STRUCTURE-BASED DRUG DESIGN

Turning Ying into Yang

Nuclear hormone receptors — ligand-dependent transcription factors that regulate many important physiological processes — have received much attention as therapeutic targets in recent years. The design of agonist drugs is facilitated by crystal structures of agonists bound to the ligand-binding domain of various nuclear hormone receptors. By contrast, the lack of antagonist-bound 'inactive' receptor structures — so far, only available for oestrogen receptor-α, the target of the breast-cancer drug tamoxifen — hinders the rational design of receptor antagonists. Writing in *Endocrinology*, Baxter *et al.* describe how agonist-bound structures can be used as the basis for the rational modification of agonists into antagonists, and the use of this approach for developing the first clear antagonist of the thyroid hormone receptor (TR), overactivity of which results in serious heart problems.

Previous structural studies had indicated that folding of the ligand-binding domain (LBD) to encapsulate the agonist might be crucial for the formation of the activated receptor surface. Noting that known antagonists of nuclear receptors seem to be analogues of agonists with a large extension group attached, the authors hypothesized that these antagonists bind in the same general orientation as agonists, but that the extension group acts as a physical barrier that prevents the receptor from attaining an active conformation. Consequently, they used the structures of agonist-bound LBDs of TR to design a potential antagonist by adding an extension group to an agonist analogue of the thyroid hormone triiodothyronine (T_3). Binding assays and cell-culture experiments showed that the

METABOLIC DISORDERS

Insulin mimetics

An enormous increase in metabolic disorders, largely characterized by obesity, insulin resistance and diabetes, has resulted in pressure for effective therapeutics. Current treatments for type 2 diabetes are unsatisfactory — although they lower blood sugar, they often result in weight gain, which further exacerbates the insulin resistance, leaving these patients in a catch-22 situation. In the February issue of *Nature Medicine*, researchers from Merck and the University of Cincinnati report that small-molecule insulin mimetics are able to increase insulin sensitivity, but reduce weight gain, in a mouse model of obesity.

Delivery of insulin into the brain reduces food intake and body weight; however, this is not the case with systemic delivery. In the periphery, insulin acts as an anabolic factor, lowering blood sugar by increasing glucose uptake. In the absence of increased energy usage, it is clear that this leads to increased adiposity. Zhang and colleagues showed that two insulin-mimetic nonpeptidyl compounds, delivered orally, are capable of mediating insulin-like signals and exerting antidiabetic effects in rodent models of diabetes. Intracerebroventricular administration of insulin, or one of the mimetics, resulted in a dose-dependent reduction of food intake and body weight in rats. Surprisingly, unlike insulin, the systemically delivered mimetic also resulted in weight loss of the animals. The compounds function by activating insulin-receptor tyrosine-kinase signalling pathways in cells. These insulin mimetics seem to have an advantage over insulin by separating the glucose-lowering action from the weight gain.

Because the entry of insulin into the brain is receptor mediated, only a small proportion of systemically administered insulin can gain access to brain insulin receptors. Peripherally administered small-molecule mimetics have greater potential to cross the blood–brain barrier than insulin. The effect of insulin sensitivity and resistance to weight gain is reminiscent of the phenotype of intracellular phosphatase *Ptp1b*$^{-/-}$ knockout mice. These mice are insulin sensitive, yet show resistance to diet-induced obesity, indicating that signalling pathways from the brain might be crucially involved. Consistent with this observation, mice that lack brain insulin receptors are hyperphagic and obese.

Current therapies for these metabolic syndromes, such as the biguanide metformin, were developed in the absence of defined molecular targets or an understanding of the disease pathogenesis. However, emerging knowledge of key pathogenic mechanisms, including glucose-stimulated insulin secretion and the role of obesity as a cause of hepatic and muscle resistance to insulin, has opened the field to a host of new molecular drug targets for diabetes and obesity. Let us hope that these exciting insulin mimetics behave the same way in humans as they do in rodents.

Melanie Brazil

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Insulin action: molecular basis of diabetes

designed compound blocks binding of thyroid hormone and thyroid-hormone mediated responses.

So, this study shows that TR antagonist activity can be obtained, and is a first step towards evalulating the potential of TR blockade as a therapeutic approach. More generally, the structure-based approach that was used could perhaps be widely applicable to the design of nuclear-receptor antagonists, although as the authors note, there is a lot more to be learned about how this antagonism results.

Peter Kirkpatrick

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ANALGESIA

Dial 'P' for pain

There is a wealth of evidence to indicate that substance P (SP), a peptide neurotransmitter that acts at the neurokinin 1 (NK1) receptor, is involved in the perception of pain (nociception). The analgesic action of opioid therapeutics, such as morphine, seems to be explained, in part, by their ability to decrease SP release, and SP levels are increased in animal models of chronic pain. But despite a clear role for SP in mediating pain states, NK1-receptor antagonists have failed to show effectiveness as analgesics in clinical trials. Now, a study that examines the balance between nociceptive transmitter systems in mice provides a hint that NK1-receptor antagonists might be more effective if used as adjuncts to opioid-based analgesia.

A number of neurotransmitters seem to act in concert to control nociception. Under normal conditions, tonic stimulation of α2-adrenoceptors by noradrenaline (NA) provides an inhibitory influence, increasing the threshold for nociception and potentiating the analgesic effects of morphine. In the present study, the authors investigated nociceptive behaviour in the absence of NA by studying mutant mice that lacked the gene for the enzyme that is responsible for synthesizing NA, dopamine β-hydroxylase. An elegant feature of this model was that normal NA levels could be restored by injecting the mutant mice with a prodrug that is converted to NA by endogenous enzymic activity. As expected from the presumed inhibitory role of NA in nociception, the mice that lacked NA had a decreased pain threshold, although unexectedly this 'hyperalgesia' was limited to thermal stimuli, but not to mechanically induced pain. Restoring NA levels normalized nociception, showing that the hyperalgesia was specifically due to the lack of NA, not to any developmental abnormality in the genetically altered mice.

In support of the hypothesis that NA exerts its inhibitory effect by reducing levels of SP release, the authors found that the mice that lacked NA had increased levels of SP immunoreactivity in key regions involved in pain transmission. Furthermore, NK1-receptor antagonists were shown to be analgesic in the mutant mice, but not in control mice with normal NA levels, implying that the extent of SP-mediated nociception was greater in mice in the hyperalgesic state. Interestingly, NK1-receptor antagonists were also able to reverse the reduction in the analgesic potency of morphine that was observed in the mutant mice, indicating that morphine cannot completely abolish SP release in the absence of NA.

Dysfunction of the NA-mediated inhibitory pain system therefore seems to produce a specific type of chronic hyperalgesia in which the balance of the opposite actions that SP and opioids have on pain behaviour is altered, and in which SP has a crucial role. This indicates that NK1-receptor antagonists, although not effective when used alone, might prove useful in cases of hyperalgesia that are characterized by a reduced sensitivity to morphine. These findings could pave the way towards pain treatment with less addictive potential than current morphine use.

Adam Smith

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