MOLECULAR PATHWAYS LINKING NON SHIVERING THERMOGENSIS AND OBESITY

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Introduction

An increase in energy intake and a decrease in energy expenditure (EE) lead to fat storage, causing overweight and obesity phenotypes. Besides reducing energy intake, increasing EE offers an important alternative approach that may produce even more beneficial effects. This is because EE represents the sum of internal heat production and external work, given that about 20% of the energy intake in food is used to produce heat through the non-shivering thermogenesis (NST) process. NST heat is produced in brown adipose tissue (BAT) by uncoupling protein-1 (UCP1), a mitochondrial inner membrane protein, leading to decreased body weight and fat stored. The purpose of this systematic review is to evaluate the literature and summarize all the recently-published evidence regarding the molecular pathways linking NST and obesity.

Methodology

PubMed and Scopus databases were scanned from 2006 to September 2012 using “brown adipose tissue” AND “uncoupling protein-1” AND “mammalian thermoregulation” AND “obesity” as key words. A total of 48 articles were retrieved using the search criteria.

Results

The articles were separated into two categories based on research methodology: “knockout studies” in which knockout gene analysis was performed (Table 1), and “other studies” in which the analysis was carried out using various substances, molecules and agonists treatments, as well as different temperature and diet conditions (Table 2).

Table. 1: Results from the “Knockout studies”.

Group	Authors	Main Results
UCP1-KO	Yamashita et al., 2008	FABP3 affects free fatty acid flux and ↑UCP1 thermogenesis.
	Feldmann et al., 2009	UCP1 activity affects obesity development in mice and humans.
	Inokuma et al., 2006	Anti-obesity effect of β3-adrenergic stimulation is largely attributable to UCP1 in BAT.
	Oelkrug et al., 2011	Functional BAT is essential for rapid arousal from torpor.
	Shabalina et al., 2010	↑shivering muscle and ↓heat loss => cold adaptations in UCP1-KO mice.
	Anunciado-Koza et al., 2011	SLC25A25 => alternative thermogenesis.
	Meyer et al., 2010	↓heat loss by ↑vasoconstriction and ↓thermal conductance in UCP1-KO mice.
Brain	Streijger et al., 2009	Inefficient neuronal transmission => dysfunction in NST.
	Chao et al., 2011	NPY is a neuromodulator of the SNS controlling both WAT lipogenesis and BAT thermogenesis.
	de Jonghe et al., 2011	PTP1B in POMC influence cold-induce thermogenesis through thyroid axis.
Receptors	Korach-Andréa et al., 2011	LXRα and LXRβ control EE and BW through UCP1 expression.
	Vila-Bedmar 2012	GRK2 homozygous (+/-) => ↑ NST, ↑ EE and ↓ BW.
	Pelletier et al., 2008	Chronic muscle shivering in mice with dysfunctional NST.
	Hudson-Davies et al., 2009	RIP140 modulates metabolism and thermoregulatory adaptations.
	Ma et al., 2011	GHS-R regulates BAT NST, adiposity, metabolism and energy homeostasis during aging.
	Lin et al., 2011	GHS-R is involved in insulin sensitivity, EE, RMR and ↑ UCP1 during aging.
	Mano-Otagiri 2010	GHS-R/ghrelin => ↓ EE and ↑ EI by suppressing the SNS innervating BAT.
	Bauwens et al., 2011	α1-AMPK does not play a key role in NST and BW.
	Gray et al., 2006	PPAR-γ is required for full activation and recruitment of brown adipocytes.
	Giralt et al., 2011	Sirt3 is essential for the differentiation of fully thermogenic competent brown adipocytes.
	Tseng et al., 2008	Important role of BMP-7 in brown adipocyte differentiation and NST.
	Jimenez-Preitner et al., 2011	Plac8 is required for BAT differentiation and thermogenic capacity.
	Kiefer et al., 2012	Inactivation of Aldh1a1 => ↑ transcription of brown fat markers in WAT.
	Bordicchia et al., 2012	Cardiac NPs => BAT thermogenesis, ↑ PGC-1α and UCP1 and ↓ WAT mass via p38 MAPK.

Table. 2: Results from the “Other studies”.

Group	Authors	Main Results
Molecule Treatment	Lehr et al., 2009	Brown adipocyte medium => differentiation of WAT stroma vascular cells in brown adipocytes-like cells.
	Bartolomucci et al., 2006	TLQP-21 ↑EE and blocks the early phase of high-fat diet-induced obesity.
	Kim et al., 2006	PE ↑ BAT thermogenesis and WAT fatty acid oxidation.
	Ma et al., 2012	TRPM8 stimulation => ↑ core temperature, ↑ UCP1, and ↓ BW.
	Romero del Mar et al., 2009	OE maintains thermogenic potential.
	Leitner and Bartness, 2009	MSG ↓BAT NST and => obesity.
	Moriya et al., 2006	QRFP43 ↑feeding, ↓EE, and => obesity.
Male-Female and Gene Polymorphisms Difference	Rodriguez-Cuenca et al., 2007a	Variation of sex steroid receptor expression in BAT of male, female, pregnant and lactating females.
	Rodriguez-Cuenca et al., 2007b	Sex hormones affect mitochondrial transcription factors and mitochondriogenesis.
	Rose 2011	UCP1 transcription is ↑ by progesterone and retinoic acid but ↓ by 17-β estradiol.
	Nikolic 2011	Sex differences effect of PKG-I activation on BAT thermogenesis and WAT lipolysis.
Temperature Difference	Liu et al., 2009	Low temperature ↑NST, ↑RMR and ↑total respiratory capacity of BAT.
	Zhang et al., 2009	Cold exposure ↑EE, ↑thermogenic capacity, and ↑EI.
	Chen et al., 2012	↑ T3 and ↓ leptin => ↑ UCP1, NST, EI and RMR.
	Kitao et al., 2012	Hibernation => ↑ UCP1, ↑BAT thermogenesis and ↓BW more than cold exposure and short photoperiod.
	Zhang et al., 2012	Cold exposure => ↑ UCP1, ↑ BW, and ↓ leptin.
	Barger et al., 2006	UCP1 is the only mediator of NST in BAT.
Diet and Reproductive State	Xiao et al., 2007	Early postnatal over nutrition => adverse BAT impact reducing NST in adulthood.
	Zhao and Wang, 2009	Changes in nutritional fibre content => impact on BAT activity, basal metabolic rate, and NST.
	Primeaux et al., 2007	Spinal cord injury => ↓ BW, ↓ WAT mass, ↓ UCP1 mRNA and ↑ caloric intake.
	Zhang et al., 2008	Lactating voles ↑ caloric intake, ↑RMR, ↓ UCP1 and ↓ body fat mass.
	Cheng et al., 2010	Leucin deprivation => ↑ EE, ↑ UCP1, ↓ EI, ↓ BW.
	Du et al., 2012	Isoleucin or valine deprivation => ↑ EE, ↑ UCP1, ↓ EI, ↓ BW.
	Noatsch et al., 2011	↑ proteins or leucine in diet => no effect on energy homeostasis and UCP1 expression.

Note: KO = knockout; FABP3 = fatty acid-binding protein 3; ↑= increase; UCP1 = uncoupling protein 1; BAT = brown adipose tissue; ↓= decrease; => = induce; SLC25A25 = Solute Carrier Family 25 (Mitochondrial Carrier, Phosphate Carrier), Member 25; NST = non-shivering thermogenesis; NPY = hypothalamic neuropeptide Y; SNS = sympathetic nervous system; WAT = white adipose tissue; PTP1B = protein tyrosine phosphatase 1B; POMC =proopiomelanocortin; BW = body weight; LXR = liver-X receptor; EE = energy expenditure; GRK2 = G-protein-coupled receptor kinase 2; RIP140 = receptor interacting protein 140; GHS-R = growth hormone secretagogue receptor; RMR = resting metabolic rate, EI= energy intake; α1-AMPK = α1-AMP-activated protein kinase; PPAR-γ = peroxisome proliferator-activated receptor γ; Sirt3 = Sirtuin 3; BMP-7 = bone morphogenetic protein 7; Plac8 = placenta-specific 8; Aldh1a1 = aldehyde dehydrogenase 1 family, member A1; NPs = cardiac natriuretic peptides; PGC-1α = Peroxisome proliferator-activated receptor gamma coactivator 1-alpha ; p38 MAPK = p38 mitogen-activated protein kinase; PE = pinellia ternate; OE = Oleoyl-oestrone; MSG = monosodium glutamate; PKG-I = Cyclic guanosine monophosphate (cGMP)–dependent protein kinase I; T3 = tri-iodothyronine.

Conclusions

Activation of UCP1 can lead to body weight loss by stimulating NST. Different molecules affect the transcription of UCP1, the BAT plasticity and, therefore, NST. Specifically:

- Tri-iodothyronine hormone and antagonist of aldehyde dehydrogenase 1 family, member A1 enzyme could play an important role in brown adipocyte differentiation and plasticity leading to BAT mass gain.
- Key roles of progesterone/17β-estradiol ratio in the regulation of UCP1 transcription and therefore in both BAT activation and energy balance.
- Growth hormone secretagogue rec eptor may be activated in BAT during aging playing a key role in the aging-related dysfunction of BAT.
- Melatonin appears to play an important role in NST and body weight.
- Isoleucine or valine deprivation increases UCP1 gene expression and EE and reduces body weight through affecting orexigenic and anorexigenic neurons activity in the hypothalamus.

References

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