reflecting either cue significance or learned sensory-motor associations.

Back in the early 1990s, Michael Stipe of the band R.E.M. wryly crooned "your head is there to move you around." Without a means for modifying movement in response to changing external conditions and internal milieu, however, Stipe's "head" would be useless. Not surprisingly, animals with even the simplest of nervous systems have evolved mechanisms for assessing the outcome, either good or bad, of behavior and linking these outcomes to salient cues in the environment. By potentiating responses to cues associated with good outcomes and inhibiting responses to cues associated with bad outcomes, the nervous system adapts behavior to the current environment and thereby achieves a positive internal milieu (Thorndike, 1898). In mammals, this type of motivationally guided learning involves neural circuits within the basal ganglia, including the dorsal and ventral striatum (VS), as well as inputs to these nuclei from dopaminergic neurons in the midbrain ventral tegmental area (VTA) and substantia nigra pars compacta (SNC; reviewed in Schultz, 2002). In turn, these circuits participate in larger signaling loops involving the amygdala (AMG), orbitofrontal cortex (OFC), and prefrontal cortex (PFC) during the learning and performance of contextually appropriate behavior (Alexander et al., 1990).

Current models posit that learning occurs following a mismatch in the response of midbrain dopamine neurons to cues that predict rewards and actual reward outcomes, thereby potentiating neural responses in target structures such as VS (reviewed in Schultz, 2002). Both VS and VTA/SNc responses have recently been observed in association with aversive events as well, suggesting that these circuits may serve a broader function in linking cues with biologically significant outcomes, either rewarding or aversive (Blazquez et al., 2002; Becerra et al., 2001; Horvitz, 2002). Until recently, relatively little was known about how such links are formed during learning and how they change when predictions fail, particularly in contexts involving both aversive and rewarding outcomes. In this issue of *Neuron*, Setlow and colleagues extend prior investigations of neural encoding in VS by examining neural responses and behavior during cue learning involving both rewarding and aversive outcomes. Their data suggest that VS processes cues associated with both aversive and rewarding outcomes and that selective neuronal responses in this area evolve over time in a fashion roughly paralleling learned behavior (Setlow et al., 2003). These data powerfully document the role of VS in linking environmental stimuli with biologically significant outcomes during learning.

In this study, Setlow and colleagues used an olfactory go/no-go task that required rats to learn to discriminate two odors, one of which predicted a palatable sucrose solution in the drinking well (positive odor) and another which predicted a bitter quinine solution (negative odor). The rat's job was to learn the significance of the odor cues and drink following presentation of the positive odor and avoid drinking following presentation of the negative odor. Behavioral performance, as well as neuronal activity in VS, including both the core region of the nucleus accumbens and the ventral caudate-putamen, was recorded during learning. In a further set of experimental sessions, behavior and neuronal activity were recorded following reversal of odor-outcome pairings.

Rats rapidly learned the significance of the odor cues, performing better than 90% correct within 100 trials of odor-outcome pairing. Moreover, rats were faster to begin drinking from the fluid well on positive odor trials than when they erroneously drank on negative odor trials, and these differences in response latency became more pronounced with experience. Changes in discrimination accuracy were not closely related to changes in response latency, suggesting that these two behavioral measures might reflect different components of the learning process.

The authors also found that, once rats had mastered the odor discrimination, about 40% of neurons in the VS responded differentially to the two odor cues. Intriguingly, about 1/4 responded more strongly to odors predicting sucrose, and about 3/4 responded more strongly to odors predicting quinine. These neuronal responses did not merely reflect impending behavior, i.e., withholding or initiating drinking, suggesting that VS neurons encode the motivational significance of behavioral cues rather than a planned or anticipated movement.