NEURODEGENERATIVE DISORDERS

Fluid dynamics

Epidemiological studies have indicated that cholesterol-lowering drugs, such as the statins, can reduce the risk of developing Alzheimer's disease (AD). Paradoxically, however, reducing cholesterol levels in the rodent brain seems to promote neurodegeneration. To try to resolve this apparent contradiction, Abad-Rodriguez and colleagues carried out a more direct investigation of the effects of neuronal membrane cholesterol levels on the production of the amyloid-β (Aβ) peptide — the main constituent of the amyloid plaques that form in the brains of patients with AD.

Cleavage of amyloid precursor protein (APP) to generate Aβ was previously thought to occur predominantly in cholesterol-rich microdomains of the neuronal membrane, known as rafts or detergent-resistant membrane (DRM) microdomains. However, the evidence for this model came largely from experiments that involved overexpression of amyloid precursor protein (APP) and the APP-cleaving secretase enzymes.

Abad-Rodriguez *et al.* showed that when APP and the β-secretase BACE1 were expressed at physiological levels in the membranes of human and rodent hippocampal neurons, APP was almost entirely excluded from the DRMs, whereas BACE1 was present in both DRM and non-DRM fractions. If the membrane fluidity was increased by reducing the cholesterol level, APP and BACE1 were co-localized more frequently, and this led to a rise in Aβ production.

These findings contradict the idea that Aβ synthesis takes place in the DRM domains — in fact, the cholesterol in these domains seems to function as a barrier to the interaction between APP and BACE1. Loss of cholesterol from the membrane probably releases BACE1 from the DRMs, making it more likely to

ADDICTION

Computer addict

It has been proposed that addictive drugs and reinforcement learning might influence the same neurophysiological pathways. In a recent paper in *Science*, Redish uses this hypothesis to generate a computational model of addiction.

One of the effects of many drugs of abuse is an increase in dopamine levels in the brain, which is thought to contribute to the addictive quality of these drugs. Natural rewards are also accompanied by an increase in dopamine, although with learning this increase shifts from the time of reward to the time of the cuing stimulus.

Reinforcement learning occurs as a result of an individual's interaction with the environment — that is, in response to experience rather than explicit teaching. This process can be modelled using temporal-difference reinforcement learning (TDRL), a reinforcement learning algorithm that relies on an error–reward signal. TDRL models aim to attain maximum future reward, and learn, by means of various calculations, to function accordingly. In these models, learning only occurs when the reward is incorrectly predicted. With correctly predicted reward, there is no error signal, and therefore no learning.

Using dopamine as the error–reward signal, the computational model established by Redish shows what happens when a positive signal, much like the dopamine surge that would accompany the use of a drug such as cocaine, is introduced neuropharmacologically rather than occurring as a result of an unexpected natural reward or cue stimulus. This overrides the reward predictions of the TDRL model and, because the positive signal does not relate to the other factors included in the model's calculations, the model is unable to predict such rewards. This means that the likelihood of the model selecting a pathway that would lead to drug reward depends on its number of experiences.

With learning, TDRL models usually achieve a stable response to natural rewards. This response depends on the time to and level of a reward and any discounting factors, which decrease the expected value of the reward. This sensitivity between natural reward and cost is called elasticity. In Redish's modified TDRL, the demand for drug reward increases disproportionately, so that although the process still shows some elasticity, it is inelastic when compared with natural reward. However, this does not necessarily mean that a drug reward would always be selected over a non-drug reward, as selection would depend on the size of the non-drug reward relative to that of the drug reward.

It is hoped that computational models of addiction such as this one will help us to understand the mechanisms and factors that are involved in addiction. Such models could be used to help explain and confirm observations, and to make further predictions that can be tested in the future.

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References and links

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