associated with various somatosensory signals, emotional state, discomfort, pain, thermal stress and thirst (Noakes et al. *Br J Sports Med.* August; 38(4): 511–514, 2004, J.W. Williamson, *Exp Physiol* 95: 1043–1048, 2010). This integrated mechanism works to preserve the integrity of the system by initiating muscle fatigue through inhibition of muscle recruitment, and as a result, maximal voluntary strength can be below the true maximal muscle force. Alteration in perceived effort, as is possible in the presence of a skeletal troponin activator, can mitigate fatigue.

[0005] The means to decrease fatigue in certain situations has therapeutic potential, especially in a number of disease settings, including heart failure. Muscle function can become compromised in disease by many mechanisms. Accordingly, there is a need for the development of new compounds that modulate skeletal muscle contractility and of new methods for improving resistance to skeletal muscle fatigue.

Summary

[0006] Provided are compounds, compositions and methods for improving resistance to skeletal muscle fatigue.

In one aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to skeletal muscle fatigue in a subject. In some ~~embodiments~~examples, the method comprises administering to a subject an effective amount of a skeletal muscle troponin activator. In some ~~embodiments~~examples, the skeletal muscle fatigue is selected from central fatigue, peripheral fatigue, and a combination thereof. In some ~~embodiments~~examples, the skeletal muscle troponin activator is a fast skeletal muscle troponin activator. In some ~~embodiments~~examples, the subject is suffering from a condition selected from peripheral artery disease, claudication, and muscle ischemia.

[0007] Also provided are methods for improving physical endurance or reducing exercise intolerance in a subject, comprising administering to the subject an effective amount of a skeletal muscle troponin activator.

[0008] In another aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to a fatigue in a skeletal muscle. Also provided are methods of improving resistance to fatigue in a skeletal muscle, comprising contacting the skeletal muscle with a skeletal muscle troponin activator, wherein the skeletal muscle troponin activator increases submaximal tension in the skeletal muscle.

[0009] Also provided are methods of improving resistance to fatigue in a skeletal muscle, comprising contacting the skeletal muscle with a skeletal muscle troponin activator, wherein the

skeletal muscle troponin activator reduces the intracellular calcium required by the skeletal muscle to generate force.

[0010] Also provided are methods for improving resistance to fatigue in a patient suffering from heart failure, comprising administering to the patient an effective amount of a skeletal muscle troponin activator. In some ~~embodiments~~examples, the method comprises administering to a

subject an effective amount of a skeletal muscle troponin activator. In some ~~embodiments~~examples, the skeletal muscle troponin activator is a fast skeletal muscle troponin activator. Similarly, the compounds, compositions and methods described and/or disclosed herein may be used to improve exercise tolerance.

[0011] In another aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for treating exercise intolerance in a patient suffering from heart failure.

Also provided are methods for treating exercise intolerance associated with heart failure in a subject, comprising administering to the subject an effective amount of a skeletal muscle troponin activator.

[0012] In another aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for improving physical endurance performance of a patient suffering from heart failure.

Also provided are methods for improving physical endurance of a patient suffering from heart failure, comprising administering to the subject an effective amount of a skeletal muscle troponin activator.

[0013] In another aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle of a patient suffering from heart failure.Also provided are methods for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle of a patient suffering from heart failure, comprising administering to the patient an effective amount of a skeletal muscle troponin activator.

[0014] In another aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for improving skeletal muscle function of a patient suffering from heart failure. Also provided are methods for improving skeletal muscle function of a patient suffering from heart failure, comprising administering to the patient an effective amount of a skeletal muscle troponin activator.

[0015] Also provided are methods for improving resistance to skeletal muscle fatigue in a subject in need thereof, comprising administering to the subject an effective amount of a skeletal muscle troponin activator, wherein the improvement in resistance to fatigue in the subject is determined by a bilateral heel-raise test. In some ~~embodiments~~examples, the bilateral heel-raise test comprises: instructing the subject to perform heel raises at regular intervals; and measuring one or more parameters selected from time to claudication onset, number of heel raises to claudication onset, work to claudication onset, time to maximal claudication fatigue, number of heel raises to maximal claudication fatigue, and work to maximal

claudication fatigue, wherein an increase in one or more of the parameters indicates an improvement in resistance to fatigue in the subject.

[0016] In this aspect, there is provided use of a skeletal muscle troponin activator in the manufacture of a medicament for determining the efficacy of a skeletal muscle troponin activator in a subject in improving resistance to a skeletal muscle fatigue; wherein said medicament is to be administered into the subject and wherein the improvement in resistance is determined by;

instructing the subject to perform heel raises at regular intervals; and

measuring one or more parameters selected from time to claudication onset, number of heel raises to claudication onset, work to claudication onset, time to maximal claudication fatigue, number of heel raises to maximal claudication fatigue, and work to maximal claudication fatigue,

wherein an increase in one or more of the parameters indicates an improvement in resistance to skeletal muscle fatigue in the subject.

Also provided are methods for determining the efficacy of a skeletal muscle troponin activator in improving resistance to skeletal muscle fatigue in a subject, comprising administering to the subject a bilateral heel-raise test.

[0017] In some ~~embodiments~~examples of any of the methods described herein, the skeletal muscle troponin activator is a fast skeletal muscle troponin activator. In some embodiments, the fast skeletal muscle activator selectively activates fast skeletal muscle.

[0018] In some ~~embodiments~~examples, the skeletal muscle troponin activator is a compound of Formula I, II, III, IV(a), IV(b), V(a), V(b), VI, VII(a), VII(b), VIII(a), VIII(b), IX, X(a), X(b), XI(a), XI(b), XII(a), XII(b), XII(c), XII(d), XII(e), XII(f), XII(g), XII(h), XII(i), XII(j), XII(k), XII(l), XII(m), XII(n), XII(o) or XIII, as defined herein.

[0019] In some ~~embodiments~~examples, the skeletal muscle troponin activator is a compound of Formula A or B, as defined herein.

[0020] Other aspects and embodiments will be apparent to those skilled in the art from the following detailed description.

Brief Description of the Figures

[0021] **FIG. 1** is a graph showing the effect of the skeletal muscle troponin activator Compound A on sub-maximal force development in a rat flexor digitorum brevis muscle *in vitro*.

[0022] **FIG. 2** is a graph showing the effect of Compound A on fatigue in a rat flexor digitorum brevis muscle *in vitro*.

[0023] **FIG. 3** is a graph showing the effect of Compound A on relaxation time in a rat flexor digitorum brevis muscle *in vitro*. The upper plot is for relaxation time and the lower plot is for force.

[0024] **FIG. 4** is a graph showing the effect of Compound A on fatigue in a rat extensor digitorum longus muscle *in situ*. The upper line is for Compound A and the lower line is for vehicle.

[0025] **FIG. 5** is a graph showing the effect of Compound A on time to fatigue in a rat flexor digitorum brevis muscle after femoral artery ligation *in vitro*. The lower plot is for FAL; the middle plot is for FAL + ≤ 0.5 mg/kg Compound A; the upper plot is for FAL + 1 mg/kg Compound A.

[0026] **FIG. 6A** is a graph showing the effect of Compound A on the isometric force-frequency relationship in a rat plantorflexor muscle *in situ* .

[0027] **FIG. 6B** is a graph showing the effect of Compound A on the isokinetic force-frequency relationship in a rat plantorflexor muscle *in situ*.

[0028] **FIG. 6C** is a graph showing the effect of Compound A on the force-velocity relationship in a rat plantorflexor muscle *in situ*.

[0029] **FIG. 6D** is a graph showing the effect of Compound A on the power output in a rat plantorflexor muscle *in situ*.

Claims:

1. ~~A method of improving resistance to skeletal muscle fatigue in a subject, the method comprising administering to the subject a therapeutically effective amount of~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to skeletal muscle fatigue in a subject.

2. The ~~method~~ use of claim 1, wherein the subject is suffering from a condition selected from peripheral artery disease, claudication, and muscle ischemia.

3. The use ~~method~~ of claim 1, wherein the subject is suffering from heart failure.

4. ~~A method of improving resistance to fatigue in a skeletal muscle, the method comprising contacting the skeletal muscle with~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving resistance to fatigue in a skeletal muscle.

5. The ~~method~~ use of any one of claims 1 to 4, wherein the skeletal muscle troponin activator increases submaximal tension in the skeletal muscle.

6. The use ~~method~~ of any one of claims 1 to 5, wherein the skeletal muscle troponin activator reduces the intracellular calcium required by the skeletal muscle to generate force.

7. The use ~~method~~ of any one of claims 1 to 3, wherein the improvement in resistance to fatigue in the subject is determined by a bilateral heel-raise test comprising:

instructing the subject to perform heel raises at regular intervals; and

measuring one or more parameters selected from time to claudication onset, number of heel raises to claudication onset, work to claudication onset, time to maximal claudication fatigue, number of heel raises to maximal claudication fatigue, and work to maximal claudication fatigue,

wherein an increase in one or more of the parameters indicates an improvement in resistance to fatigue in the subject.

8. The use ~~method~~ of claim 7, wherein the parameter is time to claudication onset.

9. The use ~~method~~ of claim 7, wherein the parameter is number of heel raises to claudication onset.

10. The use ~~method~~ of claim 7, wherein the parameter is work to claudication onset.

11. The use ~~method~~ of claim 7, wherein the parameter is time to maximal claudication fatigue.

12. The use ~~method~~ of claim 7, wherein the parameter is number of heel raises to maximal claudication fatigue.

13. The use ~~method~~ of claim 7, wherein the parameter is work to maximal claudication fatigue.

14. ~~A method for treating exercise intolerance in a patient suffering from heart failure comprising administering to the patient a therapeutically effective amount of~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for treating exercise intolerance in a patient suffering from heart failure.

15. ~~A method for improving physical endurance performance of a patient suffering from heart failure, comprising administering to the subject a therapeutically effective amount of~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving physical endurance performance of a patient suffering from heart failure.

16. ~~A method for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle of a patient suffering from heart failure, comprising administering to the patient a therapeutically effective amount of~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for increasing the function, activity, efficiency, sensitivity to calcium, or time to fatigue of skeletal muscle of a patient suffering from heart failure.

17. ~~A method for improving skeletal muscle function of a patient suffering from heart failure, comprising administering to the patient a therapeutically effective amount of~~ Use of a skeletal muscle troponin activator in the manufacture of a medicament for improving skeletal muscle function of a patient suffering from heart failure.

18. The ~~method~~ use of any one of claims 14 to 17, wherein the medicament further ~~comprising~~ comprises ~~administering to the subject~~ a second therapy.

19. The ~~method~~ use of claim 18, wherein the second therapy is selected from an antiplatelet drug, a diuretic, a calcium channel blocker, a beta blocker, an ACE inhibitor, a statin, an angiotensin II receptor antagonist, and an aldosterone antagonist.

20. The ~~method~~ use of claim 19, wherein the second therapy is selected from digoxin, aspirin, ticlopidine, clopidogrel, metoprolol, carvedilol, eplerenone, and spironolactone.

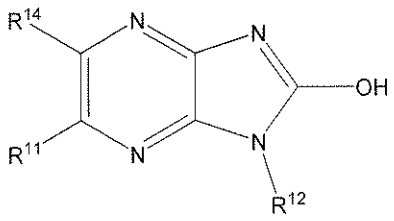
21. The ~~method~~ use of claim 18, wherein the second therapy is selected from angioplasty, stenting, and surgery.

22. The ~~method~~ use of any one of claims 18 to 21 wherein the skeletal muscle troponin activator and the second therapy are to be administered simultaneously to the subject.

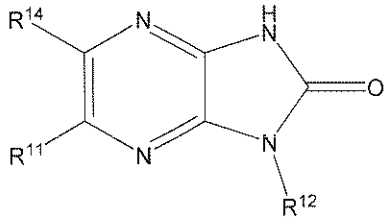
23. The ~~method~~ use of any one of claims 18 to 21 wherein the skeletal muscle troponin activator and the second therapy are to be administered sequentially to the subject.

24. The ~~method~~ use of any one of claims 1 to 23, wherein the skeletal muscle troponin activator is a fast skeletal muscle troponin activator.

25. The ~~method~~ use of any one of claims 1 to 24, wherein the skeletal muscle troponin activator is selected from compounds of Formula A and Formula B:



Formula A



Formula B

or a pharmaceutically acceptable salt thereof, wherein:

R^{11} is alkenyl or alkynyl;

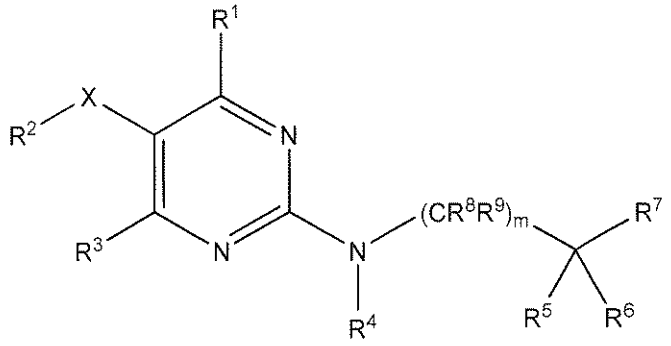
R^{14} is hydrogen; and

R^{12} is selected from 3-pentyl, 4-heptyl, 4-methyl-1-morpholinopentan-2-yl isobutyl, cyclohexyl, cyclopropyl, sec-butyl, tert-butyl, isopropyl, 1-hydroxybutan-2yl, tetrahydro-2H-pyran-4-yl, 1-methoxybutan-2-yl, 1-aminobutan-2-yl, and 1-morpholinobutan-2-yl;

provided that R^{11} is not hex-1-enyl.

26. The use ~~method~~ of claim 25, wherein the skeletal muscle troponin activator is 6-ethynyl-1-(pentan-3-yl)-1H-imidazo[4,5-b]pyrazin-2-ol, or a pharmaceutically acceptable salt thereof.

27. The use ~~method~~ of any one of claims 1 to 24, wherein the skeletal muscle troponin activator is selected from compounds of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from hydrogen, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)OR^a$, $C(O)NR^bR^c$, OR^a, NR^bR^c, C_{6-10} aryl and 5-10 membered heteroaryl;

R^2 is selected from C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl, 5-10 membered heteroaryl and NR^bR^c, wherein each of the C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl, 3-8 membered heterocycloalkenyl, C_{6-10} aryl and 5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, oxo, $(CH_2)_nOR^a$, $(CH_2)_nOC(O)R^a$, $(CH_2)_nOC(O)OR^a$, $(CH_2)_nOC(O)NR^bR^c$, $(CH_2)_nNR^bR^c$, $(CH_2)_nNR^dC(O)R^a$, $(CH_2)_nNR^dC(O)OR^a$, $(CH_2)_nNR^dC(O)NR^bR^c$, $(CH_2)_nNR^dC(O)C(O)NR^bR^c$, $(CH_2)_nNR^dC(S)R^a$, $(CH_2)_nNR^dC(S)OR^a$, $(CH_2)_nNR^dC(S)NR^bR^c$, $(CH_2)_nNR^dC(NR^e)NR^bR^c$, $(CH_2)_nNR^dS(O)R^a$, $(CH_2)_nNR^dSO_2R^a$, $(CH_2)_nNR^dSO_2NR^bR^c$, $(CH_2)_nC(O)R^a$, $(CH_2)_nC(O)OR^a$, $(CH_2)_nC(O)NR^bR^c$, $(CH_2)_nC(S)R^a$, $(CH_2)_nC(S)OR^a$, $(CH_2)_nC(S)NR^bR^c$, $(CH_2)_nC(NR^e)NR^bR^c$, $(CH_2)_nSR^a$, $(CH_2)_nS(O)R^a$, $(CH_2)_nSO_2R^a$, $(CH_2)_nSO_2NR^bR^c$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_nC_{6-10}$ aryl and $(CH_2)_n$5-10 membered heteroaryl, wherein each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $(CH_2)_n$3-8 membered heterocycloalkyl, $(CH_2)_nC_{6-10}$ aryl and $(CH_2)_n$5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 R^f substituents;

R^3 is selected from hydrogen, halogen, CN, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)OR^a$, $C(O)NR^bR^c$, OR^a, NR^bR^c, C_{6-10} aryl and 5-10 membered heteroaryl;

R^4 is selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^bR^c$ and SO_2R^a;

R^5 and R^6 are each independently selected from hydrogen, halogen, C_{1-6} alkyl and C_{1-6} haloalkyl;

or alternatively, R^5 and R^6 together with the carbon atom to which they are bound form a group selected from C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, 3-8 membered heterocycloalkyl

3-8 membered heterocycloalkenyl, C_{6-10} aryl, C_{7-11} aralkyl and 5-10 membered heteroaryl groups is optionally substituted with 1, 2, 3, 4 or 5 substituents selected from halogen, CN, OH, C_{1-6} alkoxy, C_{1-6} alkyl and C_{1-6} haloalkyl;

R^k, at each occurrence, is independently selected from halogen, CN, OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $NHC(O)C_{1-6}$ alkyl, $NHC(O)C_{7-11}$ aralkyl, $NHC(O)OC_{1-6}$ alkyl, $NHC(O)OC_{7-11}$ aralkyl, $OC(O)C_{1-6}$ alkyl, $OC(O)C_{7-11}$ aralkyl, $OC(O)OC_{1-6}$ alkyl, $OC(O)OC_{7-11}$ aralkyl, $C(O)C_{1-6}$ alkyl, $C(O)C_{7-11}$ aralkyl, $C(O)OC_{1-6}$ alkyl, $C(O)OC_{7-11}$ aralkyl, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, and C_{7-11} aralkyl substituent is optionally substituted with 1, 2 or 3 substituents selected from OH, C_{1-6} alkoxy, NH_2, $NH(C_{1-6}$ alkyl), $N(C_{1-6}$ alkyl)$_2$, $NHC(O)C_{1-6}$ alkyl, $NHC(O)C_{7-11}$ aralkyl, $NHC(O)OC_{1-6}$ alkyl, and $NHC(O)OC_{7-11}$ aralkyl;

or two R^k substituents bound to a single carbon atom, together with the carbon atom to which they are both bound, form a carbonyl group;

m is 0, 1 or 2;

n, at each occurrence, independently is 0, 1 or 2;

p is 0, 1 or 2; and

q is 0, 1 or 2.

28. ~~A method of determining the efficacy of a skeletal muscle troponin activator in a subject in improving resistance to skeletal muscle fatigue, the method comprising:~~

~~administering~~ Use of a skeletal muscle troponin activator ~~to the subject~~ in the manufacture of a medicament for determining the efficacy of a skeletal muscle troponin activator in a subject in improving resistance to skeletal muscle fatigue~~;~~, wherein said medicament is to be administered into the subject and wherein the improvement in resistance is determined by:

instructing the subject to perform heel raises at regular intervals; and

measuring one or more parameters selected from time to claudication onset, number of heel raises to claudication onset, work to claudication onset, time to maximal claudication fatigue, number of heel raises to maximal claudication fatigue, and work to maximal claudication fatigue,

wherein an increase in one or more of the parameters indicates an improvement in resistance to skeletal muscle fatigue in the subject.

29. The ~~method~~ use of claim 28, wherein the parameter is time to claudication onset.

30. The ~~method~~ use of claim 28, wherein the parameter is number of heel raises to claudication onset.

31. The ~~method~~ use of claim 28, wherein the parameter is work to claudication onset.

32. The ~~method~~ use of claim 28, wherein the parameter is time to maximal claudication fatigue.

33. The use ~~method~~ of claim 28, wherein the parameter is number of heel raises to maximal claudication fatigue.

34. The use ~~method~~ of claim 28, wherein the parameter is work to maximal claudication fatigue.