Ab085. In a related embodiment, the antibody does not compete with any one, two, three or more of antibodies selected from the group consisting of Ab053, Ab064, 83-7, Ab019, Ab088, and Ab089. Optionally, the antibody binds both human and murine insulin receptor or complex. In another embodiment, the antibody exhibits greater than or equal to 70% competition, e.g. at least 75% or at least 80% competition, with any one, two, three or all antibodies selected from the group consisting of Ab064, Ab062, Ab085, and Ab078. Optionally, the antibody exhibits no competition with any one, two, three or more of antibodies selected from the group consisting of Ab077, Ab001, Ab018, Ab030, Ab037, Ab079, Ab076, Ab083, Ab019, Ab088, Ab089, and Ab040. Optionally, the antibody binds both human and murine insulin receptor or complex.

[0054] In one aspect, there is provided a monoclonal antibody that binds to (i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or both (i) and (ii), with an equilibrium dissociation constant K_D of 10^{-5}M or less that is capable of weakening the binding affinity between insulin and insulin receptor by at least 3-fold, optionally up to 1000-fold, wherein the antibody binds (i) or (ii) in an allosteric manner. In certain embodiments, the antibody weakens the affinity between said insulin and insulin receptor by about 3-fold to 500-fold. In some embodiments, the binding affinity is any one of K_A, K_D, the ratio of on rate to off rate, or the ratio of off rate to on rate.

[0055] In some embodiments, for any of the antibodies described herein, the difference in binding affinity or binding rate parameter ranges from about 1.5-fold to about 1000-fold, or about 1.5-fold to about 500-fold, about1.5-fold to about 100-fold, or about 2-fold to 25-fold, or about 2-fold to about 50-fold, or about 1.5-fold to about 25-fold, or about 1.5-fold to about 50-fold, about 5-fold to about 500-fold, or about 5-fold to about 200-fold, e.g. at least about 1.5-fold, 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, 11-fold, 12-fold, 13-fold, 14-fold, 15-fold, 16-fold, 17-fold, 18-fold, 19-fold or 20-fold, or up to 500-fold, or up to 200-fold, or up to 150-fold, or up to 100-fold, or up to 90-fold, or up to 80-fold, or up to 70-fold, or up to 60-fold, or up to 50-fold, or up to 40-fold, up to 30-fold, up to 20-fold, or up to 10-fold, or up to 5-fold or up to 3-fold.

[0056] In a related embodiment, the antibody increases the EC50 of insulin signaling activity by about 2-fold to 1000-fold, optionally in a pAKT assay. In certain embodiments, the antibody increases the EC50 by at least about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950 or 1000-fold.

to an antibody as defined herein. Optionally small amounts of a preservative such as a bactericidal or bacteriostatic agent are also included in the composition.

[0069] In another aspect, there is provided a sterile composition comprising an antibody as defined herein and a sterile pharmaceutically acceptable diluent.

[0070] The disclosure further contemplates that the antibodies of the disclosure modulate binding between the INSR and insulin or insulin analogs or insulin mimetics. The antibodies of the disclosure preferably also exhibit desirable biological properties, including but not limited to enhancing glucose uptake in vitro or in vivo in animal models, and preferably the glucose uptake induced by exogenous insulin. In some embodiments, the antibodies are capable of increasing the rate or total amount of glucose uptake, or both.

[0071] In one embodiment, the disclosure contemplates a method of treating a disorder associated with insulin resistance, comprising administering to a subject in need thereof a positive modulating antibody or agonist antibody of the disclosure in an amount effective to treat insulin resistance. In a related embodiment, the treatment enhances glucose uptake. In a further embodiment, the enhanced glucose uptake is selected from the group consisting of an increase in the rate of glucose uptake, an increase in the total amount of glucose uptake, or both. It is further contemplated that the treatment reduces fasting blood glucose levels, in a subject having elevated levels of blood glucose, hyperglycemia or a disorder associated with insulin resistance, back toward the normal range of fasting blood glucose levels. In a related embodiment, the fasting blood glucose is reduced by approximately 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50% or more compared to an untreated subject.

[0072] In related embodiments, the treatment reduces elevated HbA1c levels, which are a marker of elevated glucose levels over the preceding several-month period, and are indicative of diabetes. In further embodiments, treatment improves impaired glucose tolerance. In one embodiment glucose tolerance is measured by glucose tolerance test (GTT).

[0073] In other embodiments, the treatment slows, reduces, or normalizes weight gain of a subject. In one embodiment, the treatment reduces or slows weight gain by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or 50% compared to an untreated subject. In some embodiments, the treatment slows, reduces, or normalizes weight loss of a subject. In one embodiment, the treatment reduces or slows weight loss by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45% or 50% compared to an untreated subject.

CLAIMS

We claim:

1. A monoclonal antibody that binds to (i) insulin receptor or (ii) a complex comprising insulin and insulin receptor, or both (i) and (ii), with an equilibrium dissociation constant K_D of 10^{-5}M or less that is capable of weakening the binding affinity between insulin and insulin receptor by at least 3-fold, optionally up to 1000-fold, wherein the antibody binds (i) or (ii) in an allosteric manner.

2. The antibody of claim 1, wherein the antibody is capable of weakening the binding affinity between said insulin and insulin receptor by 3-fold and 500-fold.

3. The antibody of claim 1, wherein the binding affinity is any one of K_A, K_D, the ratio of on rate to off rate, or the ratio of off rate to on rate.

4. The antibody of claim 1, wherein the antibody increases the EC50 of insulin signaling activity by 2-fold to 1000-fold, optionally in a pAKT assay.

5. The antibody of any of claims 1 to 4, wherein the antibody comprises a heavy chain variable region selected from the group consisting of SEQ ID NOs: 279, 241, 258, 155, and 228 and a light chain variable region selected from the group consisting of SEQ ID NOs: 139, 103, 119, 8 and 89.

6. The antibody of any of claims 1 to 5, wherein the antibody comprises

(a) the heavy chain variable region of any of Ab081 (SEQ ID NO: 279), Ab061 (SEQ ID NO: 241), Ab070 (SEQ ID NO: 258), Ab020 (SEQ ID NO: 155), Ab052 (SEQ ID NO: 228), Ab087 (SEQ ID NO: 169), Ab019 (SEQ ID NO: 160), Ab088 (SEQ ID NO: 153), Ab089 (SEQ ID NO: 154), Ab050 (SEQ ID NO: 226), Ab055 (SEQ ID NO: 231), Ab057 (SEQ ID NO: 233), Ab063 (SEQ ID NO: 244), Ab065 (SEQ ID NO: 246), Ab072 (SEQ ID NO: 260), Ab074 (SEQ ID NO: 262), and the light chain variable region of any of Ab081 (SEQ ID NO: 139), Ab061 (SEQ ID NO: 103), Ab070 (SEQ ID NO: 119), Ab020 (SEQ ID NO: 8), Ab052 (SEQ ID NO: 89), Ab087 (SEQ ID NO: 18), Ab019 (SEQ ID NO: 1), Ab088 (SEQ ID NO: 2), Ab089 (SEQ ID NO: 4), Ab050 (SEQ ID NO: 87), Ab055 (SEQ ID NO: 92), Ab057 (SEQ ID NO: 94), Ab063 (SEQ ID NO: 105), Ab065 (SEQ ID NO: 107), Ab072 (SEQ ID NO: 121), and Ab074 (SEQ ID NO: 123), or

(b) three heavy chain CDRs of any Ab081 (SEQ ID NO: 279), Ab061 (SEQ ID NO: 241), Ab070 (SEQ ID NO: 258), Ab020 (SEQ ID NO: 155), Ab052 (SEQ ID NO: 228), Ab087 (SEQ ID NO: 169), Ab019 (SEQ ID NO: 160), Ab088 (SEQ ID NO: 153), Ab089 (SEQ ID NO: 154), Ab050 (SEQ ID NO: 226), Ab055 (SEQ ID NO: 231), Ab057 (SEQ ID NO: 233), Ab063 (SEQ ID NO: 244), Ab065 (SEQ ID NO: 246), Ab072 (SEQ ID NO: 260), Ab074 (SEQ ID NO: 262), and three light chain CDRs of any of Ab081 (SEQ ID NO: 139), Ab061 (SEQ ID NO: 103), Ab070 (SEQ ID NO: 119), Ab020 (SEQ ID NO: 8), Ab052 (SEQ ID NO: 89), Ab087 (SEQ ID NO: 18), Ab019 (SEQ ID NO: 1), Ab088 (SEQ ID NO: 2), Ab089 (SEQ ID NO: 4), Ab050 (SEQ ID NO: 87), Ab055 (SEQ ID NO: 92), Ab057 (SEQ ID NO: 94), Ab063 (SEQ ID NO: 105), Ab065 (SEQ ID NO: 107), Ab072 (SEQ ID NO: 121), and Ab074 (SEQ ID NO: 123), optionally including one or two mutations in any one, two or three of such heavy or light chain CDRs, e.g., a conservative or non-conservative substitution; or

(c) all six CDRs of any of Ab081 (SEQ ID NO: 279, 139), Ab061 (SEQ ID NO: 241, 103), Ab070 (SEQ ID NO: 258, 119), Ab020 (SEQ ID NO: 155, 8), Ab052 (SEQ ID NO: 228, 89), Ab087 (SEQ ID NOs: 169, 18), Ab019 (SEQ ID NOs: 160, 1), Ab088 (SEQ ID NOs: 153, 2), Ab089 (SEQ ID NOs: 154, 4), Ab050 (SEQ ID NOs: 226, 87), Ab055 (SEQ ID NOs: 231, 92), Ab057 (SEQ ID NOs: 233, 94), Ab063 (SEQ ID NOs: 244, 105), Ab065 (SEQ ID NOs: 246, 107), Ab072 (SEQ ID NOs: 260, 121), and Ab074 (SEQ ID NOs: 262, 123).

7. The antibody of any of claims 1 to 6 that exhibits greater than or equal to 70% competition with any one, two, three or all antibodies selected from the group consisting of Ab061 (SEQ ID NO: 241, 103), Ab074 (SEQ ID NOs: 262, 123), Ab081 (SEQ ID NO: 279, 139), Ab020 (SEQ ID NOs: 155, 8), Ab019 (SEQ ID NOs: 160, 1), Ab087 (SEQ ID NOs: 169, 18), Ab088 (SEQ ID NOs: 2, 153), and Ab089 (SEQ ID NOs: 154, 4), optionally wherein the antibody binds human receptor or complex and not murine receptor or complex.

8. The antibody of claim 1 wherein the variable heavy chain is set out in SEQ ID NOs: 279, 258 or 241 and the variable light chain is set out in SEQ ID NOs: 139, 119 or 103.

9. The antibody of claim 1 comprising three heavy chain CDRs set out in SEQ ID NOs: 279, 258 or 241 and three light chain CDRs set out in SEQ ID NOs: 139, 119 or 103.

10. The antibody of claim 1 wherein the variable heavy chain is set out in SEQ ID NO: 279 and the variable light chain is set out in SEQ ID NO: 139.

11. The antibody of claim 1 comprising three heavy chain CDRs set out in SEQ ID NO: 279 and three light chain CDRs set out in SEQ ID NO: 139.

12. The antibody of any of claims 1 to 11, further comprising a human IgG1, IgG2, IgG3 or IgG4 heavy chain constant region.

13. The antibody of claim 12, further comprising a human light chain constant region.

14. The antibody of any of the preceding claims, wherein said antibody is a human antibody.

15. The antibody of any one of claims 1 to 14, wherein the antibody is conjugated to a hydrophobic moiety.

16. A method of preparing a sterile pharmaceutical composition, comprising adding a sterile pharmaceutically acceptable diluent to an antibody of any of claims 1 to 15.

17. A sterile composition comprising the antibody of any of claims 1 to 15 and a sterile pharmaceutically acceptable diluent.

18. Use an antibody of claims 1 to 15 in the manufacture of a medicament for treating a condition associated with hyperinsulinemia or excess insulin signaling.

19. The use of claim 18, wherein the condition is selected from the group consisting of cancer, insulinoma, Kaposi' s sarcoma, insulin overdose, hypoglycemia, nesidioblastosis (KATP-H1 Diffuse Disease, KATP-H1 Focal Disease, or " PHHI"), GDH-H1 (Hyperinsulinism/Hyperammonaemia Syndrome (HI/HA), leucine-sensitive hypoglycemia, or diazoxide-sensitive hypoglycemia), islet cell dysregulation syndrome, idiopathic hypoglycemia of infancy, Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI), Congenital Hyperinsulinism, hypoglycemia due to renal failure (acute of chronic), and hypoglycemia due to chronic kidney disease.

Insulin Receptor Binding Antibodies

Abstract

Antibodies that modulate insulin receptor signaling are provided.

No suitable figure