temporal insula in both groups. In contrast, opposite metabolic effects in the two groups were seen in the right medial orbital prefrontal cortex (OMPFC), a structure implicated in salience attribution, inhibitory control and compulsive behaviours. Specifically, metabolism was increased in addicted subjects, but decreased in control subjects. In all subjects, these metabolic changes were associated with an enhanced desire for methylphenidate, and in addicts with a cocaine craving.

The strong correlation between MP-induced metabolism in one area of the OMPFC [Brodmann's area (BA) 25] and yearning for either methylphenidate or cocaine suggests that the abnormal activation of this region underlies the intense desire to take the drug. At the psychological level, the authors suggest that BA25 could be involved in processing the emotional reactivity to the drug, whereas a second region of the OMPFC, BA11, might be involved with 'processing the saliency value of the drug to the subject and the motivation to procure it'. The raclopride experiment indicated that MP-induced increases in metabolism in the OMPFC were associated with an increase in dopamine in the thalamus, but not in the striatum. This result indicates that the mesothalamic dopaminergic projection regulates the responses of the OMPFC to MP, or even vice versa, given the reciprocal nature of the connections between the two structures.

In summary, the results strengthen the argument for a role of the OMPFC in cocaine addiction, and propose a mediatory role for mesothalamic dopaminergic projections. Abnormalities of the former region have also been observed in subjects addicted to a variety of other drugs (including heroin, methamphetamine, marijuana and alcohol) suggesting a common neurobiological basis to addiction amenable to therapeutic intervention.

2 Volkow, N.D. *et al.* (2005) Activation of orbital and medial prefrontal cortex by methylphenidate in cocaine-addicted subjects but not in controls: relevance to addiction. *J. Neurosci.* 25, 3932–3939

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MOLECULAR BIOLOGY

ATM is activated by the Mre11–Rad50–Nbs1 complex

DNA double-strand breaks (DSBs) must be repaired to maintain genomic stability. The kinase ATM is activated by DSBs and phosphorylates targets such as p53 and Chk2 to initiate cell cycle arrest and DNA repair. However it is not clear how ATM itself is activated. Lee *et al.* show that ATM is activated and recruited to DNA ends by the Mre11–Rad50–Nbs1 (MRN) complex [3].

ATM forms an inactive multimer *in vivo* and becomes monomeric when it is activated. Therefore the authors purified inactive multimeric ATM and showed using glycerol gradients that it was a dimer. This dimer was activated slightly by the MRE complex alone, but activity increased two orders of magnitude if linear DNA was also present. If closed-circular DNA was used no stimulation was seen, showing that DNA ends are required for activity. A complex lacking the Nbs1 subunit (MR) was not sufficient for the stimulation of activity.

The authors also examined DNA binding. Using biotinylated DNA they showed that the MRN complex bound DNA and that ATM only bound when MRN was also present. The MR complex also recruited ATM to DNA, whereas Mre11 alone did not. This shows that recruitment to the DNA requires Rad50 and that DNA binding is not sufficient to activate ATM, because activation requires Nbs1.

The MRN complex unwinds DNA and this activity requires Nbs1 and ATP. The authors used a mutant of Rad50 that inhibits the ATPase activity and showed that this prevented activation of ATM. A DNA substrate with closed hairpins on the ends did not stimulate ATM, whereas DNA with a non-complementary end did. These data show that ATP-dependent unwinding of the DNA ends is required for the activation of ATM.

3 Lee, J.-H. and Paull, T.T. (2005) ATM activation by DNA double-strand breaks through the Mre11–Rad50–Nbs1 complex. *Science* 308, 551–554

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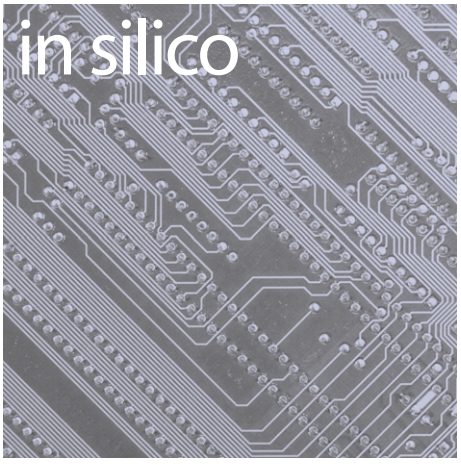

Bioavailability, divide and conquer

Drugs differ from non-drugs, and humans have a preference for simple categories. Taken together this sparked Lipinski's 'rule of five' some years ago: You are likely to encounter good absorption and permeation if you have fewer than five hydrogen bond donors, fewer than ten hydrogen bond acceptors, a molecular weight of less than 500 and a logP smaller than five. This rule generalizes across all classes of drugs, however, there are exceptions to it such as antibiotics and antifungals, but overall it provides a simple guideline for what's absorbed and what's not, from which to deviate one needs at least a good reason.

Recently, Martin, realizing that commercial ADME tools were unable to predict bioavailability reliably, discovered a new twist to this tale: the influence of charge [1]. Based on Caco-2 permeability and rat bioavailability data the 'rule of five' was not able to form a satisfactory predictor. Not on its own, that is: it failed just for anions, although giving acceptable results for neutral and positively charged compounds. For anions a different property emerged as being important, the polar surface area (PSA) of the molecule. Whereas small anions (defined as PSA $\leq 75 Å^2$) are very well absorbed, this already changes for medium-sized structures ($75 Å^2 \leq$ PSA $< 150 Å^2$), whereas large, negatively charged molecules (PSA $\geq 150 Å^2$) are very unlikely to show favourable behaviour. Martin has thus identified a hidden variable relevant for bioavailability, charge, whose particular effect on absorption and permeation is as yet unknown.

Together with the 'rule of five', the 'rule of three' (for lead-like compounds) and similar approaches the score developed here is another useful concept to cut losses early in drug development. It is overall predictive for bioavailability, yet simple enough to be understood. As always, remember, there are exceptions to every rule.

1 Martin, Y.C. (2005) A bioavailability score. *J. Med. Chem.* 48, 3164–3170

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