Migraine is a disorder of the brain, and so it seems logical, certainly to me and I think to many people, to target our treatments at neuronal structures,” stated Dr. Peter J. Goadsby, Professor of Neurology, University of California at San Francisco. He and colleagues discussed novel targets and potential therapies for migraine, some of which address both vascular and neural components of migraine.

Neuronal Targets: Hits and Misses

The discovery several years ago that sumatriptan was a partial serotonin 5-HT\textsubscript{1a} agonist led to the development of several compounds targeted at the 5-HT\textsubscript{1a} and 5-HT\textsubscript{1b} receptors as well as related receptors but only one such compound, the 5-HT\textsubscript{1b} agonist LY334370, is still in clinical development, Dr. Goadsby noted.

Another target, TRPV1 receptors, have been proposed as the potential focus of antagonists for the treatment of neuropathic pain, but studies in animal models of neurogenic dural vasodilation suggest that they are unlikely to play a significant role in migraine, Dr. Goadsby noted.

In another direction, he and colleagues at the Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK, found that cannabinoid receptor activation inhibits trigeminocervical complex neurons in the rat, making cannabinoid receptors potential therapeutic targets for migraine. The potential psychoactive or cognitive effects of drugs targeted at cannabinoid receptors, however, presents a challenge that may be too difficult to overcome, he added.

Gap Junction Inhibition

As reported by Dr. David W. Dodick, Professor of Neurology, Mayo Clinic, Scottsdale, Arizona, an agent targeted toward a different novel neuronal target—the gap junction—is currently in late clinical development. This
mechanism of action shows promise for both the prevention and treatment of migraine, he told delegates.

Gap junctions are involved in the intracellular diffusion of ions, second messengers and metabolites, and as such, appear to play an important role in the initiation and propagation of cortical spreading depression (CSD), the process believed to underlie migraine with aura. Inhibition of CSD may be a worthwhile objective for new agents. “Aura only accounts for about one-third of migraine sufferers, and even in those one-third of migraine sufferers, not all of them have just pure migraine with aura, most of them have migraine with and without aura,” confirmed Dr. Dodick. He noted that in studies where animal models received intraperitoneal injection of various agents used in migraine prophylaxis, the agents—topiramate, valproate, propranolol, amitriptyline and methysergide— inhibited CSD, suggesting that CSD-like events may underlie migraine without aura.

The anticonvulsant tonabersat is a gap junction inhibitor, which in preclinical studies has been shown to inhibit neurogenic vasodilation with no apparent effect on blood pressure, heart rate or cerebral blood flow; it has also been shown to inhibit CSD number and duration. “It also inhibits CSD-induced release of nitric oxide, so in a sense it inhibits the metabolic drive, if you will, of CSD,” Dr. Dodick commented.

However, in the largest clinical trial of tonabersat to date, which was a double-blind, placebo-controlled study of the agent in the preventive management of migraine, Dr. Goadsby and colleagues reported at IHS 2007 that the trial did not meet its primary end point of change in mean monthly migraine days from baseline to month 3, although some of the secondary end points were positive. These included a responder-rate analysis at month 3, reduction in consumption of rescue medication at month 3 and patient satisfaction. The compound appeared to be well tolerated, with treatment-emergent adverse events similar to placebo. A phase IIb study is ongoing in the US, with the primary end point of a reduction in mean monthly migraine attacks over the last eight weeks of treatment.

“I think with these gap junction inhibitors and the calcitonin gene-related peptide [CGRP] antagonists, it is a very exciting time. It is exciting not only for the patients who suffer, because we now have drugs that hopefully will have been vetted and targeted actually at the underlying process in migraine,” Dr. Dodick told delegates. “It will benefit the patients but it will also benefit the field, I think, because it will bring a respect and a credibility to the disease and to the patients who suffer from the disease.”

cGMP Inhibitors: Triptan-like Efficacy

Two CGRP antagonists are currently in clinical development: the intravenous (i.v.) agent olcegepant and the oral agent telcagepant. Both agents were shown in phase I and II studies to be effective, safe and well tolerated, reported Dr. Stewart J. Tepper, Director of Research, Center for Headache and Pain, Neurological Institute, Cleveland Clinic Foundation, Ohio. CGRP is a 37 amino acid neuropeptide belonging to a family of peptides that includes calcitonin, adrenomedullin and amylin. “It is one of the most potent endogenous vasodilators known,” remarked Dr. Tepper, “and is found in every location described in migraine genesis and processing, and depending on your point of view as to where migraine is generated, you will still find CGRP co-localized there. If one starts in the periphery and moves centrally, it is found in the meninges, it is found in the trigeminal ganglia, in the trigeminocervical complex, ascending brainstem nuclei, up to the cortex.”

CGRP antagonists were developed with the goal of blocking vasodilation peripherally and avoiding vasoconstriction, altering CGRP action in the trigeminal ganglion, reducing pain transmission and inhibiting CGRP effects centrally. Dr. Tepper pointed to a proof-of-concept study, a randomized, controlled trial of i.v. olcegepant (Olesen et al. N Engl J Med 2004; 350(11):1104-10). The pain-free, two-hour headache response following an infusion of 2.5 mg was 44% and the four-hour response was 56% vs. 2% and 10%, respectively, for placebo. There was an overall sustained response rate of 47% for the CGRP antagonist compared with 15% for placebo, and the rate of recurrence among patients treated with the compound was 19% compared with 46% for controls. Symptoms of nausea, phonophobia and photophobia also improved in parallel with response to the treatment, Dr. Tepper noted.

“The adverse events with i.v. olcegepant were also very heartening,” he reported. “At the highest dosages, the drug appeared to cause paresthesia and at the lower dosages
and clinically important dosages, the adverse events were comparable to placebo and there were no serious adverse events.”

Phase III Data Presented

Phase III data on telcagepant were reported here during the scientific sessions by Dr. Tony W. Ho, North Wales, Pennsylvania. The randomized study compared telcagepant to both placebo controls and to zolmitriptan 5 mg in 1380 patients with moderate-to-severe single-attack migraine.

The primary study end points were two-hour pain-free rates, pain relief, and absence of photophobia, phonophobia and nausea. Secondary end points included two- to 24-hour sustained pain freedom, two-hour total migraine freedom and two- to 24-hour total migraine freedom. Both the 150-mg and 300-mg doses of telcagepant were studied.

Investigators found that in each category studied, telcagepant 300 mg was significantly better than placebo and comparable efficacy to zolmitriptan 5 mg. As with olcegepant, the adverse event data for telcagepant “ended up being very favourable. It is a really heartening story in terms of drug development for out patients,” Dr. Tepper remarked.

Central Effect

There is mounting evidence that the CGRP inhibitors work primarily centrally as opposed to peripherally, stated Dr. Tepper, as suggested by the fact the clinical 300-mg dose of telcagepant is markedly higher than would be needed for peripheral meningeal effects. “A take-home message then, in addition to the fact that this class of medications works and looks safe and effective, is that it looks like central effect is necessary for the clinical effect, and it is also heartening that there were not any cognitive or central nervous system affects or intellectual changes seen with this drug or reported as side effects,” Dr. Tepper told delegates. There is also evidence to suggest CGRPs might be appropriate therapeutic targets for treatment of cluster headaches and chronic paroxysmal hemicrania, he added.

Drs. Dodick, Ho and colleagues also presented a post-hoc analysis from the telcagepant phase III trial, looking at the sustained pain freedom and no adverse events end point based on patient-level data. They found that telcagepant was nominally superior to placebo on the sustained pain freedom and no adverse events measure and on other composite efficacy and tolerability measures. They also found that zolmitriptan demonstrated superiority to placebo on some of these measures, but to a smaller extent than telcagepant 300 mg.

Treatment Effects Vary by Class

In the 2008 Harold G. Wolff Award Lecture, Dr. Marcelo Bigal, Assistant Clinical Professor of Neurology, Albert Einstein Medical College, New York, New York, examined the question of excessive use of migraine medications for symptomatic treatment and the progression from acute to chronic migraine and provided updated research from a survey of households throughout the US.

The survey included results from more than 162,000 persons and found that migraine progression occurred only in some patients, appeared to be related to headache frequency as much as to drug use, and to some specific classes of drugs but not others. For example, they found that any use of barbiturates and opioids was associated with increased risk for chronic migraine, whereas the use of NSAIDs appeared to be protective, except among patients with 10 to 14 headache days per month. “Within a class of acute therapies, the influence of a drug is modified by the frequency of use as well as headache frequency,” Dr. Bigal noted.

Timing Is Everything

Although emerging therapies and new therapeutic targets were among some of the more interesting presentations during this year’s AHS meeting, new research into established therapies was very much in evidence.

In one study, for example, investigators conducted an open-label crossover study comparing rizatriptan with almotriptan in routine clinical practice. Adult migraine patients treated two sequential attacks with either rizatriptan 10 mg or a usual-care prescription migraine medication in a crossover manner, with patients deciding which medication to take first. They used headache diaries and stopwatches to record treatment outcomes and time to relief.

In all, 79 of 146 patients enrolled used stopwatches to record both attacks, and these patients were included in the final results. The study authors found that significantly more patients who took rizatriptan (88.6%) achieved onset of headache relief within two hours after dosing than patients who took almotriptan (73.4%) (P=0.007).

Patients on rizatriptan also had significantly shorter times to headache relief at 45 vs. 60 minutes for rizatriptan (P=0.002), as well as shorter time to headache freedom, at 100 minutes compared with 135 minutes for patients on almotriptan (P=0.004).
Questions and Answers

The following question-and-answer sessions with Dr. Tony Ho, North Wales, Pennsylvania; Dr. Stewart Tepper, Cleveland Clinic Foundation, Ohio; and Dr. Peter J. Goadsby, University of California at San Francisco, took place during AHS 2008.

Q: Could you please summarize your impression of the results you have seen with telcagepant thus far?

Dr. Ho: We are certainly very encouraged with our first phase III study test results showing that telcagepant was superior to placebo in all the primary end points and those of the secondary end points, and telcagepant was also very well tolerated in these studies.

Q: Dr. Tepper likened the efficacy of telcagepant to the triptans. Is this is a fair assessment, do you think?

Dr. Ho: The active comparator in our study was zolmitriptan 5 mg, and the study was not designed for superiority or non-inferiority, but had a sizeable number [of patients]. Based on [this] number we see, the efficacy of telcagepant at the 300-mg dose looked similar to zolmitriptan 5 mg, but telcagepant was well tolerated, with an adverse event rate similar to that of placebo.

Q: Do we need to carry out studies with patients who have contraindications to using triptans, e.g. those with hemiplegic basilar migraine, coronary artery disease, peripheral artery disease or cerebrovascular disease, to determine whether CGRP antagonism is safe in those groups?

Dr. Tepper: The studies on hemiplegic and vascular type have not been done. There are two posters [presented at] this meeting, one of which was telcagepant given to 28 patients with coronary artery disease, without any adverse effect; another was a study in which telcagepant was given to 20 healthy males who were then given nitroglycerin, and the nitroglycerin effects, in terms of vasodilation, were not inhibited by the CGRP receptor antagonist, which underlines what Dr. Ho always says: there are many, many ways to get to vasodilation, including nitric oxide, and CGRP does not prevent vasodilation through these other mechanisms.

Q: Have you seen reductions in non-headache pain in clinical trials [with CGRP antagonists] such as muscle pain, perhaps dysmenorrhea, or women with menstrual migraine?

Dr. Tepper: No. The study has been so focused [on headache] that we really do not have any evidence outside it, other than the indirect evidence that CGRP is elevated in certain conditions such as hypertension, temporomandibular joint dysfunction, sepsis or post-operative ocular surgery. There are certain conditions in which CGRP is elevated and look like inviting targets.

Q: Given the complexity of these migraine mechanisms and inherent redundancy in biology, would it not make sense that we should look at multiple mechanisms when turning off the migraine process rather than finding a single magic bullet?

Dr. Goadsby: Yes. It is a complex disease with complex mechanisms, and that is likely to be the reason that any single-component approach is going to have a ceiling effect which is well below 100%. I think the right thing to do is to clearly establish mechanisms that have effect, and then, as we are doing in clinical practice, put them together and see if we can do something additive.