New shock treatment

By Michael J. Haas, Senior Writer

German researchers have found that targeting two G proteins could treat the vascular symptoms of anaphylactic shock while avoiding the cardiovascular side effects of epinephrine, the standard of care. If a selective inhibitor for the two proteins, GNAQ and GNA11, proves safer than epinephrine, the finding could result in the first new treatment for anaphylaxis in more than six decades.

Anaphylaxis is a severe, systemic allergic reaction characterized by a decrease in blood pressure due to blood vessel dilation, an increase in vascular permeability that can lead to angioedema, and constriction of airway passages, among other symptoms.

Epinephrine addresses the two main ways anaphylaxis becomes lethal: it reverses vascular permeability and opens the airways. But epinephrine is associated with serious cardiovascular side effects, including tachycardia and arrhythmia, which can be fatal in anaphylactic patients with hypertension or coronary artery disease (CAD).

Allergens trigger anaphylaxis by stimulating the release of histamine, platelet-activating factor (PAF) and other proinflammatory molecules into the bloodstream. These molecules are thought to activate G proteins on endothelial cells of the heart, blood vessels and airways. But which G proteins are involved has not been clear, due in part to the lack of mouse models that would allow the function of different members of the family of signal transducers to be examined separately.

The German group now has developed a mouse model, which they described in a paper in the *Journal of Experimental Medicine*.¹ In mice whose endothelial cells were deficient in different G proteins, the researchers found that two of the proteins appeared to be involved in anaphylaxis: G protein q polypeptide (GNAQ; Gαq) and G protein α11 (Gq class) (GNA11). Similar results were seen in human endothelial cells.

Next, the team generated mice with endothelial cells deficient in both GNAQ and GNA11 and injected the mice with molecules that play a role in anaphylaxis, such as histamine. Compared with normal mice, vascular permeability, blood pressure decreases and hypothermia were less severe in the GNAQ and GNA11 knockouts, and fewer mice died.

Finally, the team sensitized both the knockout and normal mice with an allergen. After allergen challenge, the GNAQ and GNA11 knockout mice had smaller and shorter-lasting decreases in blood pressure and higher survival than normal mice.

The team concluded that GNAQ and GNA11 signaling on endothelial cells was an essential factor in anaphylaxis and noted that the

GNAQ- and GNA11-deficient mice had no physiological side effects. As a result, the authors suggested that targeting these molecules could be a viable way to treat anaphylaxis.

Group leader Stefan Offermanns told *SciBX* that a systemic GNAQ and GNA11 inhibitor could have unwanted side effects on the CNS, which he said could be avoided by using an inhibitor that does not cross the blood brain barrier.

He added that blocking GNAQ and GNA11 signaling can inhibit platelet function, but he said “this would certainly be acceptable in the context of short-term emergency use” to treat anaphylaxis.

Offermanns is professor of pharmacology and director of the Institute of Pharmacology at the **Heidelberg University**, and professor and director of pharmacology at the **Max Planck Institute for Heart and Lung Research**. The research team also included scientists from **Goethe University Frankfurt** and the **German Cancer Research Center**.

Vascular gambit

Because a therapy based on the *JEM* findings would treat only one of the two life-threatening aspects of anaphylaxis—vascular permeability—it would have to be used in conjunction with existing drugs to treat airway constriction. But getting rid of the side effects of epinephrine would make the need for combination therapy worth the tradeoff, researchers told *SciBX*.

Larry Borish, professor of medicine at the **University of Virginia**, noted that epinephrine increases the heart rate to 180 beats per minute or more. “In young healthy people this is just uncomfortable. But if the patient has underlying coronary artery disease or high blood pressure, this could lead to arrhythmia or heart attack,” he said.

Borish also said patients with cardiovascular disease are frequently treated with β-blockers, which are known to decrease the effectiveness of epinephrine. “So ironically, the patients with the greatest risk of side effects from epinephrine are least likely to benefit from it” during an anaphylactic episode, he said.

“The *JEM* paper shows how you might target the vascular component of anaphylaxis” without epinephrine, he said. “Then you could treat the bronchial aspect of anaphylaxis with bronchodilators,” which have fewer severe side effects.

N. Franklin Adkinson Jr., professor of medicine at **The Johns Hopkins University School of Medicine**, said it was too early to say how a GNAQ and GNA11 inhibitor might measure up against epinephrine. Regardless, he said, “a novel treatment would be very welcome if it was either as effective as epinephrine but less toxic or even more effective than epinephrine.”

Adkinson did caution that rodent models of allergy—and especially of anaphylaxis—are not highly predictive of what happens in humans. “Until you get into primates, you don’t have anything that can be considered truly predictive,” he said.

Empty pipeline

There are no disclosed selective inhibitors of GNAQ or GNA11 in preclinical or clinical development. At least one such compound—a

small peptide inhibitor of GNAQ first described in 1998 by a team at **Duke University School of Medicine**²—might be developed to treat anaphylaxis.

“The peptide was specific for all Gq [GNAQ]-mediated signaling, but we envisioned it for treating hypertrophy and hypertension,” said Walter Koch, leader of the Duke team who is now professor of medicine and director of the Center for Translational Medicine at **Thomas Jefferson University**.

He said that Duke holds patents on the use of the peptide only to treat hypertrophy and hypertension. Thus Koch said he would be open to talking with researchers who were interested in developing the peptide to treat anaphylaxis.

He added that the peptide was safe in mice and should be able to target GNAQ on endothelial cells via i.v. injection.

Astellas Pharma Inc. had a selective GNAQ and GNA11 inhibitor, YM-254890, in preclinical development to treat thrombosis and neointima (thickening of the endothelial lining of vasculature).³ The compound came from Yamanouchi Pharmaceutical Co. Ltd.,^{4,5} which Astellas acquired in 2005.

Astellas spokesperson Jenny Keeney told *SciBX* that YM-254890 is no longer in active development.

Shocking trials

If a company does pick up the baton with a GNAQ/GNA11 inhibitor for anaphylaxis, clinical trial design could prove difficult.

“Clinical trials of any new agent are problematic in design and ethics because one is dealing with a life-threatening disorder for which there is a known effective treatment,” Adkinson said. “It becomes very hard to do placebo-controlled or comparison trials” because of the ethical issues involved in denying patients epinephrine therapy.

Enrolling patients in an anaphylaxis trial also would be difficult, Adkinson said. “You would have to wait for them to present in the emergency room or other medical setting with anaphylaxis,” and obtaining informed consent in those circumstances would be problematic, he said.

Borish was more sanguine about a clinical development program for GNAQ/GNA11 inhibitors.

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—**N. Franklin Adkinson,**
The Johns Hopkins University
School of Medicine

“In one sense, the JEM researchers made it easy by listing the ligands that act through this signaling pathway,” he said. Rather than waiting for patients to present with anaphylaxis, he said, “you could infuse trial participants with the ligands until you observe the early signs of anaphylaxis,” then test the new therapy. This would sidestep the ethical issues of testing a new therapy on full-blown anaphylaxis, Borish noted. He pointed out that this type of deliberate challenge is already used to test agents to treat food allergies—and that it isn’t particularly

difficult to find volunteers.

For example, Borish said, “patients with peanut allergies run the risk of inadvertent exposure to peanuts in food all of the time and many have experienced severe, life-threatening anaphylaxis as a result.” He thought patients who have had these experiences would readily volunteer for a study where exposure to the allergen is more gradual and controlled, in the interest of finding new treatments.

Offermanns told *SciBX* that his team has not planned any follow-on work to the JEM study, and that the findings are not patented.

Haas, M.J. *SciBX* 2(6); doi:10.1038/scibx.2009.214
Published online Feb. 12, 2009

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