aforementioned isolated nucleic acid molecules that encode CGRP R antigen-binding proteins described above.

Also provided is a method of preparing the antigen-binding proteins that includes the step of preparing the antigen binding protein from a host cell that secretes the antigen-binding protein. In some embodiments, the antigen binding protein is generated using an immunogen comprising soluble CGRP receptor. In some embodiments, such soluble CGRP receptor is obtained by co-expressing and purifying an N-terminal extracellular domain (ECD) of human CRLR and an ECD of human RAMP1, e.g., an ECD of human CRLR comprising SEQ ID NO: 6 and an ECD of RAMP1 comprising SEQ ID NO: 8, for example, as described in Examples 1 and 2 herein.

In one aspect, there is provided a method of making an antibody that selectively inhibits the human CGRP receptor as compared with human AM1, AM2, and AMY1 receptors, comprising:

(a) recovering antibodies from an immunized animal that bind both human CRLR polypeptide and human RAMP1 polypeptide in the human CGRP receptor, wherein the animal is one that has been administered an immunogen comprising:

(i) a soluble CGRP receptor, wherein the soluble CGRP receptor comprises the N-terminal extracellular domain (ECD) of human CRLR and the ECD of human RAMP1,

(ii) whole cells expressing full-length human CRLR and human RAMP1 polypeptides, or

(iii) membrane extracts of the cells in (ii);

(b) screening the recovered antibodies for inhibitory activity against the human CGRP receptor; and

(c) selecting antibodies that inhibit activity of the human CGRP receptor.

In yet another embodiment, a pharmaceutical composition is provided comprising at least one of the antigen-binding proteins summarized above and a pharmaceutically acceptable excipient. In one embodiment, the pharmaceutical composition may comprise an additional active agent that is selected from the group consisting of a radioisotope, radionuclide, a toxin, or a therapeutic and a chemotherapeutic group.

In one embodiment, the isolated antigen binding protein is effective to inhibit vasodialation and/or decrease neurogenic inflammation when administered to a patient. In one embodiment, the isolated antigen binding protein is effective to reduce the frequency and/or severity of headaches, for example, migraine headaches. For example, the antigen binding protein may be used as an acute treatment of migraine, and/or as a prophylactic treatment to prevent or reduce the frequency and/or severity of symptoms, particularly pain symptoms, associated with a migraine attack.

Other embodiments further provide methods for treating or preventing a condition associated with CGRP R in a patient, comprising administering to a patient an effective amount of at least one isolated antigen-binding protein summarized above. In one embodiment, the condition is a headache, for example, a migraine headache or a cluster headache or another type of pain, e.g., a chronic pain; in another embodiment it is diabetes mellitus (type II) ; in another embodiment it is inflammation, particularly neurogenic inflammation; in another embodiment it is a cardiovascular disorder; in another embodiment it is a hemodynamic derangement associated with endotoxemia and sepsis; in another embodiment it is vasodialation.

In another embodiment, also provided is a method of inhibiting binding of CGRP to human CGRP R, e.g., the extracellular portion of CGRP R, in a patient comprising administering an effective amount of at least one antigen-binding protein provided herein and/or summarized above.

WHAT IS CLAIMED IS:

1. A method of making an antibody that selectively inhibits the human CGRP receptor as compared with human AM1, AM2, and AMY1 receptors, comprising:

(a) recovering antibodies from an immunized animal that bind both human CRLR polypeptide and human RAMP1 polypeptide in the human CGRP receptor, wherein the animal is one that has been administered an immunogen comprising:

(i) a soluble CGRP receptor, wherein the soluble CGRP receptor comprises the N-terminal extracellular domain (ECD) of human CRLR and the ECD of human RAMP1,

(ii) whole cells expressing full-length human CRLR and human RAMP1 polypeptides, or

(iii) membrane extracts of the cells in (ii);

(b) screening the recovered antibodies for inhibitory activity against the human CGRP receptor; and

(c) selecting antibodies that inhibit activity of the human CGRP receptor.

2. The method of claim 1, wherein said ECD of human CRLR comprises SEQ ID NO: 6 and said ECD of human RAMP1 comprises SEQ ID NO: 8.

3. The method of claim 1 or 2, wherein the soluble CGRP receptor comprises (i) the ECD of human CRLR fused to a human IgG1 Fc region via a glycine linker and (ii) the ECD of human RAMP1 fused to a human IgG1 Fc region via a glycine linker.

4. The method of claim 1, wherein the animal is a transgenic mouse containing human immunoglobulin loci.

5. The method of claim 1, wherein the recovered antibodies are screened for ability to block CGRP ligand binding to the human CGRP receptor.

6. The method of any one of claims 1 to 5, wherein the antibodies are monoclonal antibodies.