In search of new drugs

Relieve the Pain

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Trauma, infections or diabetes can result in nerve damage, leading to neuropathic pain. Even morphine cannot relieve such patients from their suffering. New methods and therapies are in urgent need

Neuropathic pain, a major health problem, arises as a result of damage to any part of the nervous system, either peripheral or central (including the brain). Such damage may result from surgery, multiple sclerosis, tumors, disc herniation or hemorrhaging, but it may also be the consequence of other trauma, infections, ischemia or metabolic disturbances.

Despite the variety of pathogenic factors that can lead to neuropathic pain, cases of it bear common clinical hallmarks, e. g. deep aching in the extremities, superficial burning, stinging and piercing sensations. Neuropathic pain is characterized by two main phenomena: allodynia and hyperalgesia. The former occurs when a normally pleasant, light touch on the skin can cause pain. The latter is when a stimulus much weaker than the control pain threshold causes a pain reaction. Presently available therapeutic approaches can reduce but cannot eliminate these characteristic syndromes of neuropathic pain.

Three ways to go

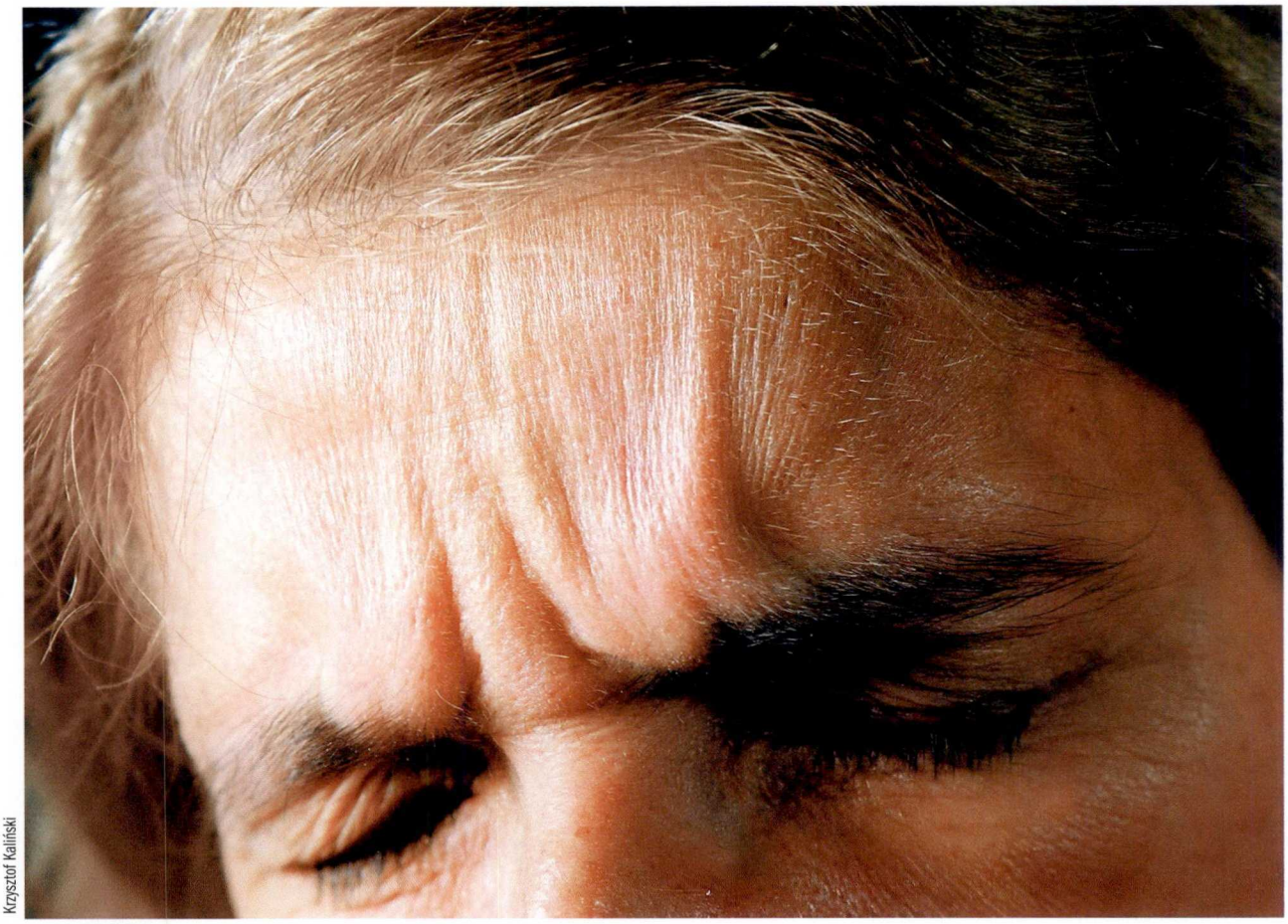
If neuropathic pain does develop, it is very difficult to treat. Why? Firstly, pain of this sort is a chronic illness, which has strong physiological and psychological effects on the patient. Secondly, long disease history involves long-term pharmacotherapy of accompanying illnesses, causing trouble with drug choice. Thirdly, morphine and other classic opiates are not effective enough in relieving neuropathic pain. Although it has been suggested that this may be attenuated by higher doses of opiates, such an approach aggravates unwanted side effects. New methods and therapies are therefore being sought in order to improve clinical practice.

Basic research into neuropathic pain focuses on several issues. In one approach, attempts are being made to clarify how such pain develops, since the current set of data cannot be used to propose more efficient therapies. The second approach tries to identify the reasons why drugs and methods that are successful in relieving pain of other origin are of diminished efficacy against neuropathic pain. The third direction searches for genes that are involved in the pathology. Newly emerging gene microarray, genomics and proteomics methods may be applied to characterize specific targets for therapy.

Neuropathic pain is the focus of studies carried out by the Department of Molecular Neuropharmacology at our Institute. Our team has for many years investigated the action of endogenous opioid peptides (β-endorphin, enkaphalin, dynorphin) and morphine (an exogenous, non-peptide substance). One of the main functions of opioid systems is an analgesic action. Hence, problems related to neuropathic pain became one of the principal aspects investigated at our department. Due to this research's strong relationship to clinical problems, we began to work together with the clinics of Jagiellonian University. Under an agreement between the University's Collegium Medicum and our Institute, the Pain Research Group was established. Certain research problems are inspired by clinical practice and jointly solved by scientists and physicians, most often anesthesiologists. Experiments are carried out

When touching hurts

Neuropathic pain is characterized by hypersensitivity: even a light touch on the skin can produce pain. This occurs in 0.5-0.8% of all patients with chronic pain. Neuropathy develops in 61% of all diabetic patients, 10% of those suffering from herpes zoster, and 4% of arm or leg amputation patients. This means that neuropathic pain is not always a consequence of nerve injury. It appears when the nervous system's ability to adapt is exhausted. Our organism usually has sufficient adaptive capacity to prevent the development of neuropathic pain. If such pain does develop, however, it is very difficult to treat.



Krzysztof Kaliński

Neuropathic pain is associated by deep aching, burning and piercing sensations

on animal models of neuropathic pain, designed to reproduce the characteristic clinical symptoms: allodynia and hyperalgesia. The alleviation of these symptoms is a measure of antinociceptive action. Drug effect is measured in terms of foot withdrawal threshold in response to mechanical stimuli. We have used so-called von Frey filaments, which apply slight pressure to the skin (in our experiment, stimulus strength ranges from 0.2 to 26 g).

The difference is the key

Our recent pharmacological studies were devoted to elucidate the differences in how opioid peptides and morphine (an alkaloid) behave in the models of neuropathic pain. Clarifying these differences would help us prevent the attenuation of morphine's effects in alleviating neuropathic pain. Our experiments have compared the effects of morphine and of two opioids produced by the body itself: endomorphin-1 and endomophin-2. All three substances are considered to activate the μ-opioid receptor (a "sensor" on the cell surface, which "turns on" after binding to the opioid).

It has been suggested that morphine's ineffectiveness in models of neuropathic pain is caused by a reduced number of μ-opioid receptors, as a result of the degeneration of neurons that join peripheral nerves to the spinal cord. Our experiments, however, have shown that endomophins, which also act via μ-opioid receptors, did not become less active in neuropathic pain,

Research on neuropathic pain focuses on clarifying how this pain develops, explaining inefficacy of some painkillers and searching for genes involved in this pathology

suggesting that there is another cause for morphine's loss of efficacy against this condition.

Recently, differences in the migration of μ-opioid receptors from the cell membrane to small "bubbles" inside the cell (lysosomes) and back were described after such receptors were activated by endomorphins but not by morphine. This phenomenon, called "internalization," is very important for decreasing receptor

sensitivity, so we investigated the importance of this process for neuropathic pain. Our results indicate that μ-opioid receptor trafficking may play a significant role in causing the differing effects of morphine and opioid peptides in neuropathic pain. Our present research has targeted the possible use of this mechanism in restoring the painkilling effects of morphine, which is even 10-20 times less effective against neuropathic than against acute pain.

Think globally, act locally

Our research has also focussed on the possible peripheral use of opioids and morphine to antagonize neuropathic pain symptoms. Apart from in the central nervous system, all three types of opioid receptors (μ, δ, and κ) have been found in sensory neurons that transfer signals from the peripheral nerves to the spinal cord and back. Our studies have shown that opioid peptides are also effective in antagonizing neuropathic pain after local, peripheral application, and that their peripheral use may be of therapeutic interest in the long-term management of chronic pain.

In summary, we expect our research to contribute to a better understanding of the mechanism underlying neuropathic pain. This may speed up the search for new drug combinations and routes of drug administration, and aid the identification of differences between how opioid peptides and alkaloids affect pain of this kind. This may be of great importance for our understanding of the molecular mechanisms of this phenomenon, and thus for the development of better and more effective drugs to treat neuropathic pain in humans. ■

Opioids may be efficient in relieving neuropathic pain, acting both on central nervous system and locally after peripheral application

Further reading:

Dobrogowski J., Wordliczek J. (eds.) (2004). *Medycyna Bólu*, Wydawnictwo Lekarskie PZWL, Warszawa

Przewłocki R., Przewłocka B. (2001). Opioids in chronic pain. *European Journal of Pharmacology*, 429 (1-3): 79-91

Ryszard Przewłocki

To test the analgesic effect of new drugs and methods, we use animal models of neuropathic pain. Rats are placed in plastic cages with a wire net floor, and delicate pressure is applied to their hind paw

Inbox: Academia

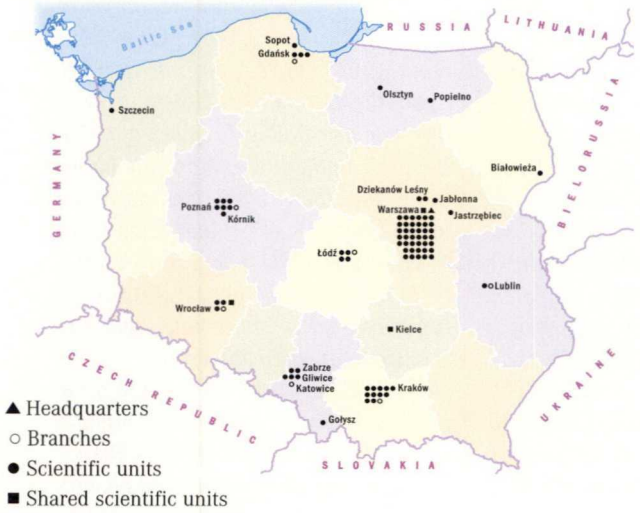
Dear Editor in Chief,
A few days ago I received the first issue of Academia. I read most of its contents with more than the usual attention. I would like to congratulate the PAN on its initiative, and especially to complement the editor on the high caliber of the articles, the broad field of disciplines involved, and the printing quality of the magazine. It certainly lives up to international standards.
This initiative has come at the right time, Poland now being one of the most important and best known of the new members slated to join the European Union next May. The people of our region are looking forward to this event with warm sympathy.
We have been actively engaged in collaboration with the PAN Institute of Agrophysics in Lublin for more than 40 years, initiated by Professor Jan Gliński, the Institute's former director, and myself. It is now still underway under our respective successors.

Yours sincerely,
Prof. Dr. Dr.h.c. Ir. M. De Boodt, Universiteit Gent

Dear Sirs,
We would like to thank you very much for sending us the first issue of Academia: The Magazine of the Polish Academy of Sciences.
We believe that this magazine will do much to foster awareness of the Polish Academy of Sciences in the international arena, including among Chinese scientific circles.
We would like to wish you the greatest success in 2004.

Yours sincerely,
Ireniusz Jagielski, Second Secretary
Polish Embassy in Beijing

PAN scientific units and branches



Dear Mr. Strelau,
I have read with much interest the issue of Academia magazine that you have been kind enough to send me, and I wanted to sincerely thank you for it.
This magazine reflects the high scientific level of the Polish research community, with which I had the opportunity to cooperate for many years. I personally think that it is a very good idea to diffuse your works abroad through this medium.

I have appreciated the great diversity of subjects under scrutiny, from problems such as the origins of life on our planet to more specific topics like the behavior of animals in the wild (the paper on martens), the use of dogs for cancer detection, or agronomical problems concerned with genetics or vernalization.
The idea of mixing hard science and the humanities also seems excellent to me. You have succeeded in providing in a single journal a very broad and nonetheless detailed outlook of Polish research.

Sincerely yours,
Jean Lambert, Professeur Honoraire
UCL Belgique

Dear Mr. Strelau,
I would like to congratulate you on the successful launch of a new magazine presenting the achievements of PAN institutions. The contents and layout of Academia live up to, and even exceed, the caliber of similar periodicals published abroad. For future issues, we would like to take this opportunity to propose articles highlighting the research work done at our Institute. I believe that this will be an excellent platform for promoting our Institute.

Sincerely,
Prof. Paweł Zięba
Deputy Director for Scientific Affairs
The PAN Institute of Metallurgy
and Materials Science, Kraków

Dear Professor Strelau,
Professor Nicholas Mann, Foreign Secretary and Vice-President of the British Academy, has asked me to write thanking you for sending us a copy of the Polish Academy's new magazine "Academia". We would like to offer our warmest congratulations to you and your colleagues responsible for producing this publication. The articles are all extremely varied and interesting, and the whole magazine presents an excellent picture of the range of the Polish Academy's work. We look forward to receiving future editions.

With cordial good wishes,
Ms Jane Lyddon, International Relation
The British Academy