doses, are only minimally addictive, in stark contrast to morphine-based opioids. 'The two other major side effects of morphine – tolerance and constipation – also do not occur with κ-opioids,' he adds. If κ-opioids can be given in combination with naloxone to induce analgesia equivalent to that obtained using morphine, the comparative lack of side effects would make κ-opioid therapy a much safer option.

'This is a very interesting study,' comments Anthony Dickenson, Professor of Pharmacology at University College (London, UK). 'It raises questions about the extent that gender differences contribute to the effects of other analgesics, or indeed other drugs with CNS actions. Clearly, this study could lead to a reappraisal of drugs acting on other pharmacological targets,' he adds.

Possible mechanism of action

The reason for the different responses is not yet known but Levine speculates that action at different κ-opioid receptor subtypes might be important. 'The anti-analgesic effect of nalbuphine might be mediated by a subset of κ-receptors that are sensitive to naloxone antagonism. Thus, naloxone might unmask the analgesic effect of nalbuphine by antagonizing this anti-analgesic effect,' explains Levine. Men might have more of the naloxone-sensitive κ-opioid receptor subtype than women. 'The effects of naloxone suggest that nalbuphine might have a complex pharmacology – whether all the observed effects are explicable by κ-opioid receptor subtypes needs to be determined,' points out Dickenson.

Future studies

Levine and colleagues are now engaged in follow-up studies to examine the analgesic potential of the κ-opioid/naloxone combination in different types of pain and to investigate how people respond to it for chronic, long-lasting pain. As both drugs are approved for use independently, Levine expects that a combi-nation therapy could be used in clinical practice 'shortly', but he also anticipates that the new findings will renew enthusiasm for developing new κ-opioid drugs. 'The field of κ-opioid analgesics has been a big mess for some time and this could begin to set it straight,' he concludes.

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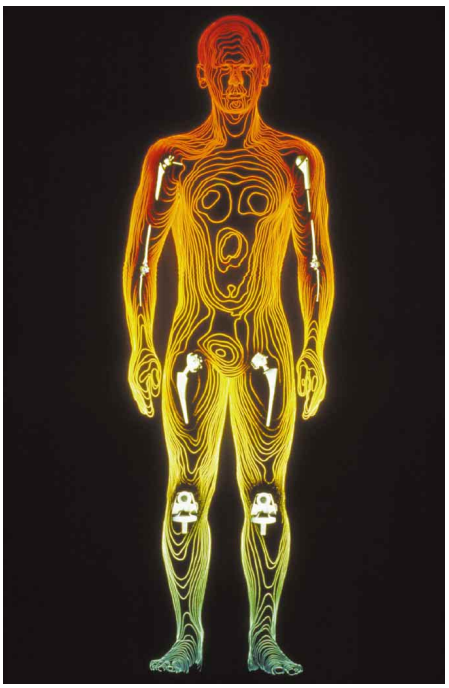
Kathryn Senior

Virtual drug resistance testing in HIV

A new computer-based technique will enable doctors to obtain rapid and accurate information on drug resistance patterns among strains of the HIV. The technique – Virtual Phenotype – was developed by Virco Laboratories (Cambridge, UK). It comprises a large database of both genotype and phenotype information on several thousand HIV variants, together with software to match test HIV samples with those already in the growing database.

Multidrug treatment for HIV reduces viral load and inhibits viral replication. However, viral mutations confer drug resistance to single antiretroviral therapies and cross-resistance to others. Such resistance is a major cause of treatment failure in patients infected with HIV and the problem is rising



rapidly. Although confirmed epidemiological data are not yet available on HIV resistance, 'Approximately 70% of HIV strains isolated from treated patients are resistant to at least one class of anti-HIV drugs. There are clear signs of resistance in newly infected people, which shows that resistant strains are also being transmitted,' says John Mellors (Chief of the Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA).

'The Virtual Phenotype system is a simple matching process that compares the genotype of an HIV sample with that of a large number of variants in the company's database. The difference between this and other resistance testing techniques is that it enables the rapid interpretation of genetic information to find out which drugs are most likely to

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be effective against the patient's virus, thus raising the chances of a good outcome for patients,' explains Mellors.

Mechanism of search

The first step is to determine the genetic sequence of the protease and reverse transcriptase genes of the HIV samples taken from patients. Mutations in these genes are identified and compared with mutations that have already been linked to resistance or cross-resistance in the database, which Mellors estimates is growing at a rate of approximately 2000 samples each month. Currently, >100 mutations are known to cause HIV drug resistance.

Each search elicits matching genotypes but, importantly, also provides the known rate of replication of strains with that genotype in the presence of all the current antiretroviral drugs (the virtual phenotype). 'If actual phenotypes are compared with virtual phenotypes, a concordance rate of over 90% is achieved. False-positive and false-negative results are very rare and most miscalls occur with strains with intermediate resistance,' says Mellors. He adds: 'This is because our knowledge of HIV mutations is incomplete, but it will improve with time.'

It takes approximately two weeks to produce an accurate virtual phenotype to enable doctors to predict which combination of the three classes of antiretroviral drugs (nucleoside and non-nucleoside reverse transcriptase inhibitors and the protease inhibitors) is likely to be most effective for each patient at the point of diagnosis. This will have the advantage of avoiding the need to try out various drug cocktails until the most effective one is found.

Future uses

'Currently, AIDS and HIV advisory bodies recommend resistance testing for newly diagnosed patients prior to starting therapy,' says Mellors and he predicts that the use of resistance testing will rise in the future. Meanwhile, the company will be working on extending the technique to other diseases, including cancer and hepatitis.

Sharon Dorrell

News in brief

Vagus nerve stimulation for Alzheimer's disease

A pilot clinical study has been approved for the examination of the effects of vagus nerve stimulation (VNS) for the treatment of Alzheimer's disease (AD). Researchers at Cyberonics (Houston, TX, USA) have initiated the study because of VNS treatment-related improvements previously seen in memory in both animal studies[1] and in patients with epilepsy[2]. The first study showed enhanced memory storage while the second study (by the same group) showed enhanced memory by verbal learning in epilepsy patients of 35%.

The three-month pilot study will be carried out at the Sahlgrenska University Hospital in Gothenburg (Sweden) and will implant up to ten patients with the NCP System to stimulate the left cervical vagus nerve. The patients will then be followed up long-term.

As well as examining changes in cognitive performance such as in memory over time, the team hope to examine the effects of VNS on disturbances in attention, mood and executive functions, which are often among the earliest symptoms of AD. Magnus Sjogren, the principal investigator of the pilot study said, 'In a separate study of patients with depression[3]…VNS has been shown to potentially have mood elevating effects. In moderate to severe AD, many patients also develop depressive symptoms, so the potential of VNS to not only enhance memory, but also improve depression is of great interest to us.'

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Competition increases in the cardiovascular market

The global cardiovascular (CV) disease therapeutic market will continue to be a high risk forum in which to launch new drugs and perform marketing, despite increases in its overall size, reports a recent Decision Resources (Waltham, MA, USA) study entitled *The Marketing Environment for Cardiovascular Agents*. The market, principally comprising the US, France, Germany, Italy, Spain and the UK, is highly competitive because of the large potential profits that are available and the overlapping nature of CV disease pathophysiologies and treatment practices.

Intense R&D effort by commercial companies has resulted in the presence of too many similar drugs which now crowd the market, making the production of a market 'blockbuster' less likely. There is now a realization that the market requires diversification to fill the niches that do exist and develop truly novel agents. Other factors that

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