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TRPV1-null mice are protected from diet-induced obesity

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Abstract **We explored a role for the capsaicin receptor, transient receptor potential channel vanilloid type 1 (TRPV1), in the regulation of feeding and body mass. On a 4.5% fat diet, wild-type and TRPV1-null mice gained equivalent body mass. On an 11% fat diet, however, TRPV1-null mice gained significantly less mass and adiposity; at 44 weeks the mean body weights of wild-type and TRPV1-null mice were ~51 and 34 g, respectively. Both groups of mice consumed equivalent energy and absorbed similar amounts of lipids. TRPV1-null mice, however, exhibited a significantly greater thermogenic capacity. Interestingly, we found that 3T3-L1 preadipocytes expressed functional calcitonin gene-related peptide receptors. Thus, these data support a potential neurogenic mechanism by which TRPV1-sensitive sensory nerves may regulate energy and fat metabolism.**

Keywords: TRPV1; Vanilloid receptor 1; VR1; Obesity; Capsaicin; Adipocyte; CGRP

1. Introduction

The capsaicin receptor, transient receptor potential channel vanilloid type 1 (TRPV1), is an ion channel expressed predominantly in sensory nerves. TRPV1 detects a variety of noxious physical and chemical stimuli including capsaicin, the pungent component of chilli-peppers [1,2]. Numerous studies support a fundamental role for TRPV1 in pain signaling; disruption of the TRPV1 gene [3,4] and TRPV1 antagonists [5] markedly attenuate thermal hyperalgesia. Interestingly, there is emerging evidence for the participation of TRPV1 and capsaicin signaling in other physiologic functions, including the regulation of feeding and body weight [6]. Dietary administration of capsaicin and other chemically-related "vanilloid" compounds can reduce food intake and increase energy expenditure in animals and humans [7–10]. Vanilloids exert both short and long-term effects. Acutely, capsaicin can reduce food intake, an effect that may be related to altered satiety [7], or alternatively, via visceral malaise and anorexia [11]. In addition, capsaicin can stimulate secretion of catecholamines producing a transient increase in metabolism [12]. Chronic administration of vanilloids reduces weight gain, adiposity and triglycerides in animals consuming high-fat diets [8,13]. Interestingly, chemical destruction of capsaicin-sensitive neurons in neonates also affords protection from diet-induced obesity [14,15]. The precise role of TRPV1 in these effects is unclear. Vanilloids exert complex pharmacological effects at TRPV1, producing an initial activation followed by a long-lasting desensitization of the channel [1,2]. In addition, capsaicin may signal independently of TRPV1 [16,17]. Further, capsaicin treatment in neonates ablates entire sensory nerves and therefore does not selectively target TRPV1. To better understand the role of TRPV1 we explored the effects of a higher-fat diet in wild-type and TRPV1-null animals. Our data reveal that disruption of the TRPV1 gene protects against diet-induced obesity. Further, we show that preadipocytes are sensitive to calcitonin gene-related peptide (CGRP), thus revealing a potential neurogenic mechanism by which TRPV1-expressing neurons may regulate adipocyte function.

2. Materials and methods

2.1. Body weight and feeding studies

All experimental procedures involving animals were approved by the Georgetown University Animal Care and Use Committee and conform to NIH guidelines. C57BL6 wild-type and TRPV1-null mice were house either individually or in a group. Body mass was monitored from 3 to 44 weeks of age while consuming either a 4.5% fat diet (Purina diet 5001; 23.0% protein, 4.5% fat, 5.3% crude fiber, 49% carbohydrate, 3.04 kcal/g metabolizable energy, 12.1% of calories provided by fat) or an 11% fat diet (Purina diet 5015; 17.0% protein, 11.0% fat, 3.0% crude fiber, 53.5% carbohydrate, 3.73 kcal/g metabolizable energy, 25.8% of calories provided by fat). For paired-feeding studies male WT and TRPV1-null mice were housed individually. TRPV1-null mice received food ad libitum while WT mice were restricted to the amount of food consumed by their TRPV1-null counterpart. Both mice received water ad libitum.

2.2. Body temperature

Body temperatures were measured in 9.5 week old mice with a rectal thermometer inserted 1.8 cm before and 1 h after exposure to 0–2 °C.

2.3. RT-PCR

Total cellular RNA was extracted using TRIzol (Invitrogen) according to the manufacturer's instructions. First strand cDNA synthesis was performed using SuperScript III Reverse Transcriptase (Invitrogen) with the supplied oligo $(dT)_{20}$ primer. Amplification of CRLR was performed using Platinum Blue PCR Super Mix (Invitrogen) with the following conditions: denaturation at 94 °C for 30 s, annealing at 54 °C for 45 s, and extension at 72 °C for 30 s for a total of 30 cycles; and primers: CRLR, forward 5′-GTTGCCAACGGATCACATTGC-3′ and reverse 5′-ACAAAGCAGCACAAATCGGACC-3′; β-actin, forward 5′-GCTGGTCGTCGACAACGGCT-3′ and reverse 5′-CAGGTCCAGACGCAGGGGGCATGG-3′. Real-time amplifications were performed using the ABI Prism 7900HT Sequence Detection

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Abbreviations: CGRP, calcitonin gene-related peptide; TRPV1, transient receptor potential channel vanilloid type 1; CRLR, calcitonin receptor-like receptor

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System (Applied Biosystems) and SYBR Green PCR Master Mix (Applied Biosystems). RNA was extracted from white and brown adipose tissues and skeletal muscle (quadriceps containing both fast-glycolytic fibres – *vastus* and oxidative fibres – *rectus femoris*). Oligonucleotide primers for mouse UCP1, UCP2, and UCP3 were the same as those previously published [8]. β-Actin was amplified in parallel reactions as an endogenous control. The amplification profile included denaturation at 95 °C for 30 s, annealing at 55 °C for 30 s, and extension at 72 °C for 30 s for a total of 40 cycles. Dissociation curve analysis was performed at the end of each real-time PCR run to ensure that primer dimers were not present. Additionally, the real-time PCR products were verified on agarose gel. The comparative threshold cycle (C_T) method was use to determine the relative quantification of target RNA. The target threshold cycle number was normalized to an endogenous reference (GAPDH), and relative amounts of UCP message were normalized to β-actin.

2.4. Lipolysis in vitro and glycerol analysis

Lipolysis was assessed in adipose explants using methods previously described [18]. Approximately, 100 mg explants of mouse gonadal adipose tissues were minced and placed into a microtube containing 500 μl Hanks buffer. Aliquots were removed at 0 and 5 h. Glycerol release and plasma glycerol were measured using a glycerol assay kit (Cayman Chemical Co., Ann Arbor, MI).

2.5. Fat absorption

Fat absorption was measured using methods previously described [19]. Wild-type and TRPV1-null mice were fed a diet containing (wt%) 16 fat, 45 non-fat dry milk, and 39 sucrose (30:15:55 fat:protein:carbohydrate energy%). The fat component was a mixture of 95% safflower oil and 5% sucrose octabehenate, a non-absorbable lipophilic marker. Fecal samples from the third day were analyzed by GC for fatty acids.

2.6. Calcium imaging

Mouse 3T3-LI preadipocytes were cultured in Dulbecco's Modified Eagle's Medium with 10% bovine calf serum. Cells were loaded with 1 μM Fluo 4-AM (Molecular Probes, Eugene, OR) for 20 min and washed for a further 10–20 min prior to recording. The dye was excited at 480 ± 15 nm. Emitted fluorescence was filtered with a 535 ± 20 nm bandpass filter, captured by a SPOT RT digital camera (Diagnostic Instruments, Sterling Heights, MI) and read into a computer. Analysis was performed offline using Simple PCI software (Compix Inc., PA). Drugs were applied via a micropipette (~5–10 μm diameter) positioned at a distance of ~100 μm from the cell of interest.

2.7. Chemicals

Capsaicin was obtained from Tocris Cookson (Ellisville, MO, USA) and prepared as a stock solution in ethanol. CGRP was obtained from Phoenix Pharmaceuticals Inc. (Burlingame, CA, USA) and prepared as a stock solution in water. Drugs were diluted into physiological solution prior to experiments.

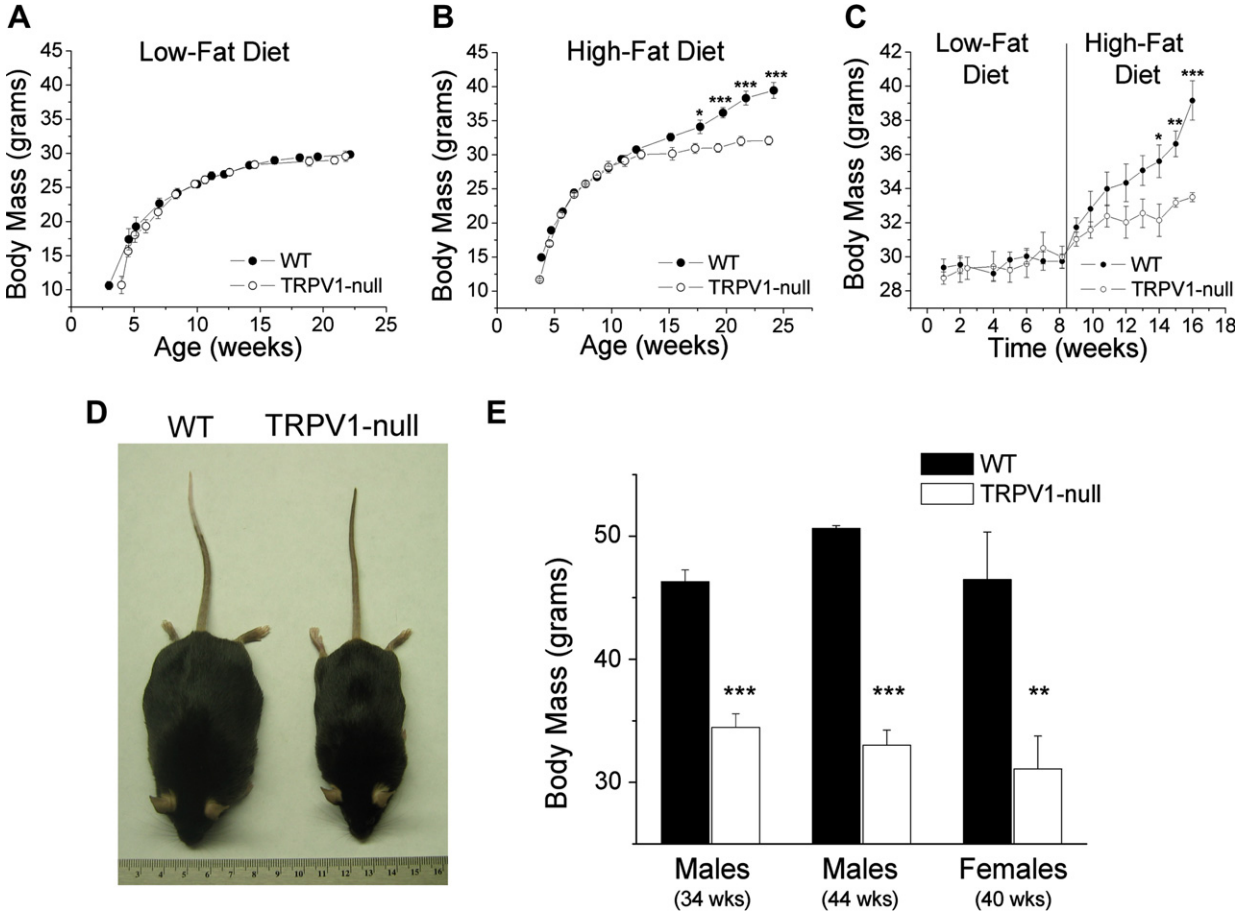

Fig. 1. TRPV1-null mice gain less body mass than wild-type mice on a high-fat diet. (A and B) Mean body mass of wild-type (WT) or TRPV1-null male mice consuming either a low-fat (4.5%) or high-fat (11%) diet from 3 to 25 weeks of age ($n = 5$ for both). (C) Male mice ($n = 5$) switched from a 4.5% fat to an 11% fat diet at 22 weeks of age. (D) Representative photograph of male WT and TRPV1-null mice on an 11% fat diet at 44 weeks of age. (E) Mean body mass of male (age 34 wks: WT $n = 11$, TRPV1-null $n = 7$ and age 44 wks: WT $n = 4$, TRPV1-null $n = 5$) and female (age 40 wks: $n = 4$ for both) mice consuming an 11% fat diet. *t*-test $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

3. Results

3.1. TRPV1-null mice have reduced body mass and adiposity on a higher-fat diet

We explored changes in body mass of wild-type (WT) and TRPV1-null mice consuming either a low-fat (4.5%) or higher-fat (11%) diet. When placed on a low-fat diet, both groups exhibited a similar weight gain from 3 to 25 weeks of age (Fig. 1A). In contrast, when placed on a higher fat diet wild-type mice gained greater body mass with significant differences beginning at ~17 weeks of age (Fig. 1B). At 44 weeks, the mean body mass of WT and TRPV1-null male mice was ~51 g and ~34 g, respectively (Fig. 1D and E). A similar difference was noted in female mice; with a mean body mass of 47 g and 31 g, respectively (Fig. 1E) at 40 weeks. We also observed differential weight gain when adult mice raised on a low-fat diet were switched to a higher-fat diet (Fig. 1C). WT mice gained significantly greater mass compared with TRPV1-null mice within a 6 week period.

Fig. 2A and B shows that this increase in body mass was associated with greater adiposity. WT animals raised on an 11% fat diet (28 weeks) had significantly greater abdominal and subcutaneous fat than their TRPV1-null counterparts (Fig. 2A and B). In addition, adipose tissue from WT mice had markedly larger adipocytes (Fig. 2C). Furthermore, both the fat content of the liver and the size of lipid droplets were greater in WT compared with TRPV1-null animals (Fig. 2C and D).

3.2. Wild-type and TRPV1-null mice consume equivalent energy but possess different thermogenic capacities

To test whether food intake accounted for differences in body mass and adiposity we monitored cumulative energy intake. Fig. 3A shows that WT and TRPV1-null animals consumed equivalent energy on low-fat and high-fat diets. To confirm this result we performed paired-feeding experiments in which WT mice consuming high-fat chow were restricted to the food intake of TRPV1-null counterparts. Fig. 3B shows that WT mice still gained significant body mass on this regimen. Thus, these data rule out differences in energy intake between WT and TRPV1-null animals. Further, to test for differences in intestinal fat absorption we performed fecal fat analysis. Fig. 3C shows that both WT and TRPV1-null animals absorbed ~98% of dietary fats.

Next, we tested for differences in energy expenditure. Previous studies have found that obese mice have a reduced thermogenic capacity compared with lean animals and this is reflected by an impaired ability to maintain body temperature in a cold environment [20]. We therefore measured core body temperatures before and after a 1 h cold exposure (0–2°C) in mice fed either a low-fat or high-fat diet. Fig. 3D shows that cold exposure produced a 2 °C drop in rectal temperature in WT mice fed a low-fat diet ($n = 8$, $P < 0.01$). A significantly greater decrease of 3.4 °C, was seen in WT animals consuming a high-fat diet ($n = 6$, $P < 0.01$). In addition, WT mice consuming a high-fat diet had a lower resting body temperature compared with animals consuming a low-fat diet ($P < 0.01$). In contrast,

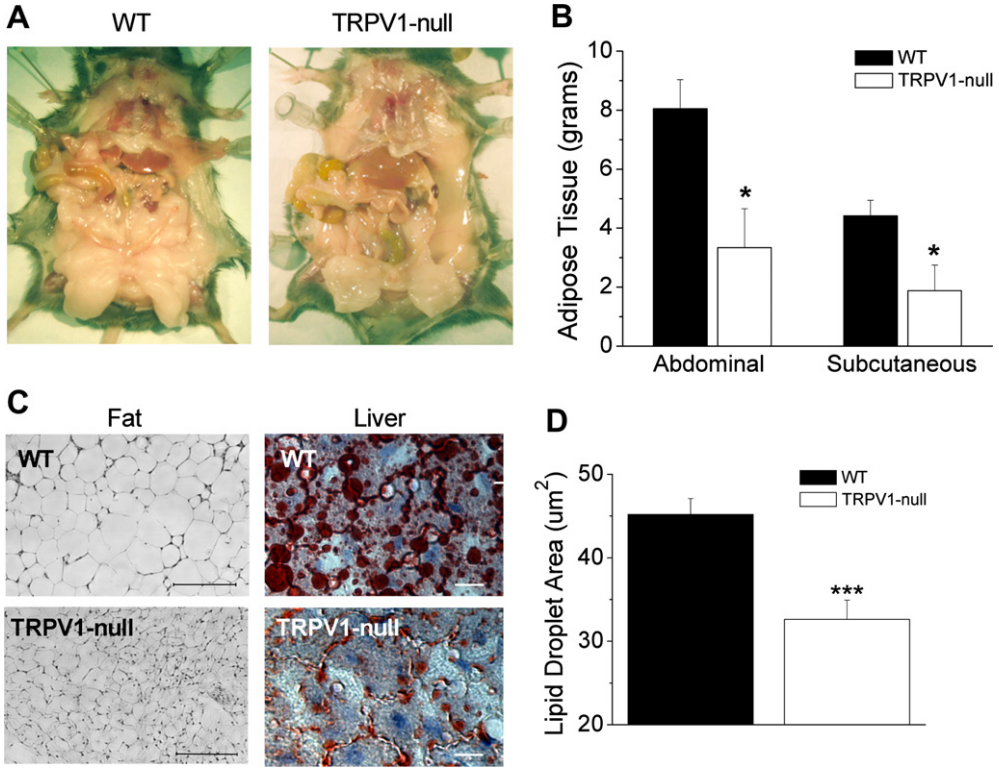

Fig. 2. TRPV1-null mice have reduced adiposity. (A) Representative photographs of visceral fat in female WT and TRPV1-null mice. (B) Mass of adipose tissue from the abdominal cavity and subcutaneous fat in WT and TRPV1-null mice on an 11% fat diet ($n = 3$, $^{*}P < 0.05$ t-test). (C) Representative cross-sections of gonadal adipose tissue (hematoxylin and eosin staining, scale bar indicates 200 μm) and liver (Oil Red-O staining, scale bar indicates 10 μm) from WT and TRPV1-null mice on a high-fat diet. (D) Mean area of hepatocyte lipid droplets ($n = 300$ from 3 WT and 3 TRPV1-null mice; $^{***}P < 0.001$ t-test).

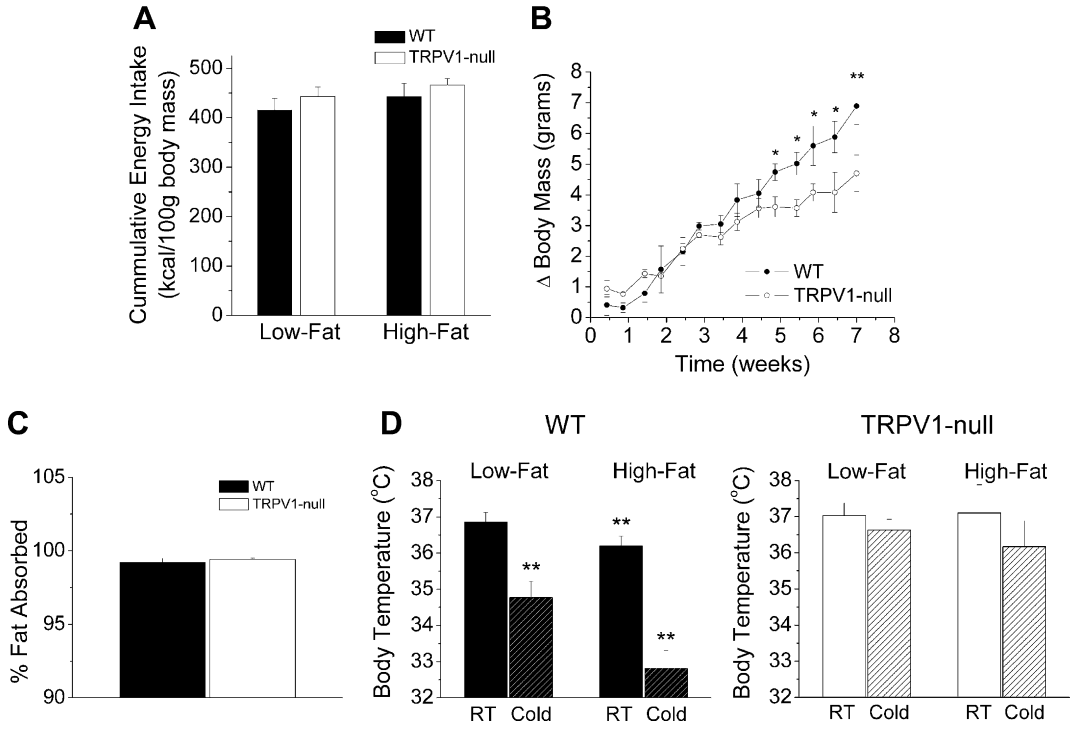

Fig. 3. Wild-type and TRPV1-null mice have the same food intake and intestinal fat absorption but different energy expenditure. (A) Cumulative energy intake of male mice on a 4.5% fat or 11% fat diet for 8 days ($n = 4$). (B) Mean gain in body mass for WT and TRPV1-null mice after 7 weeks of paired feeding ($n = 3$; $^{*}P < 0.05$, $^{**}P < 0.01$ *t*-test). (C) Total fat absorption by WT and TRPV1-null mice ($n = 3$). (D) Mean body temperatures of WT (left) and TRPV1-null (right) mice at room temperature (RT) and after one hour at 0–2 °C (Cold) while consuming either the low-fat (4.5% fat) or high-fat (11% fat) diet (WT: 4.5% fat $n = 7$, 11% fat $n = 6$, $^{**}P < 0.01$ ANOVA; TRPV1-null: 4.5% fat $n = 7$, 11% fat $n = 3$, NS by ANOVA).

cold exposure produced no significant change in body temperature in TRPV1-null mice consuming either diet (Fig. 3D, $n = 3$–7). Aside from an attenuated fever response, TRPV1-null mice display normal thermoregulation [21]. These data suggest that TRPV1-null animals have a greater capacity for thermogenesis than WT animals, and a higher resting metabolic rate when consuming a high-fat diet.

Altered thermogenesis may reflect the activity of uncoupling proteins, particularly in brown fat. Indeed, mice fed a capsaicin-rich diet exhibit increased mRNA levels for several uncoupling proteins [8]. However, we observed no differences in mRNA expression of uncoupling proteins (UCP1-3) in brown and white adipose tissue, and skeletal muscle of WT and TRPV1-null mice fed a high-fat diet (data not shown). Further, both the plasma glycerol levels (WT 25.6 ± 1.6 mg/dL; TRPV1-null 25.2 ± 3.2 mg/dL, $n = 7$–9) and in vitro lipolytic capacity (WT, 0.36 ± 0.07 mg glycerol g^{-1} h^{-1}; TRPV1-null 0.37 ± 0.09 mg glycerol g^{-1} h^{-1}, $n = 4$) were identical in both sets of animals.

3.3. Adipocytes express functional CGRP receptors

TRPV1 is predominantly expressed on sensory nerve terminals. In turn, these nerves release the neuropeptides, substance P (SP) and calcitonin gene-related peptide (CGRP). Therefore, we explored whether TRPV1 could exert an action on preadipocyte function through neurogenic mechanisms. Fig. 4A shows that CGRP (50 nM) elicited Ca^{2+} transients in a subset of 3T3-L1 preadipocytes (30%, 27 of 89 cells), consistent with activation of an inositol trisphosphate signalling pathway. RT-PCR confirmed expression of the CGRP receptor, calcitonin receptor-like receptor (CRLR) (Fig. 4B). In contrast, SP (50 nM) failed to evoke Ca^{2+} transients (data not shown, $n = 50$). Interestingly, a recent study has described expression of TRPV1 in 3T3-L1 preadipocytes [22]. However we found that the TRPV1 ligand, capsaicin (10 μM), failed to evoke Ca^{2+} responses ($n = 64$) whereas all cells responded robustly to application of 2 mM extracellular ATP (Fig. 4C and D).

4. Discussion

These results reveal a novel role for TRPV1 and sensory nerves in the regulation of obesity. We show that TRPV1-deficient mice are resistant to diet-induced increases in body mass and adiposity. The phenotype of these knock-out animals closely matches that of animals following chemical destruction of sensory afferent neurons [14,15]. Our data therefore suggest that TRPV1 is the key target of these sensory nerve lesions. Interestingly, animals that chronically consume dietary vanilloids are also protected from diet-induced obesity [8,13]. Vanilloids produce an initial activation followed by long-term desensitization of TRPV1, suggesting that their pharmacological effect may be mediated through inhibition of TRPV1. On the other hand, the possibility that vanilloids signal independently of TRPV1 cannot be excluded [16,17]. Thus, three separate methods of manipulating TRPV1: selective disruption of the TRPV1 gene, destruction of TRPV1-expressing sensory neurons and pharmacological activation/desensitization of TRPV1 produce equivalent effects on body mass and adiposity. Taken together, these data suggest that TRPV1 signalling

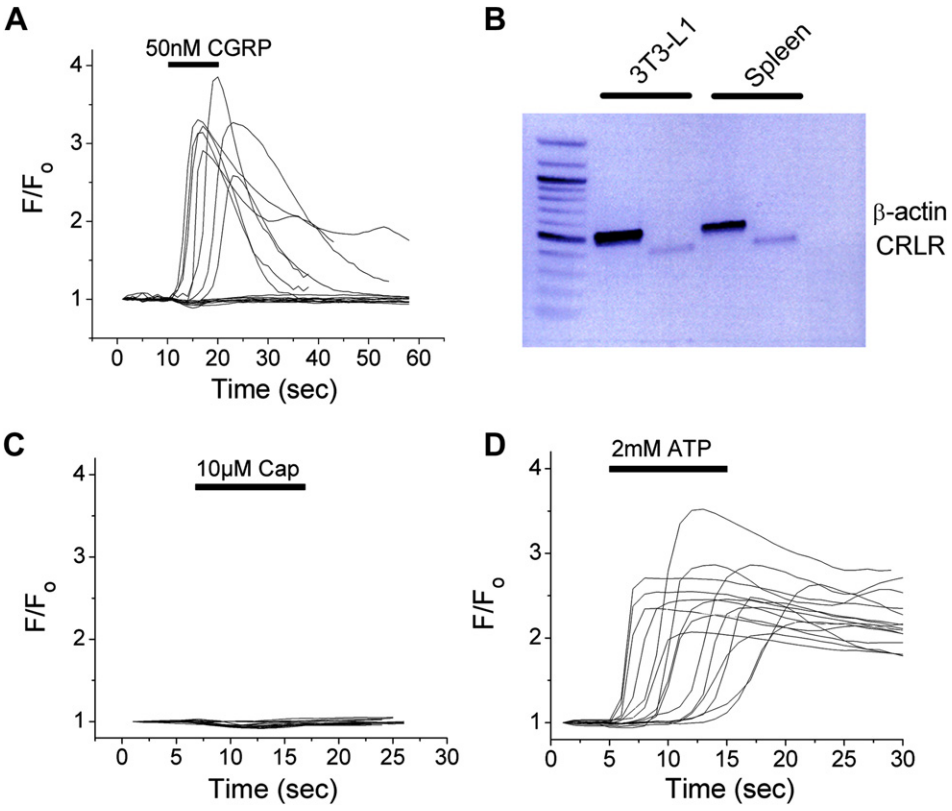

Fig. 4. Mouse 3T3-L1 preadipocytes express functional CGRP receptors. (A) CGRP (50 nM) produced Ca^{2+} transients in 3T3-L1 preadipocytes. (B) Adipocytes express mRNA for the CGRP receptor, CRLR. (C and D) Capsaicin (10 μM) failed to produce Ca^{2+} transients in adipocytes, though cells responded to ATP (2 mM).

promotes fat accumulation, and inhibition of this signalling is therefore protective.

We found that both WT and TRPV1-null animals exhibited equivalent energy intake. Further, intestinal absorption of fat was identical in both groups and this agrees with earlier findings that lipid absorption is unaffected in animals [13] or humans [10] treated chronically with capsaicin, which elicits a functional loss of TRPV1. These data suggest that altered energy utilization likely accounts for the differential weight gain. Consistent with this hypothesis, we found that WT mice have a reduced thermogenic capacity compared to TRPV1-null counterparts and this effect was more marked on a higher-fat diet. Resting body temperature was also lower in WT animals consuming a high-fat compared with a low-fat diet. This is consistent with a diet-induced reduction in metabolic rate. Obese strains of mice are known to have decreased thermogenesis and a lower resting body temperature [20]. Interestingly, TRPV1-null animals exhibit normal locomotor activity [23] suggesting that this factor per se does not account for altered energy utilization.

The precise molecular mechanism by which TRPV1 influences energy and lipid handling is unclear. One potential pathway is through insulin signalling. Activation of TRPV1 in sensory nerve terminals triggers the secretion of CGRP and SP, two neuropeptides known to modulate pancreatic islet function [24,25]. Notably, elevated levels of CGRP contribute to insulin resistance [26]. Indeed, C57/Bl6 mice are prone to age-onset diabetes and obesity and TRPV1-null animals on this background are reported to have increased glucose tolerance and insulin sensitivity [25]. In this context, it is interesting that we only observed differences in body mass in mice older than ~15 weeks. Similarly, altered weight and adiposity in capsaicin-desensitized rats is only seen after 14 weeks of age [14]. These data support a role for TRPV1 in age-onset obesity. Second, TRPV1 could directly regulate adipocyte function. Preadipocytes are reported to express TRPV1 [22] and treatment with capsaicin blocks the differentiation of these cells into mature adipocytes [17,22]. However, whether capsaicin modulates adipocyte function via TRPV1 is uncertain. Capsaicin can inhibit NF-kappa B and modulate adipocyte function independently of TRPV1 [16,17]. Moreover, we could not confirm functional TRPV1 signaling in mouse 3T3-L1 preadipocytes; these cells failed to produce elevations in $[Ca^{2+}]$ in response to capsaicin. Third, our data point to a potential neurogenic pathway by which TRPV1 may regulate adipocyte function. TRPV1 triggers the release of neuropeptides from sensory nerve terminals that are known to innervate fatty tissues. We found that 3T3-L1 preadipocytes exhibit functional responses to CGRP and express the CGRP receptor, CRLR. Interestingly, levels of CGRP are elevated in obese humans and animals [26,27]. Thus, it will be important to explore whether CGRP can promote obesity through direct modulation of adipocytes.

In summary, our data reveal a role for TRPV1 in promoting fat accumulation and weight gain. Pharmacologic inhibitors of TRPV1 are currently under development for pain treatment.

Our data suggest that TRPV1 antagonists or agonists that promote TRPV1 desensitization, may have additional utility in the treatment for obesity.

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