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 evaluating 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

References and links

ORIGINAL RESEARCH PAPER

Baxter, J. D. *et al.* Structure-based design and synthesis of a thyroid hormone receptor (TR) antagonist. *Endocrinology* **143**, 517–524 (2002)

FURTHER READING

Brzozowski, A. M. *et al.* Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature* **389**, 753–758 (1997)
Shiau, A. K. *et al.* The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen. *Cell* **95**, 927–937 (1998)

WEB SITES

Encyclopedia of Life Sciences:
<http://www.els.net>
thyroid disease

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 α 2-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 unexpectedly 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

References and links

ORIGINAL RESEARCH PAPER Jasmin, L. *et al.* The NK1 receptor mediates both the hyperalgesia and the resistance to morphine in mice lacking noradrenaline. *Proc. Natl Acad. Sci. USA* **99**, 1029–1034 (2002)

WEB SITE Jasmin & Ohara's lab:
<http://anatomy.ucsf.edu/ohara/index.html>