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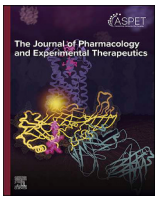

ARTICLE

An orally active estrogen receptor–related receptor agonist, SLU-PP-915, enhances aerobic exercise capacity

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ABSTRACT

Estrogen receptor–related receptors (ERRα, ERRβ, and ERRγ) are orphan nuclear receptors that regulate genes involved in mitochondrial biogenesis, oxidative phosphorylation, fatty acid oxidation, and the Krebs cycle. ERRs are essential for skeletal muscle adaptation to aerobic exercise and represent promising targets for exercise mimetic therapeutics. We previously developed an ERR pan-agonist, SLU-PP-332 (332), which improves aerobic performance in mice but lacks oral bioavailability. Here, we characterize SLU-PP-915 (915), a chemically distinct ERR pan-agonist that is orally bioavailable and exhibits potent in vivo exercise mimetic activity. Compound 915 enhances aerobic exercise performance (distance and duration) to a similar extent as 332 when administered intraperitoneally and maintains comparable efficacy when administered orally, adjusted for systemic exposure. Both compounds robustly induce the expression of DNA damage-inducible transcript 4 (*Ddit4*), a gene induced by acute aerobic exercise, with levels matching or exceeding levels induced by treadmill running, depending on the muscle examined. Notably, 915 synergizes with exercise training to further enhance *Ddit4* and mitochondrial gene expression. These findings position orally active ERR agonists such as 915 as promising agents for the treatment of metabolic disorders (eg, obesity, type 2 diabetes, and metabolic disease–associated steatohepatitis), cardiovascular disease (heart failure), and muscle-related pathologies, including sarcopenia and muscular dystrophies. SLU-PP-915 offers a valuable chemical tool for exploring the chronic therapeutic potential of ERR activation.

Significance Statement: The nuclear receptor estrogen receptor–related receptor plays an important role in driving the physiological adaptations to exercise. The article describes the ability of a pan-estrogen receptor–related receptor agonist SLU-PP-915, which also displays oral bioavailability, to enhance exercise capacity.

1. Introduction

The pleiotropic beneficial effects of exercise training on physiology integrate into multiorgan adaptations, improving overall health and mitigating the risks of cardiometabolic and age-related diseases.[1,2] Exercise mimetics are generally defined as pharmacological agents (synthetic or natural) that mimic at least some of the biological effects of physical exercise. Although physical activity remains one of the most efficacious therapeutic interventions for a range of diseases, poor long-term adherence, exercise intolerance, and preexisting disability are constraints that limit broad application.[3–5] Exercise mimetics have the ability to induce at least some aspects of exercise-training physiological adaptations independent of physical activity, thus potentially filling gaps in clinical exercise interventions.

The estrogen receptor–related receptors (ERRs) are a group of nuclear receptors composed of 3 members (ERRα, ERRβ, and ERRγ) that share substantial structural homology with the estrogen

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receptor but that do not bind estrogens.[6] ERRs are constitutively active orphan receptors expressed in high-energy-demand tissues such as skeletal muscle.[7] They play a key role in skeletal muscle physiology, including but not limited to metabolism, fiber type determination/distribution, autophagy, vascularization, and regeneration.[8–13] Whole-body ERRα deletion led to reduced skeletal muscle mass, impaired aerobic exercise capacity, and metabolic dysfunctions.[14] Skeletal muscle–specific ERRα knockout mice displayed a decrease in mitochondrial biogenesis and muscle repair.[12] Increasing the activity of ERRγ in skeletal muscles via targeted overexpression uncovered major roles of ERRγ in aerobic exercise capacity, oxidative fiber type differentiation, angiogenesis, and mitochondrial biogenesis.[15,16] Localized disruption of ERR in skeletal muscles has a tremendous impact on overall aerobic exercise performance. Deletion of both ERRα and ERRγ in skeletal muscle resulted in severe aerobic exercise intolerance, profound fiber type redistribution from oxidative to glycolytic, and impaired skeletal muscle fiber contractile functions.[17,18] A recent study demonstrates that ERRα and ERRγ play collaborative roles in the energetics of skeletal muscle directing the expression of mitochondrial energetic genes but also display distinct roles in regulation of PGC-1α–induced mitochondrial biogenesis suggesting a complex role in the regulation of both innate and adaptive bioenergetics.[19]

ERR$\alpha$was initially characterized as “undruggable” owing to the small size of the ligand-binding pocket.[20] However, ERRα inverse agonists were described, and a crystal structure of the ERRα ligand binding domain complex with an inverse agonist has been obtained.[21,22]Development of synthetic ERRα agonists has been considerably more challenging, although we and others have had recent success.[8,23–28] Strikingly, treating sedentary wild-type mice with the pan-ERR agonist SLU-PP-332 for 2 weeks enhanced their aerobic exercise capacity by 50% without any form of exercise intervention.[26] The mechanisms through which SLU-PP-332 may boost physical fitness involve skeletal muscle ERR signaling because the effects were lost in a skeletal muscle–specific ERRα knockout mouse.[26] Transcriptomic analyses of the skeletal muscles of mice treated with SLU-PP-332 pinpointed a potent induction of *Ddit4*, a gene associated with acute aerobic exercise adaptations. Altogether, these data invigorated interest in developing improved ERR agonists, particularly ones that may have oral bioavailability (SLU-PP-332 does not have oral bioavailability). Continued efforts to produce an ERR agonist with improved pharmacokinetic properties led to the development of SLU-PP-915, a more potent pan-ERR agonist arising from a distinct chemical scaffold that equipotently targets ERRα and ERRγ.[24,25] Similar to SLU-PP-332, SLU-PP-915 improves cardiac function in a mouse model of heart failure with reduced ejection fraction.[24] We have demonstrated that both SLU-PP-332 and SLU-PP-915 improve cardiac function in a heart failure model,[24] but the effects of SLU-PP-915 on aerobic exercise capacity have not yet been examined. Here, we examined the acute and chronic effects of oral administration of SLU-PP-915 on aerobic exercise capacity and demonstrated that this pan-ERR agonist displays similar activity to SLU-PP-332 even though it has a very distinct chemical structure.

2. Materials and methods

2.1. Animals

Male C57BL/6 mice (10 weeks old) obtained from Jackson Laboratories were maintained under a 12:12 light cycle at ambient temperatures (22–25 °C) and had free access to drinking water and Chow (PicoLab Rodent Diet 20; 13% kcal from fats; LabDiet). These studies were conducted at Washington University in accordance with procedures approved by the Institutional Animal Care and Use Committee.

2.2. Pharmacological intervention

Mice (n = 3–6/group) were orally or intraperitoneally administered SLU-PP-332 or SLU-PP-915 (0.2–32 mg/kg; once or twice a day with 10 ± 2 hours between doses) or vehicle (intraperitoneal formulation: 10% DMSO, 10% Cremophor EL (Sigma-Aldrich), 80% PBS; oral formulation: 100% sugar-free compounding oral suspension [HUMCO 9416001 Flavor Sweet SF]) for up to 7 days. At the end of each experiment, mice were euthanized via CO_2 asphyxiation or exsanguination. Plasma and skeletal muscles were collected between 1 and 6 hours after the last dose and stored at −80 °C until processed and analyzed.

2.3. Aerobic exercise intervention

When applicable, mice were subjected to only 1 of the following exercise interventions: a maximal aerobic exercise test or a 1-hour bout of aerobic exercise. Both interventions were performed on a treadmill (Columbus) after adequate acclimation via short walking sessions at a low speed of 2 m/min for 10 min/d. The maximal aerobic exercise capacity test began with 2 warm-up steps of 2 minutes at 10 m/min and 6 minutes at 12 m/min for 6 minutes immediately followed by a classic progressive maximal exercise test protocol increasing the speed by 2 m/min every 2 minutes until exhaustion. Exhaustion was determined by a lack of responsiveness to 10 consecutive 3-milliseconds of electrical shocks. The time and distance run from the initiation of the warm-up to exhaustion were recorded. The 1-hour bout of aerobic exercise intervention consisted of a single 1-hour run session at 14 m/min.

2.4. Gene expression analyses

RNA was extracted using TRIzol (Invitrogen) and reverse-transcribed into cDNA using qScript cDNA Synthesis Kit (Quanta Biosciences) according to the manufacturer’s instructions. Real-time polymerase chain reaction (PCR) was performed using a SYBR-green PCR master mix kit (Thermo Fisher Scientific) with custom-made primers (Integrated DNA Technologies). All samples were run in duplicates, and relative gene expression was calculated with the $2^{-\Delta\Delta Ct}$ formula using *m36B4*, a gene encoding for a ribosomal protein, as endogenous control. Primer sequences (5′–3′) used are shown in the following: Ddit4: forward sequence = CCTGCGCGTTTGCTCATGCC; reverse sequence = GGCCGCACGGCTCACTGTAT; 36b4: forward sequence = ACCTCCTTCTTCCAGGCTT; reverse sequence = CCACCTTGTCTCCAGTCTTT; mtNd1: forward sequence = GCTTTACGAGCCGTAGCCCA; reverse sequence = GGGTCAGGCTGGCAGAAGTAA; mtNd2: forward sequence = CCTCCTGGCCATCGTACTCA; reverse sequence = GAATGGGGCGAGGCCTAGTT; mtNd3: forward sequence = TAGTTGCATTCTGACTCCCCCA; reverse sequence = GAGAATGGTAGACGTGCAGAGC; mtNd4: forward sequence = CGCCTACTCCTCAGTTAGCCA; reverse sequence = TGATGTGAGGCCATGTGCGA; mtNd4l: forward sequence = AGCTCCATACCAATCCCCATCAC; reverse sequence = GGACGTAATCTGTTCCGTACGTGT; mtNd5: forward sequence = GGCCCTACACCAGTTTCAGC; reverse sequence = AGGGCTCCGAGGCAAAGTAT; mtNd6: forward sequence = CTTGATGGTTTGGGAGATTGG; reverse sequence = ACCCGCAAACAAAGATCACC; Ndufv1: forward sequence = CTTCCCCACTGGCCTCAAG; and reverse sequence = CCAAAACCCAGTGATCCAGC.

2.5. Mitochondrial DNA quantification

DNA was extracted using a commercially available kit (Qiagen) according to the manufacturer's instructions. Mitochondrial content was determined by quantitative PCR based on mitochondrial gene transcripts using SYBR Select Master Mix (Applied Biosystems), quantified via the $2^{-\Delta\Delta Ct}$ formula method, where the nuclear DNA-encoded gene *Nrduv1* served as endogenous control. Primer sequences are provided earlier.

2.6. Statistical analysis

Data are expressed as mean ± SEM. To determine significant differences across groups, data were analyzed with an appropriate statistical test with respect to the experimental design associated with the dataset. When comparing only 2 groups, Student's *t* tests were applied. When comparing 3 or more groups, one-way ANOVA followed by a post hoc test. A *P* value of $< .05$ was considered statistically significant.

3. Results

3.1. Identification of SLU-PP-915 as an exercise mimetic drug

Evaluation of potential exercise-mimetic activity began with an assessment of aerobic exercise capacity after 1 week of dosing. Specifically, we compared maximal running performance between mice treated with SLU-PP-915 and SLU-PP-332, a validated ERR agonist,[26] or vehicle. Notably, we found that SLU-PP-915 enhanced running capacity to a similar extent as did SLU-PP-332, but with less than half the dose, thus demonstrating a significant improvement in potency in vivo. Indeed, SLU-PP-332 and SLU-PP-915-treated groups performed significantly better than vehicle-treated mice on a treadmill run-to-exhaustion test with approximately 50% higher maximal running time and distance (Fig. 1, A and B). We further characterized the exercise-mimetic effects of SLU-PP-915 by examining *Ddit4* gene expression changes in skeletal muscles upon acute dosing. *Ddit4* is a gene involved in acute aerobic exercise adaptation that we previously identified as an ERR target gene and acutely induced by SLU-PP-332.[26] Here, we use it as an ERR target engagement biomarker of exercise-mimetic activity to compare the efficacy of SLU-PP-915 to that of SLU-PP-332 or a bout of aerobic exercise. In this experiment, mice from a distinct cohort were first assigned to an exercise or a pharmacological intervention. In the exercise intervention subcohort, half of the mice were subjected to a single 1-hour running session (run), whereas the other half remained sedentary and served as unexercised controls (no run). In the pharmacological intervention subcohort, mice were divided into 3 groups, each subjected to a single bolus of one of the following: SLU-PP-332, SLU-PP-915, or vehicle. Induction of *Ddit4* in skeletal muscle was assessed 1 hour after the initiation of the exercise intervention or 1 hour after respective pharmacological interventions. As previously described, an acute dose of SLU-PP-332 induced the expression of *Ddit4* gene in the quadricep and soleus muscles by approximately 3-fold versus vehicle-treated mice (Fig. 1, C and D). Importantly, in the quadricep muscle, we observed that SLU-PP-915 induced *Ddit4* expression more robustly than did SLU-PP-332, with about twice the magnitude of the effect reaching nearly 6-fold versus vehicle-treated mice (Fig. 1C). This effect was comparable to the effect of a 1-hour bout of aerobic exercise. In the soleus, a plantarflexor muscle primarily composed of type I (slow/oxidative) fibers, both SLU-PP-332 and SLU-PP-915-treated groups exhibited a significantly higher expression of *Ddit4* than the vehicle-treated group. However, an acute bout of aerobic exercise did not significantly impact *Ddit4* gene expression in this muscle (Fig. 1D).

3.2. SLU-PP-915 displays oral bioavailability and activity

In order to develop ERR agonists for potential clinical utility, we sought to identify compounds with oral bioavailability and characterize their in vivo efficacy. Additionally, for many important

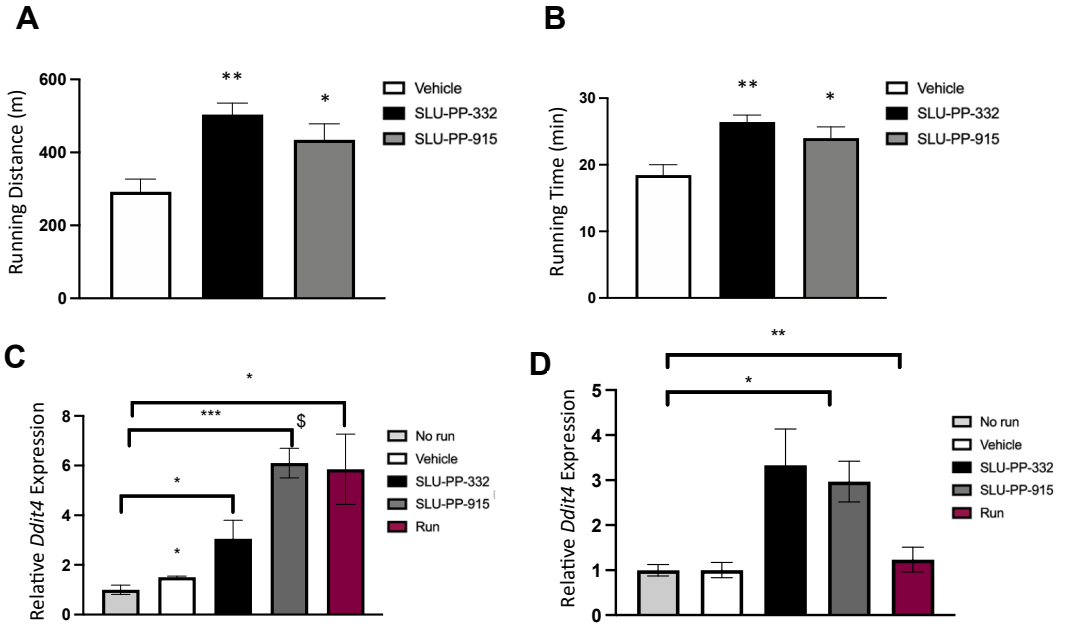

Fig. 1. SLU-PP-915 enhances exercise capacity and induces *Ddit4* expression in a similar manner to SLU-PP-332. Running distance (A) and time (B) to exhaustion of male mice treated with an acute dose of SLU-PP-332 (50 mg/kg, i.p., black bar), SLU-PP-915 (20 mg/kg, i.p., gray bar), or vehicle control (intraperitoneal, white bar) for 1 hour before running ($n = 6$/group). *Ddit4* expression from (C) quadriceps or (D) soleus from the same mice indicated earlier was determined by qPCR. Mice were euthanized when they reached exhaustion and tissues were collected ($n = 6$/group). $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$; $^{\$}P < .05$, between SLU-PP-332 and SLU-PP-915.

animal studies, intraperitoneal administration, particularly twice a day, is not feasible for long-term studies. Thus, we explored the use of micropipette-guided drug administration (MDA). This technique employs a pharmaceutical-grade oral suspension compounding routinely used in human pediatric patients. Its sweet taste is attractive to mice, and upon adequate training, mice will voluntarily consume the drug solution without restraint or penetration of body cavities.[29,30] To further characterize the pharmacokinetic properties of SLU-PP-915, we performed an acute dose–response experiment in which drug plasma levels were examined 1 hour after a single intraperitoneal or MDA bolus of SLU-PP-915. As expected, SLU-PP-915 plasma concentration increased proportionally with the administered dose (Fig. 2A). When using MDA, we used a drug suspension (instead of solution) that may explain the plateau observed in the dose–response experiment (Fig. 2A). We then assessed the oral plasma exposure and half-life SLU-PP-915 using oral gavage at 3 different doses (Fig. 2B). Plasma levels of the drug were dose proportional, and the half-life ranged from 18 to 28 minutes. To examine the impact of repeated MDA (32 mg/kg) or i.p. (20 mg/kg) administration, we compared SLU-PP-915 plasma concentration collected 1 hour after a single bolus (acute) versus 1 hour after the last dose of a chronic dosing regimen (twice a day for 7 days). Like intraperitoneal administered treatment regimens, repeated MDA did not result in the accumulation of the drug over time. One hour after a single dose or 1 hour after the 14th dose of the chronic intervention, SLU-PP-915 plasma levels were equivalent (Fig. 2C). Following the dosing, we examined *Ddit4* expression in the quadricep muscle and observed a significant drug–dependent upregulation in mice treated with either the acute or chronic dosing regimens (Fig. 2D).

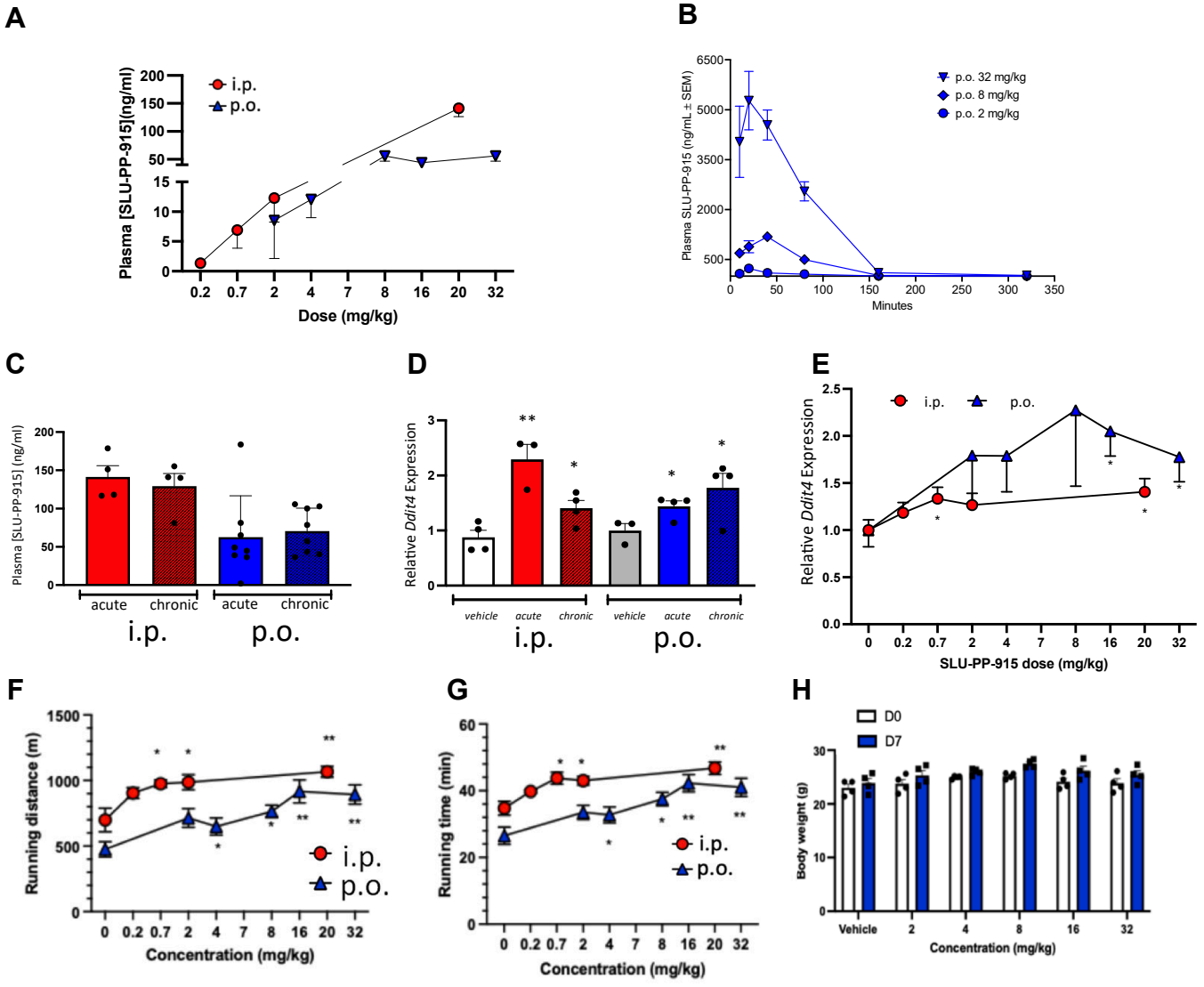

Fig. 2. Both intraperitoneal and oral administration of SLU-PP-915 display the same exercise mimetic activity. (A) Plasma concentration of SLU-PP-915 1 hour after a single dose (by mouth administration, MDA) ($n = 4$/group). (B) Plasma concentration of SLU-PP-915 after various by mouth doses (2, 8, and 32 mg/kg), illustrating a dose-dependent increase in exposure. (C) Assessment of potential accumulation of SLU-PP-915 by comparison of plasma levels following (1 hour post dose) a single intraperitoneal or by mouth dose or after 7 days of twice a day dosing (14 total doses) and plasma levels following (1 hour post dose) the last dose. Intraperitoneal doses were at 20 mg/kg, while by mouth doses were at 32 mg/kg. (D) *Ddit4* expression from quadriceps of the same mice treated in (C). Mice were sacrificed 1 hour after the last dose. (E) Comparison of quadriceps *Ddit4* expression from mice treated with a dose response of SLU-PP-915 (twice a day) for 7 days by mouth (blue) or intraperitoneal (red), ran until exhaustion, and sacrificed immediately afterward. Comparison of running distance (F), running time (G), and body weight (H) of the mice treated twice a day for 7 days with intraperitoneal injection (red) or by mouth (blue) of various doses of SLU-PP-915 ($n = 4$/ group). *$P < .05$; **$P < .01$. mt ND1-6, mitochondrial encoded NADH dehydrognease subunit 1-6.

In mice dosed intraperitoneally, the magnitude of the effect of SLU-PP-915 was 63% higher upon acute dosing than the 7-day treatment regimen (Fig. 2D). This decrease was not observed in chronic MDA group (Fig. 2D). To assess the efficacy of MDA of SLU-PP-915 to intraperitoneal administration, we submitted separate groups of mice to a chronic MDA or intraperitoneal dosing regimen (dose–response) and assessed their aerobic exercise performance via the run-to-exhaustion test on the treadmill and examined quadricep *Ddit4* induction. We observed a comparable activation of *Ddit4* expression in both intraperitoneal and MDA groups (Fig. 2E). A similar increase in running distance (Fig. 2F) and running time (Fig. 2G) was observed in the intraperitoneal and MDA groups relative to vehicle-treated control mice. Similar to SLU-PP-332, treatment with SLU-PP-915 in wild-type mice over 7 days did not result in a significant change in body weight (Fig. 2H).[26]

3.3. Oral SLU-PP-915 administration improves exercise training capacity

In order to test the effect of SLU-PP-915 on aerobic exercise performance, exercise-trained (1 hour daily running on a treadmill at 14 m/min) or untrained mice were treated with SLU-PP-915 using MDA for 7 days, twice a day (32 mg/kg). We first examined *Ddit4* induction and mitochondrial gene expression in skeletal muscle. We observed an increase in *Ddit4* expression with exercise training compared to sedentary mice treated with vehicle control, as expected (Fig. 3A). Interestingly, there was an additive effect of exercise and SLU-PP-915 treatment on *Ddit4* induction (Fig. 3A). Mitochondrial gene expression (*mtNd1*, *mtNd2*, *mtNd3*, *mtNd4*, *mtNd4l*, *mtNd5*, and *mtNd6*) as assessed by qPCR was significantly elevated in untrained mice (no run) treated with SLU-PP-915. Importantly, treatment with SLU-PP-915 increased mitochondrial DNA content in both sedentary and trained mice (Fig. 3B). To gain additional functional insight, we submitted separate groups of mice to a chronic MDA regimen (dose–response) in combination with 1 hour of daily exercise. We assessed their aerobic exercise performance via the run-to-exhaustion test on the treadmill and examined quadricep *Ddit4* induction. We observed a dose–dependent increase in *Ddit4* expression as well as increased aerobic exercise performance with increasingly higher running times (Fig. 3C) and distances (Fig. 3D). Strikingly, the dose–response curves of *Ddit4* induction and running performance followed a similar pattern, indicating that *Ddit4* induction may serve as a surrogate biomarker of ERR agonist efficacy.

4. Discussion

Lack of exercise is associated with an increased risk of obesity and metabolic disorders such as diabetes and muscle dysfunction.[31] Exercise can be classified either as aerobic (endurance-based) or anaerobic (resistance-based) activity that leads to physical and metabolic adaptations. One of the key molecular adaptations to acute aerobic exercise is a transient increase in expression of *Ddit4*. Ddit4 plays a critical role in mediating exercise capacity, as indicated by the fact that mice deficient in *Ddit4* display impaired exercise capacity as well as metabolic disorders.[32]

ERRs are known to be involved in exercise, with skeletal-specific overexpression of ERRγ increasing running capacity,[11] and ERRα-null mice have decreased muscle mass and impaired exercise endurance.[14] We and others have developed synthetic

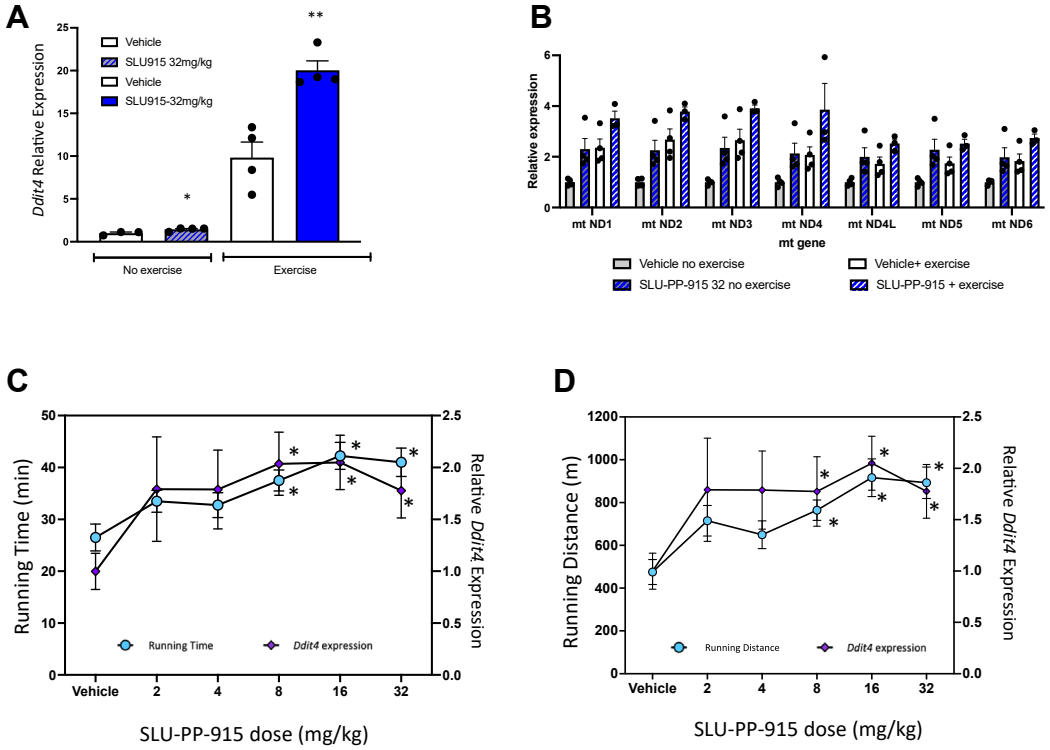

Fig. 3. Combination of chronic oral administration of SLU-PP-915 and exercise improves running capacity. Ddit4 expression in the quadriceps (A) of mice subjected to a chronic (7 days, intraperitoneal, twice a day), with SLU-PP-915 (32 mg/kg), combined with 1 hour of daily running. Mitochondrial DNA content (B) from quadriceps from the same mice as described in (A) ($n = 4$/group). Representation of Ddit4 expression compared to running time (C) and distance (D) of the mice treated for 7 days (by mouth, twice a day) with a dose response of SLU-PP-915 and ran for 1 hour each day ($n = 4$/group). For all experiments, mice were sacrificed 1 hour after the last dose. *$P < .05$; **$P < .01$.

ligands capable of activating ERRα both in vitro and in vivo.[8,23–26,28] We have identified SLU-PP-332, an ERR agonist, as an exercise mimetic drug, inducing running capacity and activating *Ddit4* expression. We recently described that SLU-PP-332 administration leads to a decrease in obesity and improves glucose homeostasis in mice fed with a chow diet and in 2 models of metabolic disorders (diet-induced obesity and *ob/ob* mice).[23] However, SLU-PP-332 demonstrated an unfavorable pharmacokinetic profile, including low solubility and lack of oral bioavailability, which restricts its overall utility for a range of long-term preclinical translational studies. Here, we have demonstrated that SLU-PP-915, a structurally distinct pan-ERR agonist with improved pharmacokinetic properties, replicates 3 key exercise mimetic adaptations produced by SLU-PP-332: (1) an acute induction of Ddit4 in skeletal muscles, (2) an enhancement of aerobic exercise performance, and (3) an increase in muscle mitochondrial DNA content. More importantly, this study provides the initial evidence of the first orally bioavailable ERR agonist with demonstrated in vivo efficacy, thereby opening new avenues for translational research.

The World Health Organization estimates that 3.3 million people die around the world each year due to a lack of physical activity, making it the fourth leading underlying cause of mortality. Physical activity has beneficial effects on diverse diseases, such as diabetes and cancer. Inactivity increases the risk of the costliest medical conditions, such as stroke, cardiovascular diseases, falls and hip fractures, and depression. Obesity is another condition that can reduce capacity for physical activity, and therefore, exercise mimetics could deliver therapeutic benefits and enhance fat mass loss. The combination of exercise mimetics with lifestyle interventions (enhancing physical activity and dietary health) might act synergistically to deliver long-lasting therapeutic efficacy. Our data suggest that ERR agonists act as exercise mimetics and may hold utility for the treatment of these diseases, where physical activity/exercise is therapeutic. Exercise mimetics would be particularly relevant to patients living with conditions that can be reversed by exercise training interventions, but who have limited physiological ability to reach the amount (volume) and vigor (intensity) required to achieve substantial therapeutic benefits. Morbid obesity is a critical condition that could greatly benefit from exercise training interventions. However, such interventions are often hindered by severe mobility limitations and/or deficiencies in aerobic fitness. In this case, exercise mimetics may serve as a standalone long-term “exercise” treatment or as a strategy to elevate baseline fitness to a level where adequate exercise intervention becomes feasible. Another ever-continuing constraint that could be addressed by exercise mimetics is the poor long-term adherence to exercise training interventions. In the general population, more than 95% of people who register at a traditional gym (unsupervised exercise) drop out within a year.[33] In bariatric surgery patients, rates of nonadherence to supervised exercise intervention as high as 51% have been reported.[34] Exercise mimetics may also aid in addressing this issue.

Physical activity has been considered to be a promising intervention for the prevention and treatment of cardiovascular diseases.[35] Cardiovascular benefits of exercise training include enhanced cardiac and vascular functions, skeletal muscle remodeling, and improved insulin sensitivity.[35] One of the challenges to implementing exercise intervention in patients with cardiovascular disease is reduced exercise tolerance. Exercise mimetics might be particularly valuable in mimicking the beneficial effects of exercise in individuals whose capacity for physical activity is reduced. Furthermore, exercise mimetics could benefit patients with stroke not only via cardiovascular benefits but also via neuroprotective impacts on the brain. In more general terms of cognitive function, physical exercise has clearly been demonstrated to have beneficial effects on cognition both in rodent models and in humans.[36–42] Interestingly, mice lacking neuronal ERRγ display reduced mitochondrial oxidative phosphorylation and reduced cognitive function as well[43] which suggests that increasing ERR activity via ERR agonism in the brain may have beneficial effects.

5. Conclusion

We have demonstrated that an ERR pan-agonist (SLU-PP-915) with a distinct chemical scaffold from that of SLU-PP-332 displays similar exercise mimetic activity. Importantly, both of these compounds also induce a key gene that is a driver of the acute aerobic exercise transcriptional program, *Ddit4*. SLU-PP-915 dose-dependently increases maximal exercise capacity, which is also correlated with the level of *Ddit4* induction. Finally, SLU-PP-915 is the first ERR agonist shown to have oral bioavailability and demonstrated efficacy when administered orally. Such compounds may have wide utility in the treatment of a range of diseases where physical exercise improves the pathology.

Abbreviations

Ddit4, DNA damage inducible transcript 4; ERR, estrogen receptor–related receptor; MDA, micropipette-guided drug administration; PCR, polymerase chain reaction.

Financial support

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Conflict of interest

SLU-PP-915 is covered under the intellectual property of Saint Louis University, with Thomas P. Burris as an inventor. Thomas P. Burris is also a stockholder in Myonid Therapeutics, Inc, and Pelagos Pharmaceuticals, Inc, which are both active in developing ERR agonists.

Data availability

The raw data supporting the conclusion of this article will be made available by the authors without undue reservation.

CRediT authorship contribution statement

Cyrielle Billon: Conceptualization, Investigation, Methodology, Writing – original draft. **Kevin Appourchaux**: Investigation, Methodology. **Isabelle Côté**: Investigation, Methodology. **Thomas P. Burris**: Conceptualization; Writing – review and editing.

References

1. Febbraio MA. Exercise metabolism in 2016: health benefits of exercise—more than meets the eye!. *Nat Rev Endocrinol*. 2017;13(2):72–74. https://doi.org/10.1038/nrendo.2016.218
2. Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. *Nat Rev Cardiol*. 2018;15(12):731–743. https://doi.org/10.1038/s41569-018-0065-1
3. Collins KA, Huffman KM, Wolever RQ, et al. Determinants of dropout from and variation in adherence to an exercise intervention: the STRRIDE randomized trials. *Transl J Am Coll Sports Med*. 2022;7(1):e000190. https://doi.org/10.1249/tjx.0000000000000190

4. Sachdev V, Sharma K, Keteyian SJ, et al. Supervised exercise training for chronic heart failure with preserved ejection fraction: a scientific statement from the American Heart Association and American College of Cardiology. *Circulation*. 2023;147(16):e699–e715. https://doi.org/10.1161/CIR.0000000000001122
5. Fan W, Evans RM. Exercise mimetics: impact on health and performance. *Cell Metab*. 2017;25(2):242–247. https://doi.org/10.1016/j.cmet.2016.10.022
6. Giguère V, Yang N, Segui P, Evans RM. Identification of a new class of steroid hormone receptors. *Nature*. 1988;331(6151):91–94. https://doi.org/10.1038/331091a0
7. Giguère V. Transcriptional control of energy homeostasis by the estrogen-related receptors. *Endocr Rev*. 2008;29(6):677–696. https://doi.org/10.1210/er.2008-0017
8. Losby M, Hayes M, Valfort A, et al. The estrogen receptor-related orphan receptors regulate autophagy through TFEB. *Mol Pharmacol*. 2024;106(4):164–172. https://doi.org/10.1124/molpharm.124.000889
9. Sopariwala D, Nguyen H, Narkar V. Estrogen-related receptor signaling in skeletal muscle fitness. *Int J Sports Med*. 2023;44(9):609–617. https://doi.org/10.1055/a-2035-8192
10. Sopariwala DH, Rios AS, Park MK, Song MS, Kumar A, Narkar VA. Estrogen-related receptor alpha is an AMPK-regulated factor that promotes ischemic muscle revascularization and recovery in diet-induced obese mice. *FASEB Bioadv*. 2022;4(9):602–618. https://doi.org/10.1096/fba.2022-00015
11. Narkar VA, Fan W, Downes M, et al. Exercise and PGC-1α-independent synchronization of type I muscle metabolism and vasculature by ERRγ. *Cell Metab*. 2011;13(3):283–293. https://doi.org/10.1016/j.cmet.2011.01.019
12. LaBarge S, McDonald M, Smith-Powell L, Auwerx J, Huss JM. Estrogen-related receptor-α (ERRα) deficiency in skeletal muscle impairs regeneration in response to injury. *FASEB J*. 2014;28(3):1082–1097. https://doi.org/10.1096/fj.13-229211
13. Sopariwala DH, Likhite N, Pei G, et al. Estrogen-related receptor alpha is involved in angiogenesis and skeletal muscle revascularization in hindlimb ischemia. *FASEB J*. 2021;35(5):e21480. https://doi.org/10.1096/fj.202001794RR
14. Perry MC, Dufour CR, Tam IS, B'Chir W, Giguère V. Estrogen-related receptor-alpha coordinates transcriptional programs essential for exercise tolerance and muscle fitness. *Mol Endocrinol*. 2014;28(12):2060–2071. https://doi.org/10.1210/me.2014-1281
15. Rangwala SM, Wang X, Calvo JA, et al. Estrogen-related receptor gamma is a key regulator of muscle mitochondrial activity and oxidative capacity. *J Biol Chem*. 2010;285(29):22619–22629. https://doi.org/10.1074/jbc.M110.125401
16. Sopariwala DH, Rios AS, Saley A, Kumar A, Narkar VA. Estrogen-related receptor gamma gene therapy promotes therapeutic angiogenesis and muscle recovery in preclinical model of PAD. *J Am Heart Assoc*. 2023;12(16):e028880. https://doi.org/10.1161/JAHA.122.028880
17. Sopariwala DH, Rios AS, Pei G, et al. Innately expressed estrogen-related receptors in the skeletal muscle are indispensable for exercise fitness. *FASEB J*. 2023;37(2):e22727. https://doi.org/10.1096/fj.202201518R
18. Wattez JS, Eury E, Hazen BC, et al. Loss of skeletal muscle estrogen-related receptors leads to severe exercise intolerance. *Mol Metab*. 2023;68:101670. https://doi.org/10.1016/j.molmet.2023.101670
19. Fan W, Oh TG, Wang HJ, et al. Estrogen-related receptors regulate innate and adaptive muscle mitochondrial energetics through cooperative and distinct actions. *Proc Natl Acad Sci U S A*. 2025;122(20):e2426179122. https://doi.org/10.1073/pnas.2426179122
20. Hyatt SM, Lockamy EL, Stein RA, et al. On the intractability of estrogen-related receptor alpha as a target for activation by small molecules. *J Med Chem*. 2007;50(26):6722–6724. https://doi.org/10.1021/jm7012387
21. Willy PJ, Murray IR, Qian J, et al. Regulation of PPARgamma coactivator 1alpha (PGC-1alpha) signaling by an estrogen-related receptor alpha (ERRalpha) ligand. *Proc Natl Acad Sci USA*. 2004;101(24):8912–8917. https://doi.org/10.1073/pnas.0401420101
22. Kallen J, Lattmann R, Beerli R, et al. Crystal structure of human estrogen-related receptor alpha in complex with a synthetic inverse agonist reveals its novel molecular mechanism. *J Biol Chem*. 2007;282(32):23231–23239. https://doi.org/10.1074/jbc.M703337200
23. Billon C, Schoepke E, Avdagic A, et al. A synthetic ERR agonist alleviates metabolic syndrome. *J Pharmacol Exp Ther*. 2024;388(2):232–240. https://doi.org/10.1124/jpet.123.001733
24. Xu W, Billon C, Li H, et al. Novel pan-ERR agonists ameliorate heart failure through enhancing cardiac fatty acid metabolism and mitochondrial function. *Circulation*. 2024;149(3):227–250. https://doi.org/10.1161/CIRCULATIONAHA.123.066542
25. Hampton CS, Sitaula S, Billon C, et al. Development and pharmacological evaluation of a new chemical series of potent pan-ERR agonists, identification of SLU-PP-915. *Eur J Med Chem*. 2023;258:115582. https://doi.org/10.1016/j.ejmech.2023.115582
26. Billon C, Sitaula S, Banerjee S, et al. Synthetic ERR$\alpha/\beta/\gamma$ agonist induces an ERRα-dependent acute aerobic exercise response and enhances exercise capacity. *ACS Chem Biol*. 2023;18(4):756–771. https://doi.org/10.1021/acschembio.2c00720
27. Shahien M, Elagawany M, Sitaula S, et al. Modulation of estrogen-related receptors subtype selectivity: conversion of an ERRβ/γ selective agonist to ERR$\alpha/\beta/\gamma$ pan agonists. *Bioorg Chem*. 2020;102:104079. https://doi.org/10.1016/j.bioorg.2020.104079
28. Mao L, Peng L, Ren X, et al. Discovery of JND003 as a new selective estrogen-related receptor alpha agonist alleviating nonalcoholic fatty liver disease and insulin resistance. *ACS Bio Med Chem Au*. 2022;2(3):282–296. https://doi.org/10.1021/acsbiomedchemau.1c00050
29. Schalbetter SM, Mueller FS, Scarborough J, et al. Oral application of clozapine-N-oxide using the micropipette-guided drug administration (MDA) method in mouse DREADD systems. *Lab Anim (NY)*. 2021;50(3):69–75. https://doi.org/10.1038/s41684-021-00723-0
30. Scarborough J, Mueller F, Arban R, et al. Preclinical validation of the micropipette-guided drug administration (MDA) method in the maternal immune activation model of neurodevelopmental disorders. *Brain Behav Immun*. 2020;88:461–470. https://doi.org/10.1016/j.bbi.2020.04.015
31. Heath GW, Gavin 3rd JR, Hinderliter JM, Hagberg JM, Bloomfield SA, Holloszy JO. Effects of exercise and lack of exercise on glucose tolerance and insulin sensitivity. *J Appl Physiol Respir Environ Exerc Physiol*. 1983;55(2):512–517. https://doi.org/10.1152/jappl.1983.55.2.512
32. Qiao S, Dennis M, Song X, et al. A REDD1/TXNIP pro-oxidant complex regulates ATG4B activity to control stress-induced autophagy and sustain exercise capacity. *Nat Commun*. 2015;6:7014. https://doi.org/10.1038/ncomms8014
33. Sperandei S, Vieira MC, Reis AC. Adherence to physical activity in an unsupervised setting: explanatory variables for high attrition rates among fitness center members. *J Sci Med Sport*. 2016;19(11):916–920. https://doi.org/10.1016/j.jsams.2015.12.522
34. Toussi R, Fujioka K, Coleman KJ. Pre- and postsurgery behavioral compliance, patient health, and postbariatric surgical weight loss. *Obesity (Silver Spring)*. 2009;17(5):996–1002. https://doi.org/10.1038/oby.2008.628
35. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. *Front Cardiovasc Med*. 2018;5:135. https://doi.org/10.3389/fcvm.2018.00135
36. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. *Br J Sports Med*. 2018;52(3):154–160. https://doi.org/10.1136/bjsports-2016-096587
37. Firth J, Stubbs B, Vancampfort D, et al. Effect of aerobic exercise on hippocampal volume in humans: a systematic review and meta-analysis. *Neuroimage*. 2018;166:230–238. https://doi.org/10.1016/j.neuroimage.2017.11.007
38. De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, et al. Physical exercise in the prevention and treatment of Alzheimer's disease. *J Sport Health Sci*. 2020;9(5):394–404. https://doi.org/10.1016/j.jshs.2020.01.004
39. Jia RX, Liang JH, Xu Y, Wang YQ. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. *BMC Geriatr*. 2019;19(1):181. https://doi.org/10.1186/s12877-019-1175-2
40. Choi SH, Bylykbashi E, Chatila ZK, et al. Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model. *Science*. 2018;361(6406):eaan8821. https://doi.org/10.1126/science.aan8821
41. Sahay A, Scobie KN, Hill AS, et al. Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature*. 2011;472(7344):466–470. https://doi.org/10.1038/nature09817
42. Intlekofer KA, Cotman CW. Exercise counteracts declining hippocampal function in aging and Alzheimer's disease. *Neurobiol Dis*. 2013;57:47–55. https://doi.org/10.1016/j.nbd.2012.06.011
43. Pei L, Mu Y, Leblanc M, et al. Dependence of hippocampal function on ERRgamma-regulated mitochondrial metabolism. *Cell Metab*. 2015;21(4):628–636. https://doi.org/10.1016/j.cmet.2015.03.004