Activation of the vasoactive intestinal peptide 2 receptor modulates normal and atrophying skeletal muscle mass and force

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Hinkle, Richard T., Elizabeth Donnelly, David B. Cody, Russell J. Sheldon, and Robert J. Isfort. Activation of the vasoactive intestinal peptide 2 receptor modulates normal and atrophying skeletal muscle mass and force. J Appl Physiol 98: 655–662, 2005; doi: 10.1152/japplphysiol.00736.2004.—Of the two known vasoactive intestinal peptide receptors (VPAC1R and VPAC2R), the VPAC2R is expressed in skeletal muscle. To evaluate the function of the VPAC2R in the physiological control of skeletal muscle mass, we utilized the VPAC1R selective agonist [K15,R16,L27]VIP(1-7)GRF(8-27)-NH2 and the VPAC2R selective agonist Ro-25-1553 to treat mice and rats undergoing either nerve damage-, corticosteroid-, or disuse-induced skeletal muscle atrophy. These analyses demonstrated that activation of VPAC2R, but not VPAC1R, reduced the loss of skeletal muscle mass and force during conditions of skeletal muscle atrophy resulting from corticosteroid administration, denervation, casting-induced disuse, increased skeletal muscle mass, and force of nonatrophying muscles. These studies indicate that VPAC2R agonists may have utility for the treatment of skeletal muscle-wasting diseases.

Vasoactive intestinal peptide (VIP) and its functionally and structurally related analogs are known to have many physiological functions, including smooth muscle relaxation (bronchodilation, intestinal mobility), regulation of microvascular tone (vasodepression) and permeability, regulation of mucus secretion, modulation of various immune functions (anti-inflammation, immune cell protection), neurological effects (memory improvement, hypnogenesis, food intake, circadian rhythm control, sexual behavior), maintenance of salivary gland function, developmental growth regulation, and stimulation of hormone secretion (prolactin, growth hormone, insulin) (13). VIP and related functional/structural analogs mediate their effects through VIP receptors via both neuronal (as putative neurotransmitters) and neuroendocrine pathways. The two VIP receptors identified to date (VPAC1R and VPAC2R) belong to the putitary adenylate cyclase-activating polypeptide (PACAP) type II receptor subclass (13, 16, 33, 38, 44, 46). VPAC1R/2R can be differentiated both molecularly and pharmacologically. Pharmacological agents that selectively activate VPAC1R and VPAC2R have been described (10–12). These agonists and antagonists are able to differentiate these receptors functionally and have been useful in matching biological activity with a specific VIP receptor.

Both rodent and human VPAC1R and VPAC2R have been cloned, with splice variants of each receptor demonstrating unique tissue expression distributions (1, 8, 13, 16, 20, 21, 28, 38, 39, 41, 44). VPAC1R and VPAC2R belong to the G protein-coupled receptor class and are positively coupled to Gαs. Agonist binding to G protein-coupled receptors coupled to Gαs results in the activation of adenylyl cyclase and the subsequent formation of cAMP, which, as a second messenger, has pleotropic effects, including the activation of protein kinase A and phospholipase C, intracellular Ca2+ release, mitogen-activated protein (MAP) kinase activation, etc. (13, 26, 34, 43, 45). Additional G-protein coupling has been described for VPAC1R and VPAC2R, including coupling to either Gi or Gq (26, 43). Importantly, the specificity of coupling is dependent on the particular tissue under study. Expression of VPAC1R and VPAC2R differ depending on the tissue, such that VPAC1R is expressed in humans in brain, adipose, liver, and heart, whereas VPAC2R is expressed in humans in lung, pancreas, brain, kidney, skeletal muscle, stomach, heart, and placenta; in the rat, VPAC1R is predominantly expressed in the pineal gland, small intestine, liver, spleen, pancreas, lung, aorta, vas deferens, and brain, whereas VPAC2R is expressed in the stomach, intestine, skeletal muscle, spleen, pancreas, thymus, adrenal, heart, lung, aorta, brain, pituitary, and olfactory bulb (1, 41, 44).

Skeletal muscle readily adapts in a tightly regulated manner to changes in use or metabolic need. Skeletal muscle atrophy can be initiated by a variety of stimuli including, for example, disuse, nerve damage, and glucocorticoid use (2, 15, 17, 19, 31, 37, 40). Atrophy induces multiple changes in skeletal muscle that are independent of the atrophy-inducing stimuli, including decreased protein synthesis, increased protein degradation, alterations in contractile and metabolic enzyme protein isozymes, loss of vasculature, and remodeling of the extracellular matrix (2, 5, 6, 22, 24, 25, 27). Atrophy and hypertrophy are conserved processes across mammalian species. This is probably due to the fact that muscles serve the same function in all mammals, including physiological movement and the storage of amino acids/energy. For example, atrophy in both rodents and humans, induced by a variety of means, results in similar changes in muscle anatomy, cross-sectional area, function, fiber-type switching, contractile protein expression, and histology (2). In addition, several agents have been demonstrated to modulate skeletal muscle atrophy, induced by a variety of methods, in rodents and in humans, including anabolic steroids, growth hormone, insulin-like growth factor I, and β-adrenergic agonists (18, 29, 30, 32, 35, 42).

In this report, we demonstrate that activation of VPAC2R with a selective agonist reduces the loss of skeletal muscle mass and force resulting from atrophic stimuli and increases skeletal muscle mass in nonatrophyng muscles.

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MATERIALS AND METHODS

Materials. The nonselective VIP receptor agonist VIP was purchased from Bachem (Bachem, King of Prussia, PA). The VPAC1R-selective agonist [K15,R16,L27]VIP(1-7)/GRF(8-27) (4) and the VPAC2R-selective agonist Ro-25-1553 (11) were synthesized at Procter and Gamble Pharmaceuticals. All peptides synthesized at Procter and Gamble Pharmaceuticals were checked for purity by HPLC and for composition by mass spectrometry. Dexamethasone, clenbuterol, and theophylline were purchased from Sigma (St. Louis, MO). Male C57Bl6 mice weighing 20–30 g and female Sprague-Dawley rats weighing 225–250 g (Charles River, Raleigh, NC) were single housed and acclimatized to the conditions of the facility for ~1 wk before use. Mice and rats had access to lab chow and water ad libitum. Animals were subjected to standard conditions of humidity, temperature, and a 12-h light cycle. All studies described in this report were conducted in compliance with the US Animal Welfare Act and rules and regulations of the State of Ohio Departments of Health.

Tissue bath and cAMP measurements. Skeletal muscle tissue baths were prepared by dissecting the medial gastrocnemius (MG) and tibialis anterior (TA) muscles from both the right and left legs of mice and pinning the muscles at resting length on glass slides. The muscles were then incubated with continuous aeration with 95% oxygen-5% carbon dioxide in 25 ml of a 30°C Krebs-Ringer solution, pH 7.4. After 15 min, this solution was changed and replaced with 25 ml of Krebs-Ringer solution, pH 7.4, containing 25 mM theophylline, and the muscles were incubated at 30°C with continuous aeration; 15 min later, the test compounds were added to the Krebs-Ringer solution, pH 7.4, containing 25 mM theophylline, and the muscles were incubated for 1 h, after which they were removed from the baths, blotted dry, and snap frozen in liquid nitrogen. The muscles were prepared for cAMP analysis by grinding the muscles into a fine powder in liquid nitrogen in a mortar and pestle followed by dissolving the powdered muscle in lysis buffer and incubating for 30 min as specified by the cAMP kit manufacturer (Amersham Pharmacia Biotech, Piscataway, NJ). cAMP levels were then measured using the Amersham Pharmacia Biotech cAMP measurement kit (RPN225), essentially as recommended by the manufacturer. Each experiment was performed in triplicate. The data are presented as fold increase over control, with onefold being equivalent to background rate.

Glucocorticoid-induced atrophy model. Glucocorticoid-induced skeletal muscle atrophy was achieved by including 6 mg/ml of dexamethasone in the drinking water, resulting in a 1.2 mg·kg⁻¹·day⁻¹ dosage. Test materials were administered by twice daily subcutaneous injection in the midscapular region in conjunction with twice daily intraperitoneal injections of theophylline. Nine days after the initiation of dexamethasone dosing, mice were euthanized by carbon dioxide asphyxiation followed by cervical dislocation. The TA and MG muscles were dissected rapidly from both legs, and the muscles were cleaned of tendons and connective tissue and weighed.

Sciatic nerve damage atrophy model. Mice and rats were anesthetized with isoflurane. The right sciatic nerve was isolated and lifted out with a surgical hook, a 3- to 5-mm segment was removed, and the incision was closed with surgical staples. The test materials were administered either by twice daily subcutaneous injection in the midscapular region or by continuous infusion via subcutaneous implantation of an osmotic minipump (Alza) in the midscapular region. Ten days after casting, animals were euthanized by carbon dioxide asphyxiation followed by cervical dislocation. The cast was removed, the TA and MG muscles were dissected rapidly from both legs, and the muscles were cleaned of tendons and connective tissue and weighed.

RESULTS

To evaluate the functionality of the VIP receptors expressed in skeletal muscle and to validate the observation that only VPAC2R is expressed in skeletal muscle, skeletal muscles in organ bath were stimulated with either the VPACR-nonselective agonist VIP, the VPAC1R-selective agonist [K15,R16,L27]VIP(1-
7)/GRF(8-27), or the VPAC2R-selective agonist Ro-25-1553, and cAMP generation was evaluated. As can be seen in Fig. 1, stimulation of mouse MG and TA muscles with the nonselective VPACR agonist VIP and the VPAC2R-selective agonist RO-25-1553 induced cAMP generation.

**Fig. 2.** Effects of VPAC1R and VPAC2R agonist administration on tibialis anterior and medial gastrocnemius muscle mass in the mouse glucocorticoid (dexamethasone)-induced atrophy model. **A:** Graphical presentation of the effects of VPAC1R and VPAC2R agonists on tibialis anterior muscle (combined mass of both left and right tibialis anterior muscles). **B:** Graphical presentation of the effects of VPAC1R and VPAC2R agonists on medial gastrocnemius muscle (combined mass of both left and right medial gastrocnemius muscles). Glucocorticoid-induced skeletal muscle atrophy was performed as described in MATERIALS AND METHODS. The VPAC1R agonist [K15,R16,L27]VIP(1-7),GRF(8-27)-NH2, VPAC2R agonist RO-25-1553, β2-adrenergic receptor agonist clenbuterol (positive control), and physiological saline (vehicle control) were administered via twice daily subcutaneous injection at the indicated doses in combination with theophylline (except clenbuterol). Theophylline (30 mg/kg) was administered twice daily intraperitoneally to potentiate the action of the VPAC1R and VPAC2R agonists. Dexamethasone (6 mg/l) was included in the drinking water. Saline without dexamethasone (left-most saline dose group not under dexamethasone heading) are muscles from saline-injected animals not receiving dexamethasone in their drinking water. Saline with dexamethasone (saline dose group under dexamethasone heading) are muscles from saline-injected animals that received dexamethasone in their drinking water. *Statistically significant response vs. saline (vehicle) control (*P < 0.05; analysis of covariance (ANCOVA)).

**Fig. 3.** Effects of VPAC1R and VPAC2R agonists treatment on skeletal muscle mass in the mouse denervation-induced atrophy model. **A:** Graphical presentation of the effects of VPAC1R and VPAC2R agonists treatment on tibialis anterior muscle mass. **B:** Graphical presentation of the effects of VPAC1R and VPAC2R agonists treatment on medial gastrocnemius muscle mass. Denervation-induced atrophy was performed as described in MATERIALS AND METHODS. The VPAC1R agonist [K15,R16,L27]VIP(1-7),GRF(8-27)-NH2, VPAC2R agonist RO-25-1553, β2-adrenergic receptor agonist clenbuterol (positive control), and water (vehicle control) were administered by subcutaneous continuous infusion using osmotic minipumps at the indicated doses. *Statistically significant response vs. saline (vehicle) control (*P < 0.05; ANCOVA).
agonist Ro-25-1553, but not the VPAC1R-selective agonist $[^{15}K^{16},L^{27}]$VIP(1-7)/GRF(8-27), resulted in an increase in cAMP levels in the TA and MG muscles, confirming that only VPAC2 is expressed and active on skeletal muscle.

Next, we evaluated the effects of the VPAC1R-selective agonist $[^{15}K^{16},L^{27}]$VIP(1-7)/GRF(8-27) and the VPAC2R-selective agonist Ro-25-1553 on skeletal muscle mass in animals undergoing corticosteroid, denervation, and casting-in-
duced skeletal muscle atrophy. All three atrophy models were performed using mice; in addition, the denervation atrophy model was also performed in rats to evaluate species effects. The lower leg muscles MG, TA, EDL, and soleus (and plantaris in rats) were studied in all the models because they were atrophying muscles common to all atrophy models; EDL and soleus muscle were utilized for functional analysis because they possessed the optimal architecture and size for this type of analysis. Dosing of the VPAC2R agonists was performed either by twice daily subcutaneous injection (coadministered with theophylline to maximize cAMP activation in skeletal muscle because peptide half-lives are relatively short) or by continuous subcutaneous infusion using osmotic minipumps (without theophylline). In several of the models, both the VPAC1R and VPAC2R agonists were evaluated even though only the VPAC2R agonist demonstrated efficacy in the muscle bath experiment to evaluate whether activation of VPAC1R had a role in modifying skeletal muscle mass via activation at a site distant from skeletal muscle (indirect effect). In addition, treatment with the β2-adrenergic agonist clenbuterol was included as a positive control because clenbuterol has been previously demonstrated to inhibit the loss of skeletal muscle mass resulting from atrophy in mice and rats (30).

The results of treating mice undergoing corticosteroid-induced atrophy with the VPAC1R-selective agonist [K15,R16,L27]VIP(1-7)/GRF(8-27) and the VPAC2R-selective agonist Ro-25-1553 are shown in Fig. 2. In this experiment, eight mice per treatment group were given either water or water containing 6 mg/l dexamethasone for 9 days. The mice were dosed with the test materials as follows: twice daily subcutaneous injections of saline (vehicle control); twice daily intraperitoneal injections of 30 mg/kg theophylline; twice daily subcutaneous injections of 0.1 mg/kg [K15,R16,L27]VIP(1-7)/GRF(8-27) in combination with twice daily intraperitoneal injections of 30 mg/kg theophylline; twice daily subcutaneous injections of 0.3 mg/kg [K15,R16,L27]VIP(1-7)/GRF(8-27) in combination with twice daily intraperitoneal injections of 30 mg/kg theophylline; twice daily subcutaneous injections of 0.1 mg/kg Ro-25-1553 in combination with twice daily intraperitoneal injections of 30 mg/kg theophylline; twice daily subcutaneous injections of 0.3 mg/kg Ro-25-1553 in combination with twice daily intraperitoneal injections of 30 mg/kg theophylline; and once daily injections of 3 mg/kg clenbuterol. As can be seen in Fig. 2, addition of dexamethasone to the drinking water resulted in loss of TA (Fig. 2A) and MG (Fig. 2B) muscle mass (compare saline to saline + dexamethasone). Treatment with theophylline alone did not inhibit the dexamethasone-induced TA and MG muscle mass loss. In contrast, treatment with clenbuterol resulted in 96 and 82% inhibition of dexamethasone-induced TA and MG muscle mass loss, respectively. Treatment with [K15,R16,L27]VIP(1-7)/GRF(8-27) + theophylline did not inhibit dexamethasone-induced TA and MG muscle mass loss.

Fig. 4. Effects of VPAC2R agonist treatment on skeletal muscle mass in the rat denervation atrophy model. A: graphical presentation of the effects of VPAC2R agonists on tibialis anterior muscle mass. B: graphical presentation of the effects of VPAC2R agonists on extensor digitorum longus muscle mass. C: graphical presentation of the effects of VPAC2R agonists on plantaris muscle mass. D: graphical presentation of the effects of VPAC2R agonists on soleus muscle mass. E: graphical presentation of the effects of VPAC2R agonists on medial gastrocnemius muscle mass. Denervation-induced atrophy was performed as described in MATERIALS AND METHODS. The VPAC2R agonist RO-25-1553, β2-adrenergic receptor agonist clenbuterol (positive control), and physiological saline (vehicle control) were administered via twice daily subcutaneous injection at the indicated doses in combination with theophylline (except clenbuterol). Theophylline (30 mg/kg) was administered twice daily intraperitoneally to potentiate the action of the VPAC2R agonist. *Statistically significant response vs. saline (vehicle) control (P < 0.05; ANCOVA).

Fig. 5. Effects of VPAC2R agonist treatment on skeletal muscle mass in the mouse casting atrophy model. A: graphical presentation of the effects of VPAC2R agonist treatment on tibialis anterior muscle mass. B: graphical presentation of the effects of VPAC2R agonist treatment on medial gastrocnemius muscle mass. Casting-induced atrophy was performed as described in MATERIALS AND METHODS. The VPAC2R agonist RO-25-1553 and physiological saline (vehicle control) were administered by subcutaneous continuous infusion using osmotic minipumps at the indicated doses. *Statistically significant response vs. saline (vehicle) control (P < 0.05; ANCOVA).

Treatment with Ro-25-1553 resulted in a 40 and 35% inhibition of dexamethasone-induced TA and MG muscle mass loss, respectively, at the 0.1 mg·kg−1·day−1 dosage but had no effect at the 0.3 mg·kg−1·day−1 dose. The reason for the lack of dose response in this model but not the other atrophy models is at present unclear but may be a model-specific effect because this model, unlike the two disuse models, denervation and casting, is physi-
The results of VPAC1R- and VPAC2R-selective agonist treatment on denervation-induced skeletal muscle mass loss are demonstrated in Fig. 3. In this experiment, the muscles in the lower right leg were denervated by removing a short segment of the sciatic nerve. Nine days after denervation, the indicated skeletal muscles were harvested and weighed. [K15,R16,L27]VIP(1-7)/GRF(8-27), Ro-25-1553, and clenbuterol were administered by continuous subcutaneous infusion using an osmotic minipump. As can be seen, denervation resulted in an ~25% loss in TA (Fig. 3A) and MG (Fig. 3B) muscle mass. Clenbuterol treatment resulted in an ~60% inhibition of denervation-induced TA and 50% inhibition of denervation-induced MG muscle mass loss. Treatment with Ro-25-1553 resulted in a 35% inhibition of denervation-induced TA muscle mass loss but had no effect on denervation-induced MG muscle mass loss. [K15,R16,L27]VIP(1-7)/GRF(8-27) did not inhibit denervation-induced TA or MG muscle mass loss. In the innervated TA and MG muscles, treatment with Ro-25-1553 and clenbuterol resulted in a statistically significant increase in TA and MG muscle mass. A second denervation-atrophy study was performed with rats to evaluate the skeletal muscle effects of the VPACR-selective agonist in a second rodent species. As can be seen in Fig. 4, treatment with Ro-25-1553 plus theophylline resulted in a statistically significant 30, 22, and 12% inhibition of denervation-induced TA, soleus, EDL, and MG muscle mass loss, respectively. Ro-25-1553 treatment had no statistically significant effect on denervation-induced soleus muscle mass (Fig. 4B) but not soleus muscle mass (Fig. 6A). Casting resulted in a statistically significant 58, 32, 60, 25, and 36% inhibition of denervation-induced TA, soleus, EDL, plantaris, and MG muscle mass loss, respectively. Treatment with theophylline had no effect on muscle mass in any of the muscles examined. In addition, clenbuterol treatment increased innervated TA, MG, EDL, plantaris, and soleus muscle mass.

The results of a mouse disuse (casting) atrophy study utilizing the VPAC2R-selective agonist Ro-25-1553 are shown in Fig. 5. In this experiment, Ro-25-1553 was administered by continuous subcutaneous infusion using an osmotic minipump. The VPAC1R-selective agonist [K15,R16,L27]VIP(1-7)/GRF(8-27) was not evaluated in this model because no effect was observed in any of the previous atrophy models and because the functional studies performed on muscles from this study were time intensive and technically challenging, thereby limiting the number of experimental groups available for inclusion in the study. As can be seen, casting resulted in an ~20% decrease in TA (Fig. 5A) and MG (Fig. 5B) mass; treatment with Ro-25-1553 resulted in a 65% inhibition of casting-induced TA muscle mass loss and a 44% inhibition of casting-induced MG muscle mass loss. Treatment with Ro-25-1553 increased innervated TA muscle mass by 16% and MG muscle mass by 10%.

To evaluate the effect of VPAC2R activation on skeletal muscle mass and function, Ro-25-1553 treated and untreated, atrophied and normal, soleus and EDL muscles were utilized in an in vitro function analysis. As can be seen in Fig. 6, A and B, casting results in an ~25% loss in EDL and soleus muscle mass after 10 days (compare vehicle uncasted to vehicle casted muscle); Ro-25-1553 treatment reduced casting-induced loss of EDL (Fig. 6A) but not soleus muscle mass (Fig. 6B). Casting results in an ~25% loss in EDL and soleus absolute force (compare vehicle uncasted to vehicle casted muscle) (Fig. 6, C

Fig. 6. Effects of VPAC2R agonist treatment on casted and uncasted skeletal muscle mass and function in the mouse casting model. A and B: graphical presentation of the effects of VPAC2R agonist Ro-25-1553 treatment on extensor digitorum longus (A) and soleus (B) muscle mass, respectively. C and D: graphical presentation of the effects of VPAC2R agonist Ro-25-1553 treatment on extensor digitorum longus and soleus muscle absolute force production (Po), respectively. Casting-induced atrophy was performed as described in MATERIALS AND METHODS. The VPAC2R agonist RO-25-1553 (3 mg·kg⁻¹·day⁻¹) and vehicle (physiological saline) were administered by subcutaneous continuous infusion using osmotic minipumps. *Statistically significant response vs. saline (vehicle) control (P < 0.05; ANCOVA).
and D); Ro-25-1553 treatment reduced casting-induced loss of EDL (Fig. 6C) but not soleus absolute force (Fig. 6D).

**DISCUSSION**

In this report, we demonstrate, for the first time, that treatment of mice and rats with the VPAC2R-selective agonist, Ro-25-1553 inhibited skeletal muscle mass and function loss resulting from denervation, disuse, or corticosteroid-induced atrophy and increased nonatrophying skeletal muscle mass. In contrast, treatment of animals with the VPAC1R-selective agonist [K^{15},R^{16},L^{27}]VIP(1-7)/GRF(8-27) did not inhibit atrophy-induced skeletal muscle mass loss or modulate nonatrophying skeletal muscle mass. Together, these data demonstrate that VPAC2R, the VIP receptor expressed in skeletal muscle, modulates skeletal muscle mass in rodents.

Several interesting observations were made from these studies. First, VPAC2R-mediated modulation of skeletal muscle mass was observed in predominantly fast-twitch muscle types. However, predominantly slow-twitch fiber-containing muscles, such as the soleus muscle, did not respond to VPAC2R stimulation. In contrast, muscles composed of predominantly fast-twitch, mixed, and slow-twitch fibers responded to clenbuterol treatment. Thus differences in either receptor distribution or signal transduction may exist between the VPAC2R and the β2-adrenergic receptor, even though both receptors act via Gs to increase cAMP levels in skeletal muscle. Second, there was a difference in response observed between mice and rats. In mice, the MG responded to VPAC2R activation, whereas in the rat the MG muscle did not appear to respond to VPAC2R activation. The reason for this difference is at present unknown, although it may be due to differences in either VPAC2R-receptor numbers or coupling in mouse MG muscle compared with the rat MG muscle. Additional research is required to understand these differences in response.

VPAC2R is one of two members of the VIP/PACAP type II family of receptors. This family includes two members: VPAC1R and VPAC2R (16, 44). Of the two receptors, only VPAC2R is expressed in skeletal muscle. What then is the function of VPAC2R in skeletal muscle biology? The PACAP-receptor family and associated ligands have been shown to have an important role in energy homeostasis (14). In particular, VPAC2R functions in the pancreas and adipose tissue to control glucose deposition and fat deposition, respectively (44). In addition, VPAC2R knockout mice have alterations in lean and fat body composition, as well as IGF-I levels, indicating that VPAC2R has multiple effects on metabolism (3). Alternatively, ligands of VPAC2R function as neuopeptides in skeletal muscle to modulate many functions, including the facilitation of acetylcholine release from the motor nerve terminals (4, 7, 23, 36). Thus the regulation of skeletal muscle mass by VPAC2R may be due to either the hormone-like effect of VPAC2R agonists on metabolism or the neural transmitter-like effect on motor endplates, effectively acting as a trophic factor. Future experimentation designed to understand the role of VPAC2R activation in the modulation of skeletal muscle mass should provide a better understanding of this phenomenon.

The observation that activation of VPAC2R results in the modulation of skeletal muscle mass suggests that VPAC2R agonists may have clinical utility for the treatment of muscle-wasting diseases, such as cachexia associated with acquired immunodeficiency syndrome and cancer; muscle atrophy associated with congestive heart failure and chronic obstructive pulmonary disease; age-associated muscle loss or sarcopenia; and acute skeletal muscle atrophy resulting from disuse due to immobilization, nerve damage, corticosteroid use, and autoimmune disease. In addition, because activation of VPAC2R results in skeletal muscle hypertrophy, VPAC2R agonists may have utility in the treatment of muscle weakness or frailty observed in the elderly; in improving muscle function in individuals afflicted with muscular dystrophies by maximizing the effectiveness of the remaining functional muscle; and in preventing or maintaining muscle mass during periods of exposure to low gravity, such as that experienced in space. Future experimental work should help determine the effectiveness of VPAC2R agonists in the treatment of skeletal muscle-wasting diseases.

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VPAC2R ACTIVATION MODULATES SKELETAL MUSCLE MASS


