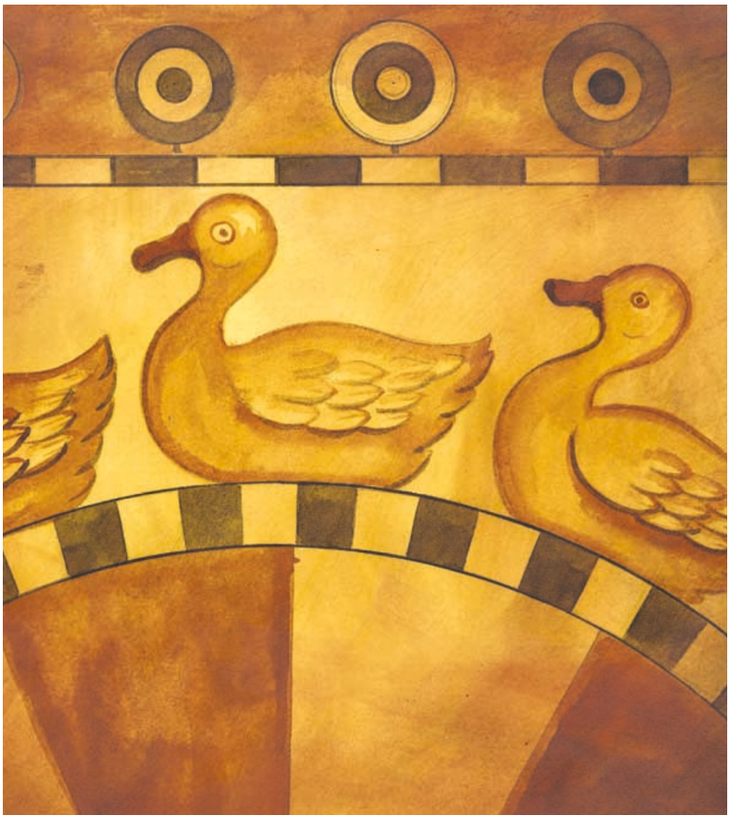

ANTICANCER DRUGS

Next in line?

The success of the kinase inhibitor Gleevec in the treatment of chronic myelogenous leukaemia — which is caused by the aberrant activity of the BCR–ABL tyrosine kinase — has given much encouragement for the development of other molecularly targeted therapies. As two reports in *Cancer Cell* now indicate, inhibitors of the FLT3 kinase, which is mutated in ~30% of patients with acute myelogenous leukaemia (AML), could be promising candidates for targeted treatment of this disease.

The first study involved the kinase inhibitor CT53518, which is selective for FLT3 and two other kinases, platelet-derived-growth-factor receptor (PDGFR) and KIT, *in vitro*. CT53518 was found to inhibit several different constitutively active *FLT3* mutants that were cloned from patients with AML and expressed in Ba/F3 cells, and also to induce apoptotic cell death in human AML cell lines with mutations in *FLT3*. Encouraged by these observations, Kelly *et al.* tested CT53518 *in vivo* in two mouse models of mutant-FLT3-mediated AML, and found that CT53518 resulted in a significant decrease in disease progression, as assessed by spleen weight and white blood cell (WBC) count, and an increase in survival. Furthermore, CT53518 was shown to have suitable pharmacokinetic and toxicity profiles for clinical use.

The second study, by Weisberg *et al.*, assessed the activity of the kinase inhibitor PKC412 — which targets FLT3, and also the kinases KDR, PDGFR, KIT and protein kinase C — and found it to be highly toxic to Ba/F3 cells that expressed mutant FLT3 receptors from AML patients. And in a

STRESS-RELATED DISORDERS

Controlling emotion

The process of proving that a promising compound can have a viable therapeutic application is more often than not a case of having the right tools for the task.

Take, for example, stress-related disorders. It is widely accepted that arginine vasopressin (AVP) is involved in various behavioural processes. It has also been shown that chronic immobilization stress increases levels of vasopressin V_{1b} receptor in the brain, and that this receptor is involved mainly in modulating the effect of AVP on corticotropin secretion — a crucial component in the response to stress or emotional situations. But, without the existence of a V_{1b} receptor antagonist, the role of the V_{1b} receptor in controlling emotional processes could not be proved.

Now, two papers from the same laboratory report the characterization of SSR149415, a selective, non-peptide, orally active V_{1b} receptor antagonist, which they hope will be an innovative approach for the treatment of stress-related disorders.

In the first paper, published in *The Journal of Pharmacology and Experimental Therapeutics*, Serradeil-Le Gal and colleagues showed that SSR149415 has high affinities for both native and recombinant human and rat V_{1b} receptors, has a much lower affinity for other vasopressin receptors, and was inactive in >90 binding assays for neurotransmitters and peptides. They also showed that SSR149415 is a potent antagonist, as it inhibited both AVP-induced Ca^{2+} increase in Chinese hamster ovary cells that expressed the human or rat V_{1b} receptor, and AVP-induced corticotropin secretion in rats.

The second report, published in the *Proceedings of the National Academy of Sciences*, looked at the effects of SSR149415 in animal models of anxiety and depression. When Griebel and colleagues tested SSR149415 in classical models of anxiety (such as the light/dark, the elevated plus-maze and the punished drinking tests), it produced anxiolytic (reduced anxiety) effects, although the magnitude of these effects were less than that of the benzodiazepine diazepam. However, the authors found that SSR149415 produced a clear anxiolytic effect in models of traumatic stress exposure (the social defeat paradigm and the defence test battery).

When Griebel and colleagues looked at classical models for depression (forced swimming and chronic mild stress tests), they found that SSR149415 showed a dose-dependent antidepressant-like activity, which was comparable to those that were observed with the antidepressants fluoxetine and imipramine.

So, it seems that V_{1b} receptor antagonists could provide a new strategy for the treatment of some depressive and anxiety disorders. And although the site of action of SSR149415 is uncertain, it should serve as a useful tool for investigating the functional importance of the brain AVP in emotional processes.

Simon Frantz

References and links

ORIGINAL RESEARCH PAPERS

Serradeil-Le Gal, C. *et al.* Characterization of (2*S*,4*R*)-1-[5-Chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-4-hydroxy-*N*,*N*-dimethyl-2-pyrrolidine carboxamide (SSR149415), a selective and orally active vasopressin V_{1b} receptor antagonist. *J. Pharmacol. Exp. Ther.* **3**, 1122–1130 (2002) | Griebel, G. *et al.* Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V_{1b} receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. *Proc. Natl Acad. Sci. USA* **9**, 6370–6375 (2002)