Name of disorder

Migraine (without aura)

Essay title

Recent advances in our understanding of migraine related to the neuropeptide CGRP

Dr Christine Barry PhD.
Flinders University
27/06/2013

Migraine involves recurrent, moderate to severe headaches that are associated with nausea or sensitivity to light or sound. Fifteen per cent of the population suffer from migraine (Vos, et al. 2012) and despite the available treatments it remains a disabling condition for many people. Drug treatment recommended to reduce the frequency and severity of migraine includes divalproex sodium, sodium valproate, topiramate, metoprolol and timolol, and frovatriptan to prevent menstrual migraine (Silbertstein et al. 2012). In recent years our understanding of the causes of migraine has advanced and this has led to better therapies. However, for some people the current treatments remain inadequate, due to lack of effectiveness or complications. The neurobiological disorder that causes migraine is still unclear and further research will deliver improved treatments.

Ongoing research includes basic science studies to understand the cause of migraine so that ultimately, specific management can target this and migraine can be prevented. Other research includes clinical trials, which assess the safety and effectiveness of treatments for patients. Clinical trials can be viewed as experiments that compare a drug treatment with a placebo, compare different drugs or compare different doses of the same drug. The results of these trials are analysed by committees of experts, who use them to develop recommended guidelines for therapies to prevent and treat migraine.

A wide range of recent research, including basic science experiments and large, multicentre clinical trials, has shown that a small protein called calcitonin gene-related peptide (CGRP) plays an important role in migraine. CGRP was discovered around 30 years ago (Amara et al. 1982) and was found to exist in sensory nerves and be involved in functions including nociception (pain perception) (Rosenfeld et al.1983). Very soon after CGRP was first discovered, scientists found that stimulation of the trigeminal ganglion, which contains the cell bodies of nerves that provide sensation to most structures of the head, caused these nerves to release CGRP (Mason et al.1984). The following year it was announced that binding sites for CGRP had been discovered in the human spinal cord and various parts of the brain, particularly areas where pain signals are processed (Tschopp et al.1985). At the same time a different research group published their discovery that CGRP is a potent vasodilator

(Brain et al.1985). By causing small arteries to relax CGRP can increase blood flow to various regions. This is the source of the redness we see when there is irritation or trauma to our skin. Damage such as sunburn causes release of CGRP leading to dilation of blood vessels and increased blood flow to the skin. The CGRP that causes blood vessels to dilate is released from nerve fibres around blood vessels (McCulloch, Uddman et al. 1986). As brain blood vessels are pain sensitive it is hypothesised that CGRP contributes to migraine by causing dilation of blood vessels in the brain or in the connective tissue surrounding the brain, the meninges.

People with migraine have increased levels of CGRP the blood returning from their brain (Goadsby, Edvinsson and Ekman 1990) and in their saliva (Bellamy 2006). They also have increased sensitivity to exposure to CGRP. If CGRP is injected into the blood of people who are prone to migraine it triggers headache and sometimes other symptoms, but in people not susceptible to migraine it does not cause symptoms (Hansen, Hauge et al. 2010). Drug treatments to block CGRP binding sites have been used in clinical trials and are found to prevent and relieve migraine (Connor, Shapiro et al. 2009; Hewitt, Aurora et al. 2011).

Further studies need to be undertaken to clarify the actions of drugs that block CGRP binding sites (CGRP receptor antagonists), so that they can be used safely and effectively in the management of migraine. So far it appears these drugs do not cause the cardiovascular side effects that are associated with some other drug treatments for migraine. However a recent clinical trial using a CGRP receptor antagonist for prevention of migraine was ceased due to concerns that some patients had high blood levels of the liver enzyme transaminase (Tepper and Cleves 2009). Further knowledge about the actions of CGRP and further development of drugs against CGRP receptors offer promise for treatment of migraine in the future.

References

Amara, S.G., Jonas, M.G., Ong, E.S. and Evans, R.M. (1982). “Alternate RNA processing in calcitonin gene expression generates mRNA encoding different polypeptide products.” Nature **1298**(587):240-4

Brain, S.D., Williams, T.J., Tippins, J.R., Morris, H.R. and MacIntyre, I. (1985) “Calcitonin gene-related peptide is a potent vasodilator.” Nature 1985 **313**(5997);54-6

Connor, K. M., R. E. Shapiro, et al. (2009). "Randomized, controlled trial of telcagepant for the acute treatment of migraine." Neurology **73**(12): 970-977.

Goadsby, P.J., Edvinsson, L. and Ekman, R. (1990). “Vasoactive peptide release in the extracerebral circulation of humans during migraine headache.” Ann Neurol **28**(2):183-7

Hansen, J. M., A. W. Hauge, et al. (2010). "Calcitonin gene-related peptide triggers migraine-like attacks in patients with migraine with aura." Cephalalgia **30**(10): 1179-1186.

Hewitt, D. J., S. K. Aurora, et al. (2011). "Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine." Cephalalgia **31**(6): 712-722.

Mason, R.T., Peterfreund, R.A. Sawchenko, P.E., Corrigan, A.Z., Rivier, J.E. and Vale, W.W. (1984). Nature **308**(5960):653-5

Rosenfeld, M.G., Mermod, J.J., Amara, S.G., Swanson, L.W., Sawchenko, P.E., River, J., Vale, W.W. and Evans, R.M. (1983). "Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing." Nature **304**(5922):129-5

Silbertstein, S., Holland, F., Freitag et al.(2012). "Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society." Neurology **78**:1337

Tepper, S.J., and Cleves, C. (2009) "Telcagepant, a calcitonin gene-related peptide antagonist for the treatment of migraine." Current Opinion on Invetsigational Drugs **10** 711-720

Tschopp, F.A., Henke, H., Petermann, J.B., Tobler, P.H., Janzer, R., Hokfelt, T., Lundberg, J.M., Cuello, C. and Fisher, J.A. (1985). "Calcitonin gene-related peptide and its binding sites in the human central nervous system and pituitary." Proc Natl Acad Sci USA **82**(1):248-52

Vos, T., A. D. Flaxman, et al. (2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010." Lancet **380**(9859): 2163-2196.