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spurred a public debate focused on a potential cooling of northern Europe, which has the compensating flow just off the coast. Note that this part of the North Atlantic THC is especially dependent on ventilation north of the Greenland-Scotland Ridge, overflow, and entrainment (3).

The concept of a weakened THC is supported by some numerical climate models (8), but not by all. Increased salinity of the compensating flow may balance the salinity decrease from the increased freshwater supply and maintain ventilation (9). Climate models, so far, do not provide a unique answer describing the future development of the THC, but what is the present observational evidence?

It is argued that early evidence for changes should primarily be sought in the ventilation and overflow rates. Indeed, some such changes have been reported. Since around 1960, large parts of the open sea areas north of the Greenland-Scotland Ridge have freshened (10), and so have the overflows (11). At the same time, low-latitude Atlantic waters became more saline in the upper layer (12), and this is also reflected in the compensating flow. Long-term observations in both of the main branches of compensating flow across the Greenland-Scotland Ridge have shown increasing salinity since the mid-1970s, with a record high in 2003.

Even more convincing evidence for a reduction of the North Atlantic THC has been gained from monitoring both the overflows and the compensating northward flow by direct current measurements (13). For the Denmark Strait overflow, no persistent long-term trends in volume transport have been reported (2, 14), but the Faroe Bank Channel overflow was found to have decreased by about 20% from 1950 to 2000 (15).

We find evidence of freshening of the Nordic Seas and a reduction of the strength of the overflow, both of which will tend to weaken the North Atlantic THC. On the other hand, the compensating northward flow is getting more saline, which may maintain ventilation and counterbalance the THC decrease. So the jury is still out. This emphasizes the need for more refined climate models and long-term observational systems that are capable of identifying potential changes in our climate system.

North Atlantic flow. The exchange of water across the Greenland-Scotland Ridge is a fundamental component of the North Atlantic THC. Arrows on the map indicate the main overflow (blue) and compensating inflow (red) branches. On the schematic section to the right, temperatures in °C and volume transports in Sv (1 Sv = 10⁶ m³/s) are approximate values. DS, Denmark Strait; FBC, Faroe Bank Channel.

References

NEUROSCIENCE

NAD to the Rescue
Antonio Bedalov and Julian A. Simon

The cofactor nicotinamide adenine dinucleotide (NAD)—once consigned to the oblivion of metabolic pathway wall charts—has recently attained celebrity status as the link between metabolic activity, cellular resistance to stress or injury, and longevity. NAD influences many cell fate decisions—for example, NAD-dependent enzymes such as poly(ADP-ribose) polymerase (PARP) are important for the DNA damage response, and NAD-dependent protein deacetylases (Sirtuins) are involved in transcriptional regulation, the stress response, and cellular differentiation. On page 1010 of this issue, Araki and colleagues (1) extend the influence of NAD with their demonstration that an increase in NAD biosynthesis or enhanced activity of the NAD-dependent deacetylase SIRT1 protects mouse neurons from mechanical or chemical injury (2).

Axonal degeneration (termed Wallerian degeneration) often precedes the death of neuronal cell bodies in neurodegenerative diseases such as Alzheimer’s (AD) and Parkinson’s (PD). Mice carrying the spontaneous dominant WldΔ mutation show delayed axonal degeneration following neuronal injury. The WldΔ mutation on mouse chromosome 4 is a rare tandem triplication of an 85-kb DNA fragment that harbors a translocation. The translocation encodes a fusion protein comprising the amino-terminal 70 amino acids of Ufd2a (ubiquitin fusion degradation protein 2a), an E4 ubiquitin ligase, and the entire coding region of Nmnat1 (nicotinamide mononucleotide adenyltransferase 1), an NAD biosynthetic enzyme. Although the C57BL/WldΔ mouse was described 15 years ago (3) and expression of the WldΔ fusion protein is known to delay Wallerian degeneration (4), the mechanism of neuroprotection has remained elusive. Given that proteasome inhibitors block Wallerian degeneration both in vitro and in vivo (5), the Ufd2a protein fragment (a component of the ubiquitin proteasome system) has been the prime candidate for mediator of neuroprotection in the WldΔ mouse. Indeed, ubiquitin-mediated protein degradation by the proteasome...
has been identified as a potential target for developing drugs to treat neurodegenerative diseases such as AD, PD, and multiple sclerosis (6, 7).

Araki et al. (1) developed an in vitro model of Wallerian degeneration comprising cultures of primary dorsal root ganglion neurons derived from wild-type mice. The neurons overexpressed either the Wld$^+$ fusion protein or one of the fusion protein fragments. Surprisingly, the authors found that overexpression of the Ufd2a protein fragment alone did not delay degeneration of axons injured by removal of the neuronal cell body (transection) or treatment with the neurotoxin vincristine. In contrast, overexpression of Nmnat1 or the addition of NAD to the neuronal cultures before injury delayed Wallerian degeneration (1). This suggests that the direct result of increased Nmnat1 expression is to increase nuclear NAD levels, which in turn increases the activity of NAD-dependent deacetylase Sir2 (8).

In intact neurons of C57BL/ Wld$^+$ mice, the Wld$^+$ fusion protein is expressed almost exclusively in the nucleus (4). In fibroblasts (9)—and, presumably, in neurons—SIRT1 also is expressed in the nucleus. SIRT1 and other NAD-dependent deacetylases alter gene expression by targeting histone proteins as well as key nuclear transcription factors such as p53 (9, 10), forkhead (11, 12), and NF-κB (13). In addition, Sirtuins also deacetylase cytoplasmic proteins, including α-tubulin. The protective effect of the Wld$^+$ fusion protein appears to be exerted in the nucleus, because addition of NAD after removal of cell bodies in the neuronal cultures is no longer protective. This suggests that an alternative program of gene expression is initiated by elevated NAD levels in the nucleus, leading to the production of protective factors that actively block Wallerian degeneration. The therapeutic implication of this finding is that it may be possible to design neuroprotective drugs that boost SIRT1 activity and prevent further neurodegeneration in diseases like AD and PD.

The Araki et al. study (1) addresses the long-standing question of how the Wld$^+$ fusion protein prevents Wallerian degeneration. As with most groundbreaking studies, new questions emerge. For example, what is the direct result of increased Nmnat1 expression? Overexpression of Nmnat1 leads to increased activity of this enzyme but does not change total NAD levels or the ratio of NAD to NADH, raising the possibility that increased Nmnat1 activity may result in a decrease in nicotinamide or other inhibitory molecules. It is possible that the relevant target of SIRT1’s neuroprotective activity may be a transcription factor that responds to changes in the cell’s metabolic state by switching on expression of genes that encode neuroprotective proteins. Identifying the targets of SIRT1 that mediate the neuroprotective effect may broaden the options for therapeutic intervention in AD, PD, and other neurodegenerative diseases.