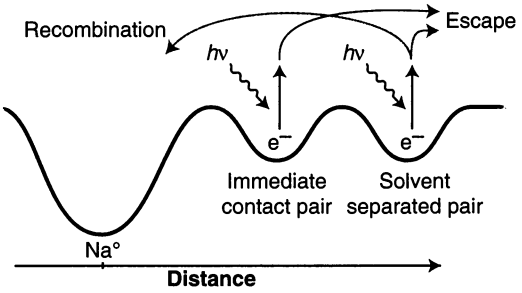
serve the creation, relaxation, and recombination of the wayward electron in detail.

The apparent simplicity of the solvated electron has made it the subject of many studies. Pioneering work by Eisenthal and Antonetti established that electrons created by direct ionization of simple solutes in water undergo a complex relaxation process that involves distinct solvation states [reviewed in (*3*, *4*)]. More recent studies (*5*–*10*) have concentrated on the dynamics of electron recombination in water under a variety of conditions. In particular, Barbara and co-workers at the University of Texas have clarified the nature of the electron's excited states by quantifying their spatial extent and relaxation times in water (*9*). Very recently, they have demonstrated how recombination can be suppressed by direct excitation of the solvated electron to very delocalized conduction band states (*10*).



Wayward electrons. In the sodide/tetrahydrofuran system, the initially excited electron can exist in an immediate contact pair or a solvent-separated pair. Electrons in immediate contact pairs will leave when the control pulse is applied, but some solvent-separated pairs recombine with the sodium atom.

In Martini *et al.*'s experiment, the electron is originally localized in a cavity that it shares with a sodium atom, forming a "sodide" ion in room temperature tetrahydrofuran. As in water, the escape probability of the electron can be enhanced by providing extra energy from a second pulse. But the authors do not stop there. They show that by delaying the second pulse an appropriate amount of time, one can enhance the rate of recombination as well.

To accomplish this, the authors exploit a subtlety of the sodide/tetrahydrofuran system, namely that the initially excited electron can exist in two different sites: a closely held immediate contact pair and a more distant solvent-separated pair (see the figure). The two species have different relaxation times, and the key is to wait long enough so that the control pulse excites only the more separated sites. Electrons that originally stayed close to home in immediate contact pairs will leave when the control pulse is applied, but some that originally ventured farther afield in solvent-separated pairs can be persuaded to return more quickly. The authors have thus found an experimental handle to control whether an electron continues to wander off into the solvent or returns home to its original solvent cavity.

It is important to point out that the observed enhancement in recombination rate is small and that the net effect of adding energy to the system with the control pulse, no matter what the delay, is to enhance the escape probability. In other words, the control pulse provides a transient acceleration of the recombination rate, but the time-integrated reaction yield only changes in one direction—toward enhanced escape.

In some sense, this is academic because the main goal of the research is the characterization of the electron's dynamics in liquids. The authors point out that this "control" experiment confirms their previous hypothesis about the existence of two states of the electron. But to what extent can electron dynamics in complex fluids be controlled?

Wasielewski and co-workers have demonstrated that femtosecond pulse sequences can be used to turn electron transfer on and off in designed molecular assemblies (*11*). And recent advances in pulse shaping and feedback control have demonstrated impressive results in the control of gas phase molecular dissociation (*12*). Can such an approach be extended to find a combination of pulse delays and excitation wavelengths that will create and then turn off a delocalized electron state in a liquid, in effect creating an ultrafast polarizable switch? The results reported here suggest that it may be worth trying.

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PERSPECTIVES: BIOMEDICINE

Huntingtin—Profit and Loss

Yvon Trottier and Jean Louis Mandel

An aberrant expansion of glutamines in the protein huntingtin causes Huntington's disease (HD), a neurodegenerative disorder that strikes in middle age. It has been presumed that mutant huntingtin with its extra glutamines is toxic to neurons possibly because it has a tendency to form aggregates (*1*). In HD, there is selective destruction of the medium-sized spiny neurons in the striatum of the brain, which has been attributed either to the accumulation of mutant huntingtin aggregates or to the continued expansion of glutamine repeats (*1*, *2*). On page 493 of this issue, Zuccato *et al.* (*3*) present evidence that mutant huntingtin affects cortical neurons producing brain-derived neurotrophic factor (BDNF), which is necessary for the survival of striatal neurons. They propose that partial loss of the beneficial effects of wild-type huntingtin combined with the toxicity associated with mutant huntingtin conspire to selectively destroy the striatum of the brain.

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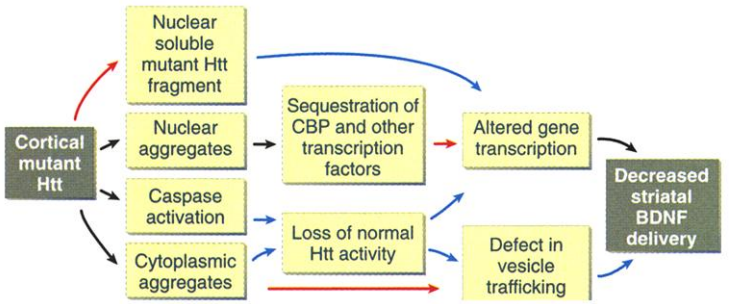
Huntingtin is a widely expressed protein that resides in the cell cytoplasm and may be important for transport of vesicles in the endosomal and secretory pathways, and for preventing cells from undergoing apoptosis (*4*). Mutant huntingtin is proteolytically processed, and the resulting amino-terminal fragments containing the glutamine expansions form aggregates, which are deposited in nuclear and cytoplasmic inclusions in the brains of HD patients and HD mice. It is still not clear whether the primary cause of HD pathology is the soluble or aggregated form of mutant huntingtin.

BDNF is a key player in the maintenance of nerve cells. Like other neurotrophic factors, it is secreted by one group of neurons, and is then taken up by the axons and nerve endings of other neurons (retrograde transport) that require this factor for survival. BDNF is also a neuromodulator that moves by anterograde transport along nerve axons and is released when neurons become depolarized, moving across the synapse and triggering action potentials in target cells (*5*). BDNF produced by cortical and nigral neurons

reaches nerve cells in the striatum by anterograde transport (*6*). Zuccato *et al.* show that BDNF mRNA and protein are decreased in the brain cortex of HD patients and of transgenic mice that express human mutant huntingtin (*7*). In the transgenic HD mice, a decrease in cortical BDNF correlated with a decrease in BDNF in the striatum, suggesting that the integrity of striatal cells may be compromised by a drastic reduction in cortical BDNF.



One too many glutamines. Mutant huntingtin (Htt) may decrease production and delivery of BDNF to striatal neurons. The mutant form of huntingtin has a tendency to form aggregates in the nucleus, which could sequester transcription factors needed to switch on BDNF gene expression. Alternatively, such aggregates in the cytoplasm could interfere with the trafficking of vesicles including those carrying BDNF by anterograde transport. However, mutant huntingtin also activates caspases (enzymes that induce cells to undergo apoptosis), which may lead to cleavage of wild-type huntingtin and to a partial loss of its beneficial activities. Black arrows indicate evidence of a causal connection, red arrows indicate connections yet to be proven, and blue arrows indicate hypothetical connections.

Impaired neuronal signaling was originally invoked to explain selective neurodegeneration of striatal neurons in HD (*8*, *9*). The striatum receives abundant excitatory glutamatergic projections from the cortex. Inducing excessive glutamatergic signals by treating rats with excitatory amino acid agonists results in many of the neuropathological changes found in HD, including the selective loss of striatal medium spiny neurons. In this rat model, BDNF prevents the death of striatal neurons (*10*). Depletion of cortically derived BDNF could render striatal medium spiny neurons more sensitive to excitotoxic stress.

How does mutant huntingtin decrease BDNF expression? With a reporter-gene assay, Zuccato *et al.* show that mutant huntingtin reduces transcription of the *BDNF* gene driven by three of the four *BDNF* promoters. Previous reports have implicated dysregulation of transcription in HD pathogenesis (*11*). It has been proposed that transcription factors and accessory proteins could become trapped by mutant huntingtin aggregates. Indeed, CREB-binding protein (CBP), a coactivator for the CREB transcription factor, has been found in nuclear inclusions in HD patient brains (*12*). Depletion of CBP may alter the regulation of many genes including those encoding neurotrophic factors. Intriguingly, *BDNF* gene transcription is known to be regulated by CREB (*13*, *14*). It will be interesting to learn whether CBP is involved in the decreased transcription of BDNF in HD patients.

Zuccato *et al.* propose a different (but not necessarily exclusive) mechanism for HD pathogenesis in which loss of the beneficial effects of wild-type huntingtin could play a part in the selective death of striatal neurons. Wild-type huntingtin in neurons is protective and can block processing of procaspase-9, an enzyme required for apoptosis (*15*). Switching off expression of the normal *hd* gene in the adult mouse brain causes both the striatum and cortex to degenerate (*16*). Zuccato *et al.* demonstrate that overexpression of wild-type human huntingtin stimulates BDNF mRNA expression in cultured neurons and in the brains of transgenic mice. They propose that mutant huntingtin in cortical neurons induces caspase activation that leads to cleavage of wild-type huntingtin and to partial loss of its transcriptional activity (see the figure). This, in turn, would result in a decrease in cortical BDNF production and striatal cell death. In HD patients, however, it is not yet clear whether there is partial loss of wild-type huntingtin activity (*4*). How wild-type huntingtin promotes transcription of the *BDNF* gene is not known—its cytoplasmic localization suggests that it does not affect transcription directly, although a growing list of transcriptional regulators seem to interact with both wild-type and mutant huntingtin (*4*). As wild-type huntingtin is required for efficient vesicle trafficking, it is also possible that mutant huntingtin causes disturbances in the anterograde transport of cortical BDNF, contributing to BDNF depletion in the striatum. Either way, as Zuccato *et al.* point out, the finding that BDNF production is altered in HD hints that BDNF and perhaps other neurotrophins may be valuable therapeutics for treating HD.

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PERSPECTIVES: POLYMER DYNAMICS

Chance Encounters

Thomas P. Russell

When long, flexible chain molecules are tethered to a surface, they can form an exceptionally large number of conformations. However, the probability that a configuration exists depends on an associated energy, which accounts for the stretching of the chain at the interface and the interactions between the chain and the surrounding medium. Consequently, not all configurations are equally probable. It is tempting to think that configurations with a low probability are unimportant, but as Jeppesen *et al.* demonstrate on page 465 of this issue (*1*), some of the least probable configurations nevertheless play an important role in recognition.

As we know from classical rubber elasticity, as a chain is stretched, the chain configuration becomes energetically unfavorable, and the retractive force increases rapidly as the elongation of the chain increases. In the presence of a good solvent, the osmotic pressure counteracts this retractive force. Compressed configurations are then not favored, and the chains will extend from the surface to maximize favorable interactions between the chain segments and the solvent.

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