BEHAVIOURAL NEUROSCIENCE

Hare-brained flies

Using the fruitfly (pictured) as a model to investigate human traits such as attention span might seem odd. But the power of *Drosophila* genetics, together with previous studies pointing to sophisticated behavioural responses in this organism, in fact makes it an ideal choice for studying how our minds wander.

Bruno van Swinderen suspended flies in a cylindrical arena with rotating walls on which one of two simple visual stimuli was displayed (B. van Swinderen *Science* **315,** 1590–1593; 2007). He found that, each time the stimuli were switched, the fly's local field potential (LFP) activity — a measure of the total electrical activity at the junctions between neurons — increased. When the same object was displayed on both sides of the rotating cylinder there was no increased LFP response when it appeared anew. This ruled out the possibility that the elevated LFP response to a second object was simply due to a startle reflex.

When alternating the two visual stimuli, van Swinderen found that an interval of at least 50 seconds was required since the flies last saw the object for that stimulus to regain its novelty value, as measured by increased LFP activity. This response lasted an average of 9 seconds before the object lost its salience once more.

The author next performed these tests on two fly mutants — *dunce* and *rutabaga*. The proteins encoded by these genes normally alter levels of the same molecule, cAMP, and the mutants show similar defects in short-term memory. Van Swinderen found that the LFP activity in the brains of these mutants did not fluctuate appropriately in response to novel visual stimuli.

Might it simply be that the general responsiveness to visual cues is defective in these mutants? Surprisingly, the answer seems to be no. Van Swinderen found not only that visual responsiveness was unaffected, but also that, following an initial delay, it was in fact far higher in the *dunce* mutants than in normal flies. Further experiments confirmed that although the mutant flies responded normally to visual stimuli, they were defective in identifying a new stimulus.

These results highlight the importance of the ability not just to pay attention, but also to divert it when necessary. The excessive responsiveness of the mutant flies to one visual stimulus seems to compromise short-term-memory activities such as shifting attention, or simultaneously paying attention, to another object. When the product of the *dunce* gene, the enzyme cAMP phosphodiesterase, was expressed throughout brain development, the attention defects associated with the mutation were overcome. This indicates that the developmental activity of cAMP is crucial for characteristics resembling attention in adult flies. Further analysis of both gene and enzyme should improve our understanding of what it takes to grab flies' — and perhaps humans' — attention.

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the overall efficiency of a synthesis.

It wasn't always like this. Protection strategies simply weren't an option in the early days of organic chemistry, because many of the protecting groups widely used today were developed only in the past 50 years. Accordingly, some exemplary syntheses were devised that do not use protecting groups. For example, a useful method was developed in the early 1900s for converting sugars known as pentoses into larger sugars called hexoses[5]. Pentoses contain many reactive hydroxyl (OH) groups that chemists today would almost certainly protect. This three-step method has been invaluable for making sugars that are difficult to obtain from natural sources. More complex syntheses have also been reported. In 1957, a nine-step synthesis of muscarine — a natural product that mimics the action of certain neurotransmitters — did not use a single protecting group[6].

Another approach for avoiding protection strategies is to imitate biochemical routes found in nature. A landmark synthesis of this type was reported by Robert Robinson[7] in 1917; Robinson went on to win the Nobel Prize in Chemistry partly in recognition of this work. He prepared tropinone — a synthetic precursor of the drug atropine — in one step from simple starting materials, without protecting groups. This is considered to be an early example of a biomimetic cascade sequence[8], in which an initial reaction triggers a defined chain of other reactions, like dominoes toppling in a line. An extreme version of the biomimetic approach uses enzymes to mediate organic reactions[9,10]. Enzymes have evolved to work with naturally available molecules that clearly do not incorporate synthetic protecting groups.

But the early examples of syntheses free of protecting groups are not the norm. As time passed, the number of organic synthetic methods and chemical reagents expanded markedly. This led to an increased use of protecting groups in multi-step reaction sequences — so much so that this approach is hardly questioned today, and potentially interesting reactions that depend on the innate reactivity of unprotected molecules might be missed.

So Baran and co-workers[1] have gone back to basics. They describe synthetic routes to structurally complex compounds: ambiguine H and other related molecules that have been isolated from marine organisms. Each molecule is beautifully constructed by the authors without the use of any protecting groups. A good example of their approach is a step in which an aromatic, nitrogen-containing compound (an indole) reacts with another molecule known as a terpene (Fig. 1), mediated by a strong base and a copper salt[11]. This intriguing reaction relies on the presence of a hydrogen atom attached to the nitrogen of the indole fragment. But this hydrogen would not have been present if the nitrogen had been capped with a protecting group. After the introduction of an isonitrile group ($R–\overset{+}{N}\equiv\overline{C}$) into the terpene structure, the authors went on to append a hydrocarbon fragment (a prenyl group; Fig. 1) using an unorthodox reaction that relies again on the unprotected indole nitrogen, and on the innate reactivity of the isonitrile functional group. Remarkably, the syntheses of ambiguine H and related molecules required only 7–10 steps, in contrast to the 20–25 steps for previous routes to these syntheses that used protecting groups.

This study by Baran and co-workers shows that complex natural products can be synthesized more efficiently by reducing the use of protecting groups. But there are far greater implications of this work — the authors' strict avoidance of such groups will inspire new chemistry by exposing the intrinsic reactivity of chemical reagents and reactive intermediates. Further work on chemical synthesis using 'undressed' molecules should lead to many more advances and innovative developments in organic synthesis. And it might let chemists rest easy at night, safe in the knowledge that years of lab work won't be destroyed by recalcitrant protecting groups. ■

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