MUG – UOM - April 2011, Mauritius

Management of Obesity and Diabetes by targeting thermogenesis and fat oxidation:

From Pharmaceuticals to Nutraceuticals

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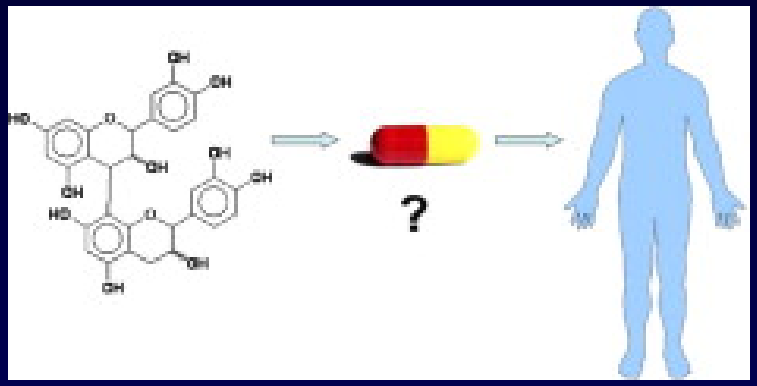
Switzerland

What are Nutraceuticals ?



Nutraceuticals are pharmaceutical forms

(pills, powders, capsules, vials, etc.)

containing food ingredients as active principles,

(bioactive food ingredients)

Phytochemicals:
several groups of polyphenols
(anthocyanins, proanthocyanidins, flavanones, isoflavones, resveratrol and ellagic acid)
are currently used in the nutraceutical industry

What are bioactive food ingredients ?

Bioactive constituents of :

Plants
fruits/seeds

Vegetables

Herbs

Spices

Animal products

Bacterial, algae & fungal products
(oils rich in AA or DHA)

Phytochemicals
Methyxanthines *(caffeine, theobromine)*
Antioxidant polyphenols from
black tea , green tea , Cocoa
Grape seeds, Citrus species
Flaxseed lignans, *Olive oil*

Soy bean phytoestrogens

Capsaicinoids from red pepper & chillies

Animal products
Milk bioactive peptides, whey protein
Dairy calcium, alpha-lipoic acid
Specific aminoacids: leucine, arginine

Specific fatty acids*:*
MCT, n6 PUFA, AA, Conjugated Linoleic Acid, marine n3 PUFAs (EPA,DHA)

Nutraceuticals & Functional food ingredients

Functional foods
in the management of obesity and type 2 diabetes

Riccardi et al. *Curr Opin Clin Nutr Metab Care*. 2005; 8:630-5. Review.

Foods (& food ingredients) can be regarded as ***functional***

if proven to affect beneficially one or more target functions in the body,

beyond adequate nutritional effects, in a way relevant to improved state of health and well-being, reduction of risk of diseases, or both.

Are functional foods redefining nutritional requirements ?

Jones PJ, Varady KA.

Appl Physiol Nutr Metab. 2008 ;33(1):118-23.

Search for bioactive food ingredients
which modulate energy expenditure & body composition

What ? **Why ?** **How ?**

1. **What** are bioactive food ingredients ?

2. **Why** interest in this search ? :

   physiological rationales for obesity management

3. **How** are we searching ?

   past, present & future

Physiological rationale for stimulating thermogenesis

- Low BMR is a risk factor for later obesity

  (Griffiths et al. Lancet 1990; Ravussin et al. NEJM, 1993;)

- Low capacity to increase thermogenesis in response to energy surplus enhances susceptibility to obesity

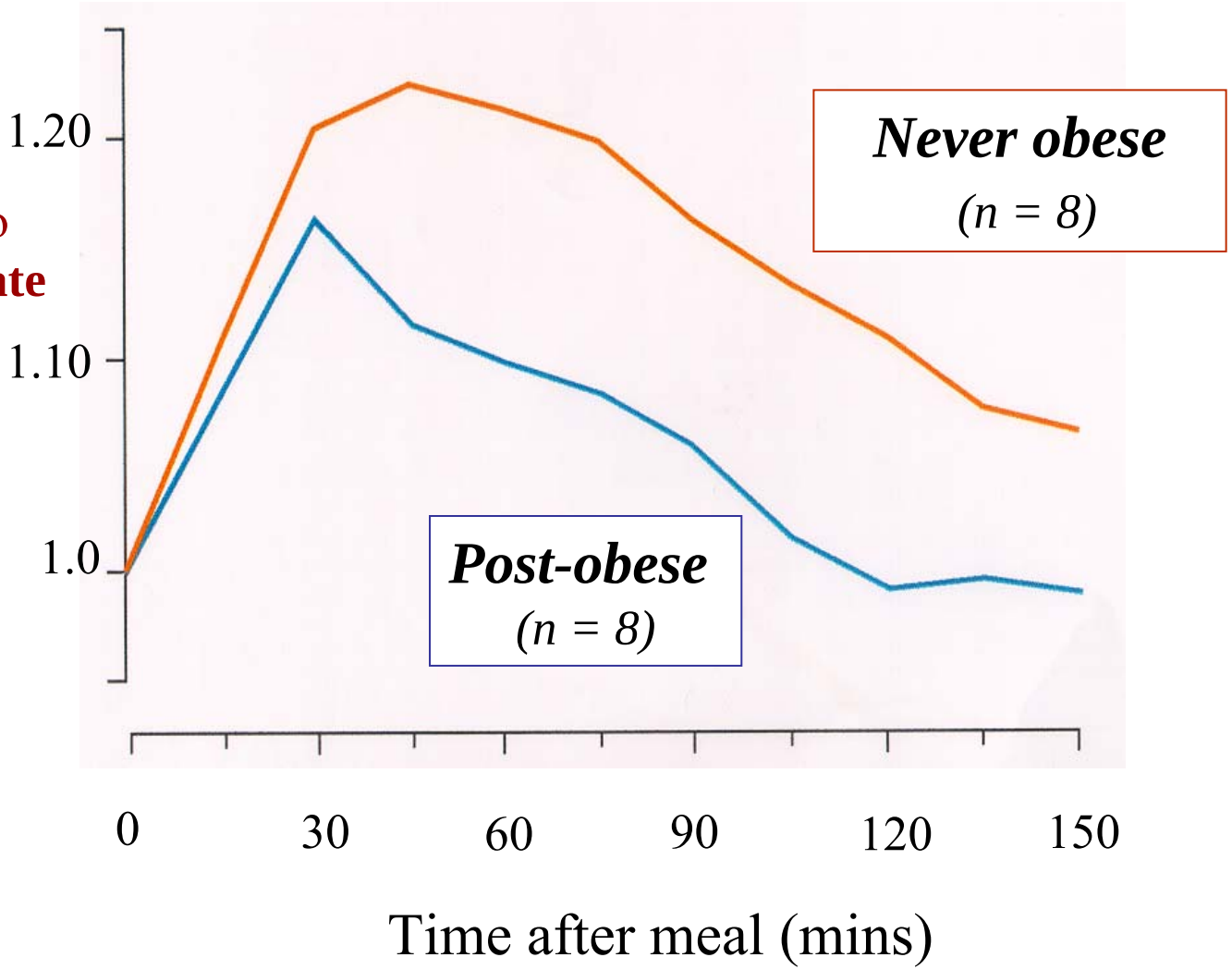
  (Levin et al Science 1999; Stock IJO 1999)

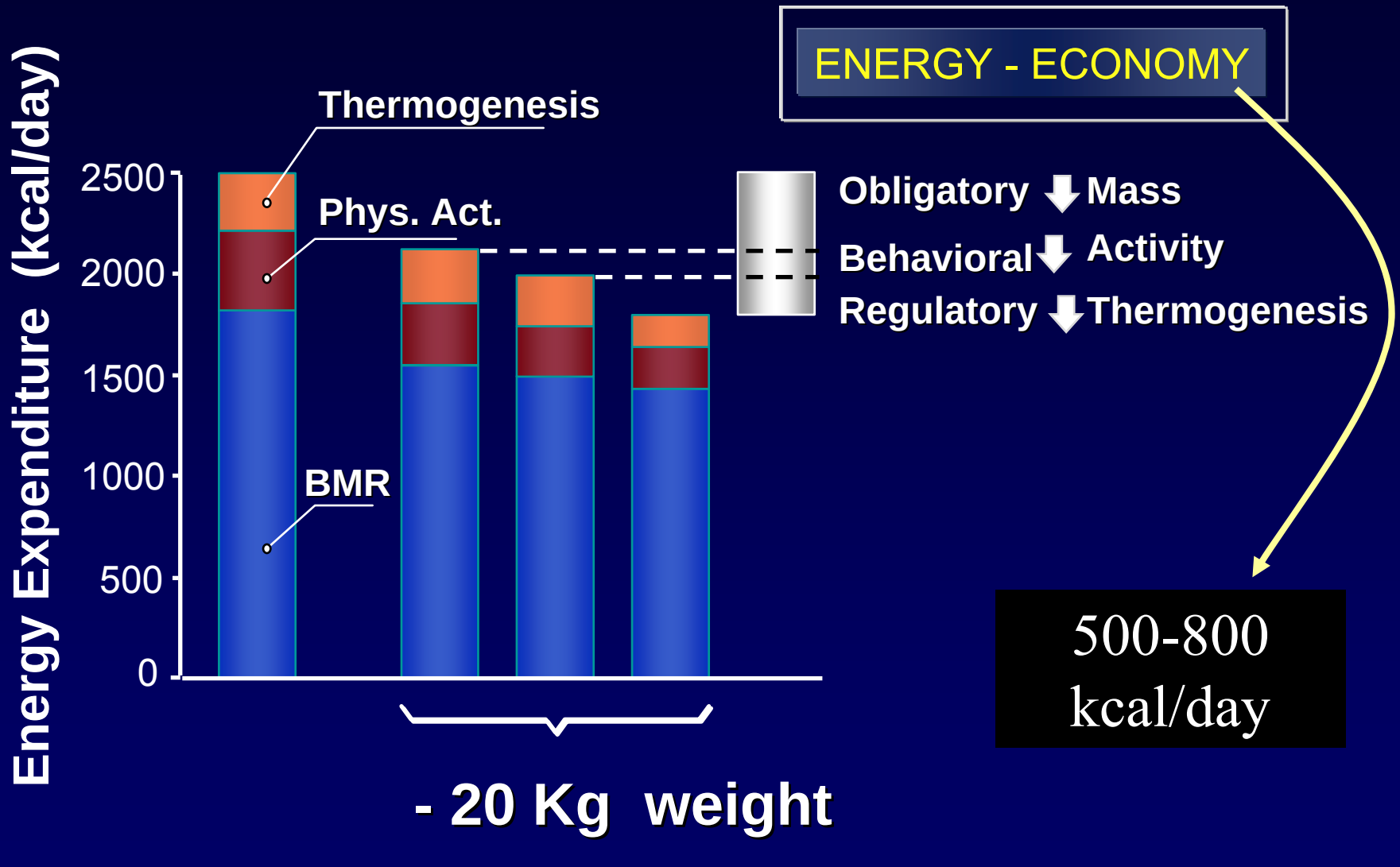
- Formerly obese (post-obese) patients have a 5-fold higher risk of having a low BMR than the never obese

  (Astrup et al. AJCN 1996)

Reduced postprandial thermogenesis in response to a mixed meal (300 kcal) in young women.

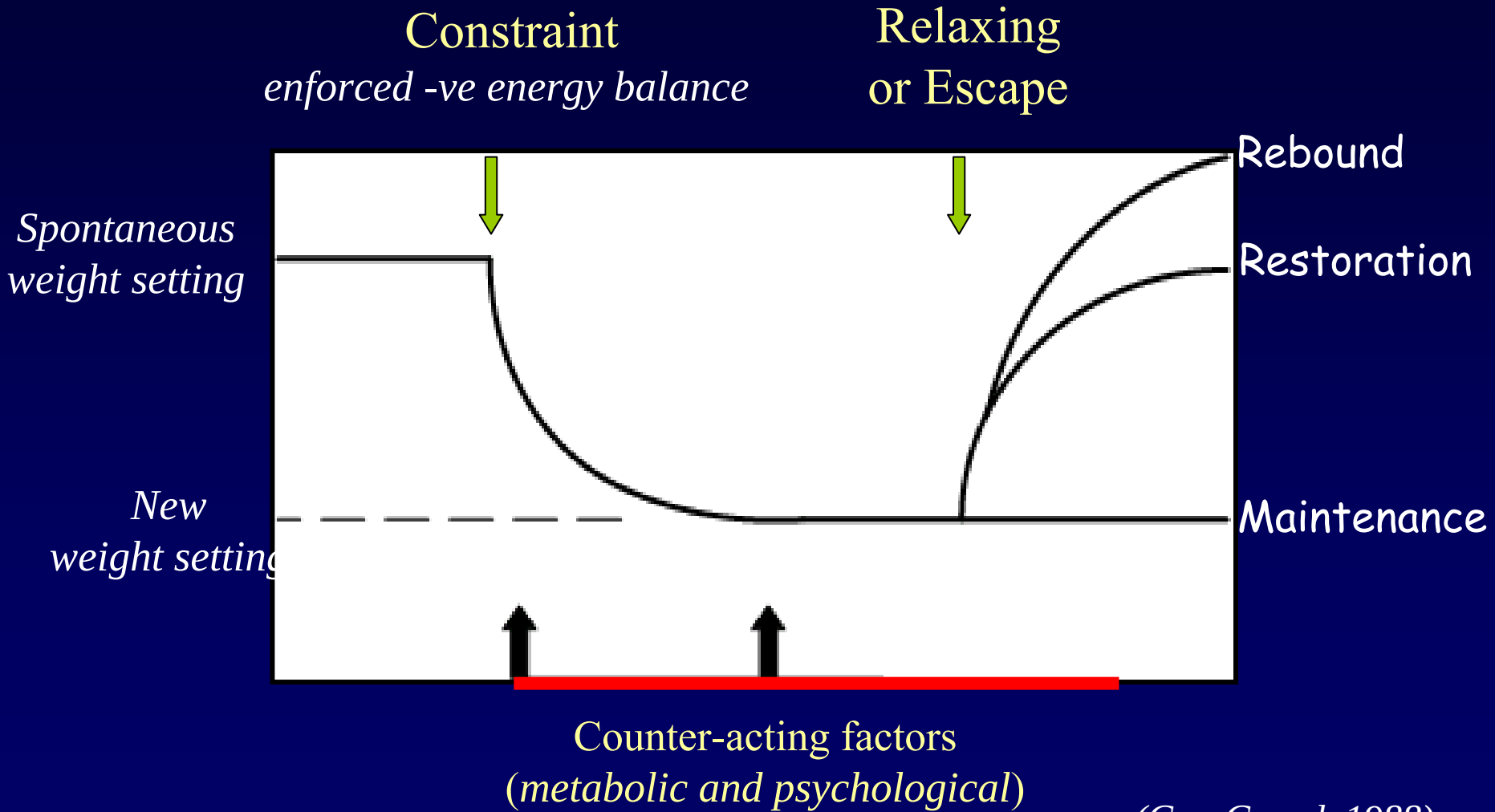
(Dulloo and Miller: *Am J Clin Nutr* 49: 44-50, 1989)





From Dulloo *Nutrition* (1993)

Evolution of body weight in the 'treated' obese



(Guy-Grand, 1988)

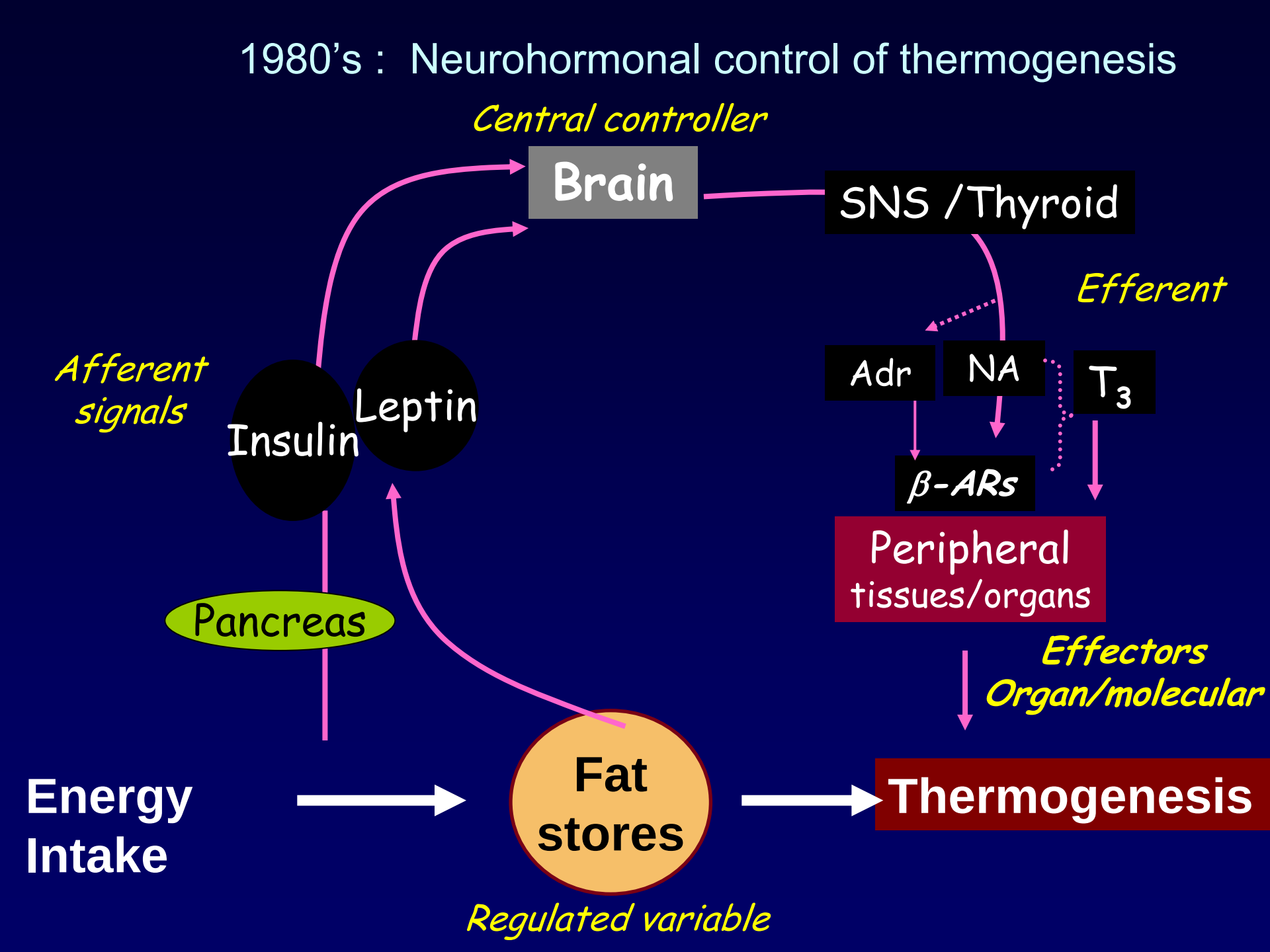
The past :
Pre-1980 Classification of thermogenic compounds

Derek Miller (QEC, London University)

Hormones	*Synthetics*	*Foods*
Thyroid extracts	Uncouplers (DNP)	Amino acids
Oestrogens	Anti-inflammatory	Liebig extract
Growth hormone	Vasodilators	Citrus extract
Glucagon	Ouabain	Caffeine
Gonadotropin	Isocitrate	(Alcohol)
		(Nicotine)

* Thermogenic drugs of everyday life

1980's : Neurohormonal control of thermogenesis



1980's

Rationale underlying systematic search for anti-obesity sympathomimetics

Sympathetic Nervous System (SNS)

Noradrenaline (NA)

Thermogenesis

Etiology

Susceptibility to obesity

Treatment

Counteract efficacy of hypocaloric regimens

Synergistic interactions between methylxanthines (Mx) and stimuli of the SNS on thermogenesis in humans

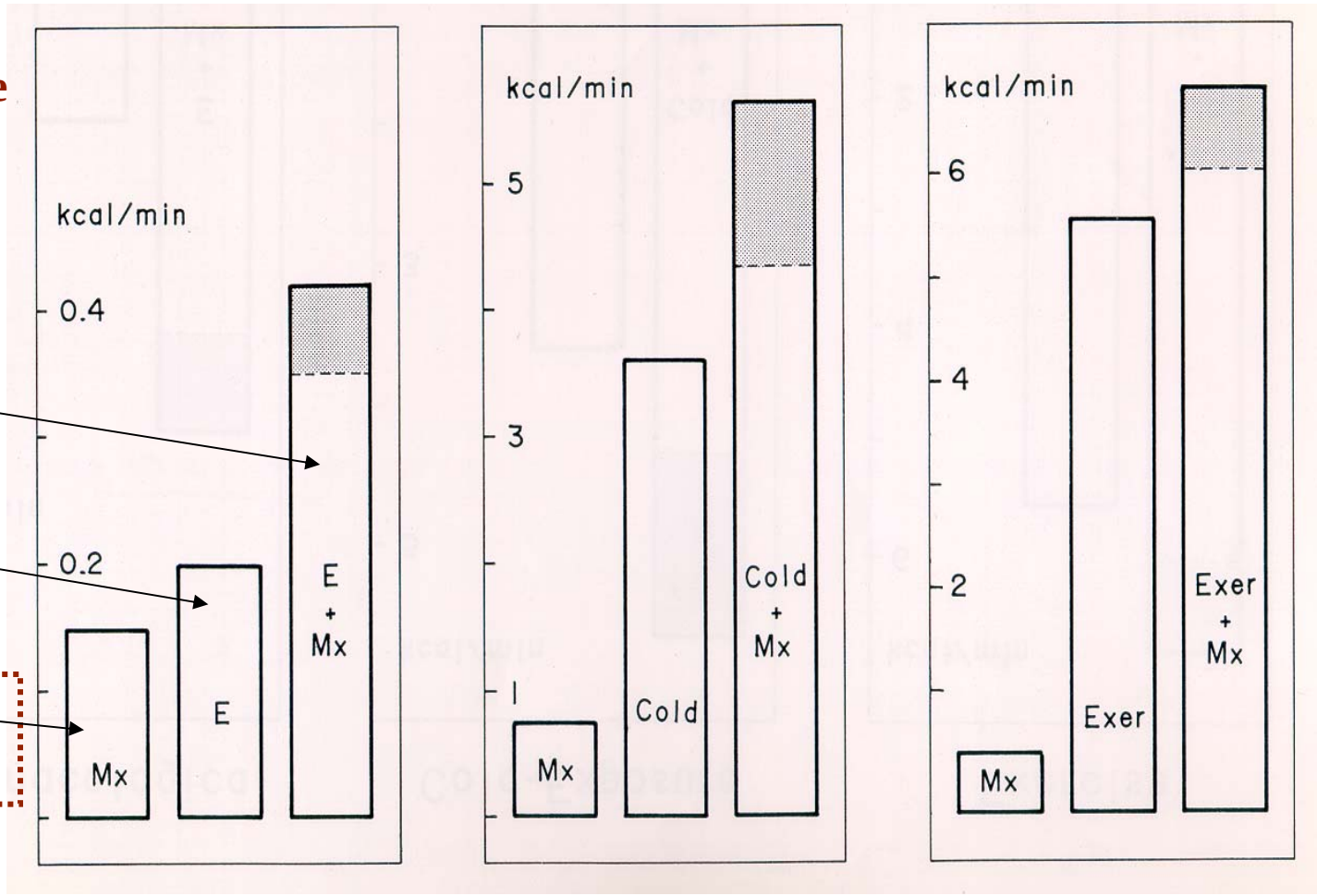
Pharmacological | **Cold exposure** | **Exercise**

Increase above Basal metabolic rate (BMR)

The Do-Do pill

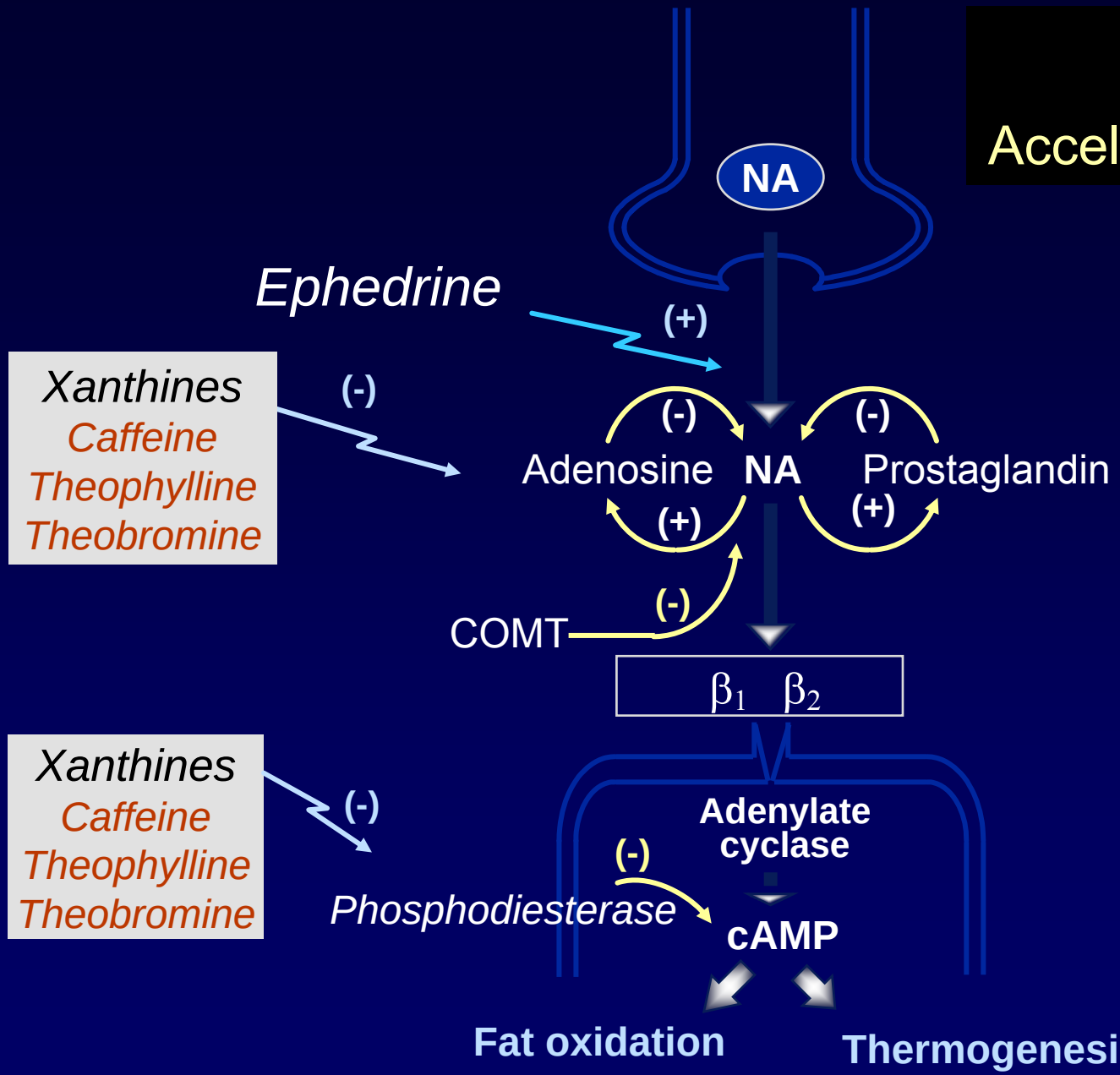
Ephedrine: 22 mg

Caffeine : 50mg
Theophylline: 30mg



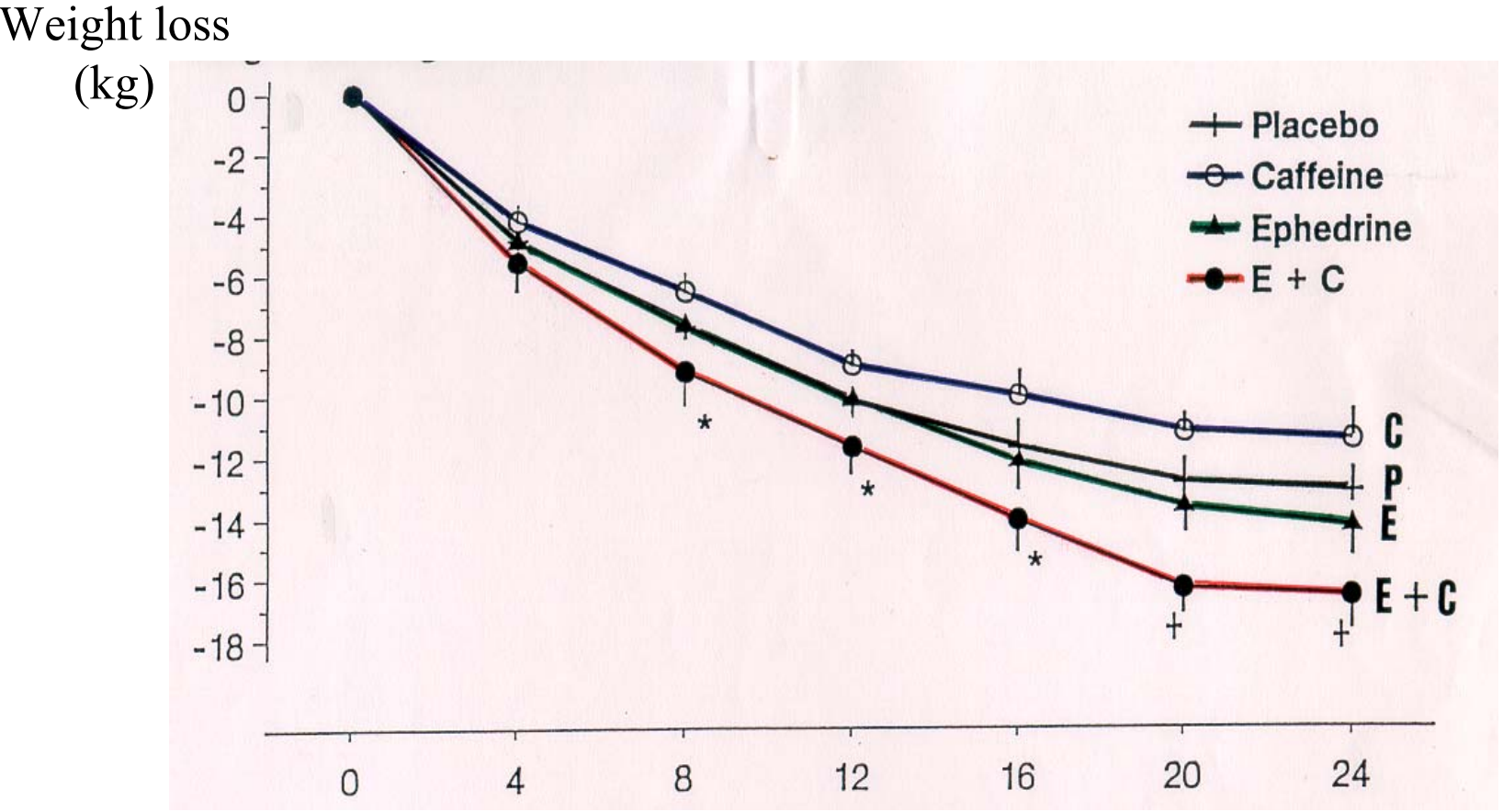
Dulloo & Miller (1986) *MacNaughton et al (1990)* *Chad & Quigley (1989)*

Concept of Accelerators and Brakes



Reviewed in *Dulloo Int J Obes (1993)*

Greater efficacy of E+C than E or C in inducing weight loss on a hypocaloric regimen



Astrup et al IJO (1992)

Side-effects : mild and transient

Number of adverse events

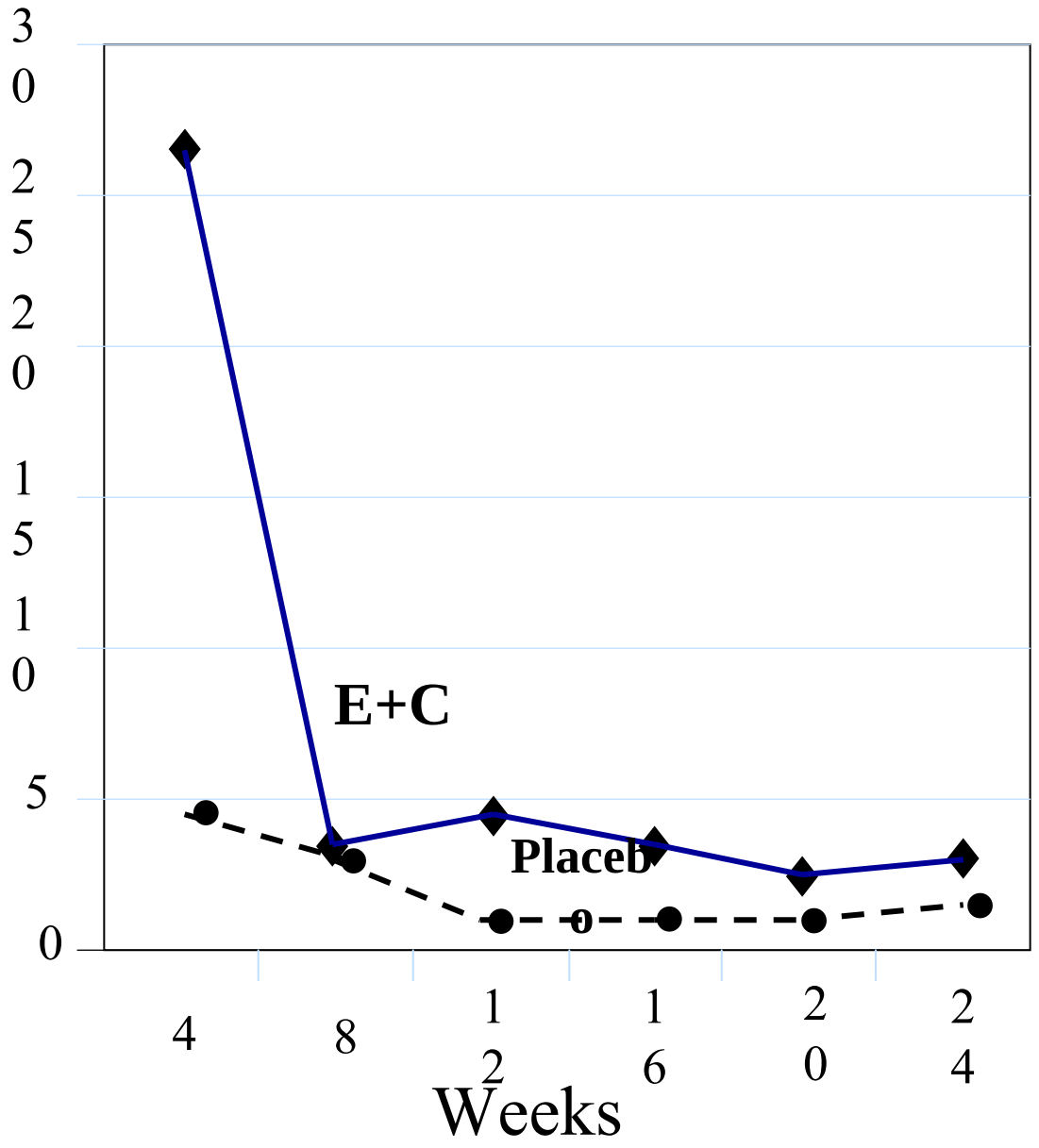
Dizziness

Tremor

headache

anxiety

insomia

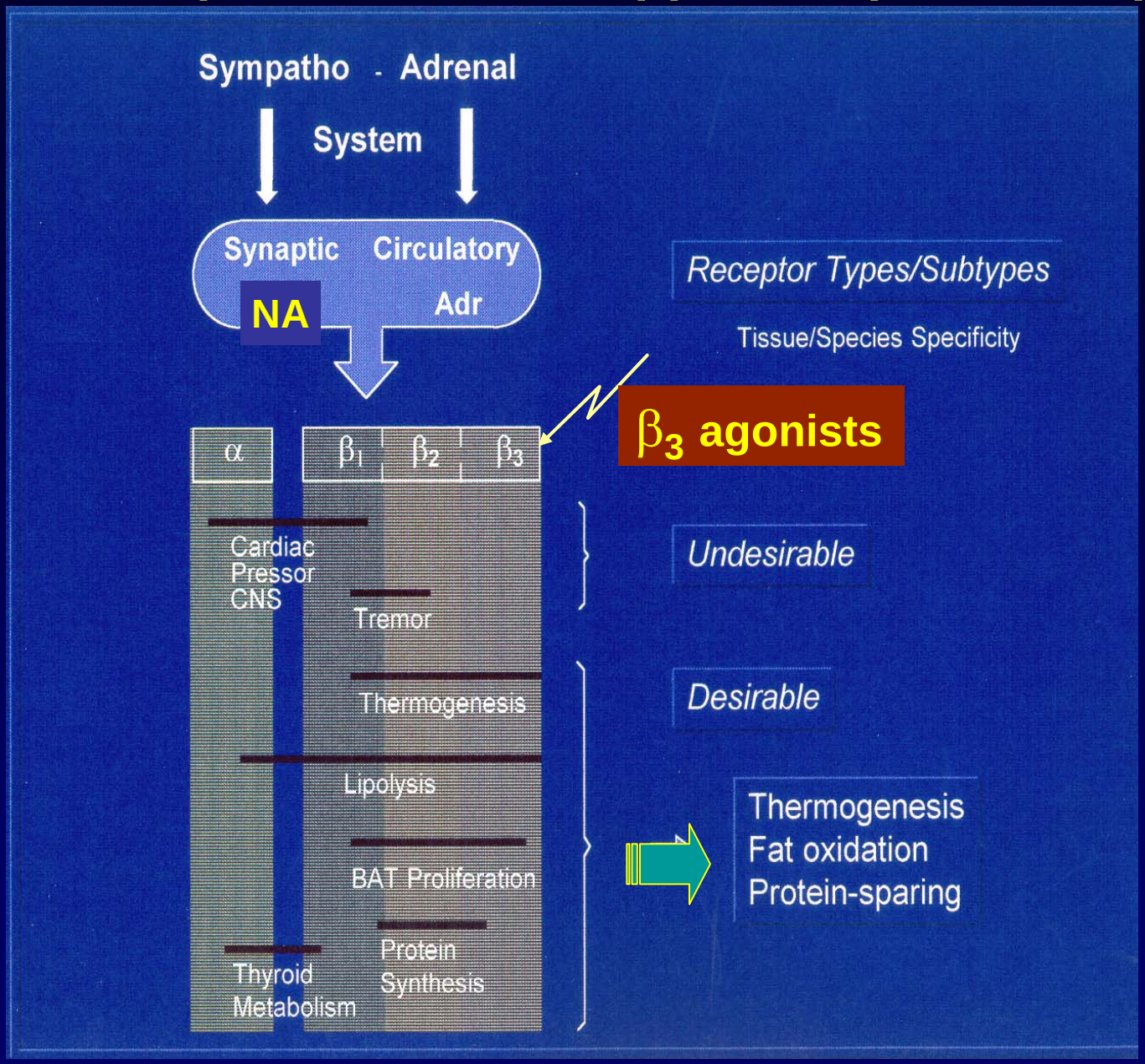


From F. Greenway *Obesity reviews* (2001)

Ephedrine + Caffeine as thermogenic anti-obesity drug cocktail ?

- Issues of patentability for putting these ‘old’ drugs to a new purpose,
- Risks for hypertension, tachycardia and tremor associated with drugs that could be acting on classical (α1, β1 and β2) adrenoceptors among a broad spectrum of the population, many of whom may have unrecognized risk factors
- Belief that more selective, safer and more efficacious novel sympathomimetics in development by pharmaceutical companies would soon become available.

The pharmaceutical approach (1984-2000)



Adapted from : Dulloo *Int J Obes* (1993); Dulloo AG : *Science* **297**: 780 (2002)

β_3-agonists : where are we ?

- Very effective thermogenic anti-obesity and anti-diabetic agents in rodents

- In humans, failure to produce a compound with good efficacy, selectivity and pharmacokinetic properties suitable for the stimulation of the small numbers of β_3- adrenoceptor

A vacuum filled

by potential thermogenic dietary food ingredients

Potential ‘thermogenic’ dietary/herbal ingredients

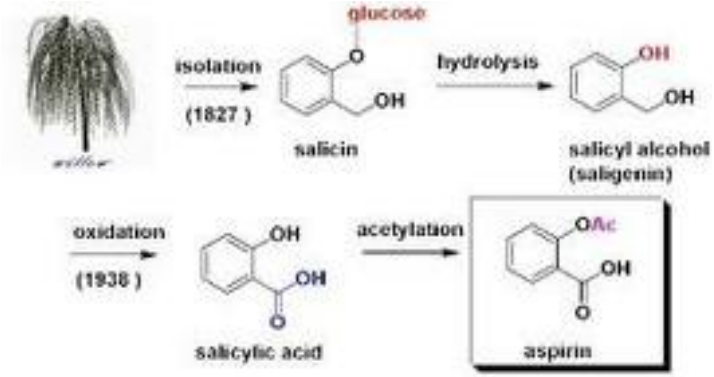
MA HUANG (Ephedra sinica) ephedrine + isomers

Coffee & Guarana Caffeine

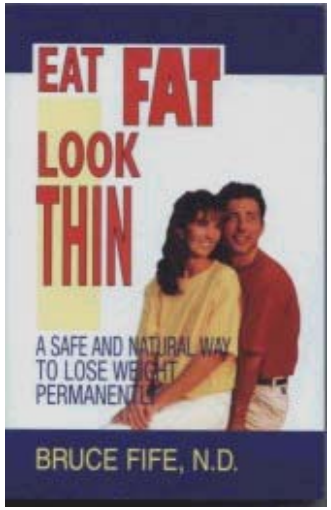
Coleus forskohlii forskoline:

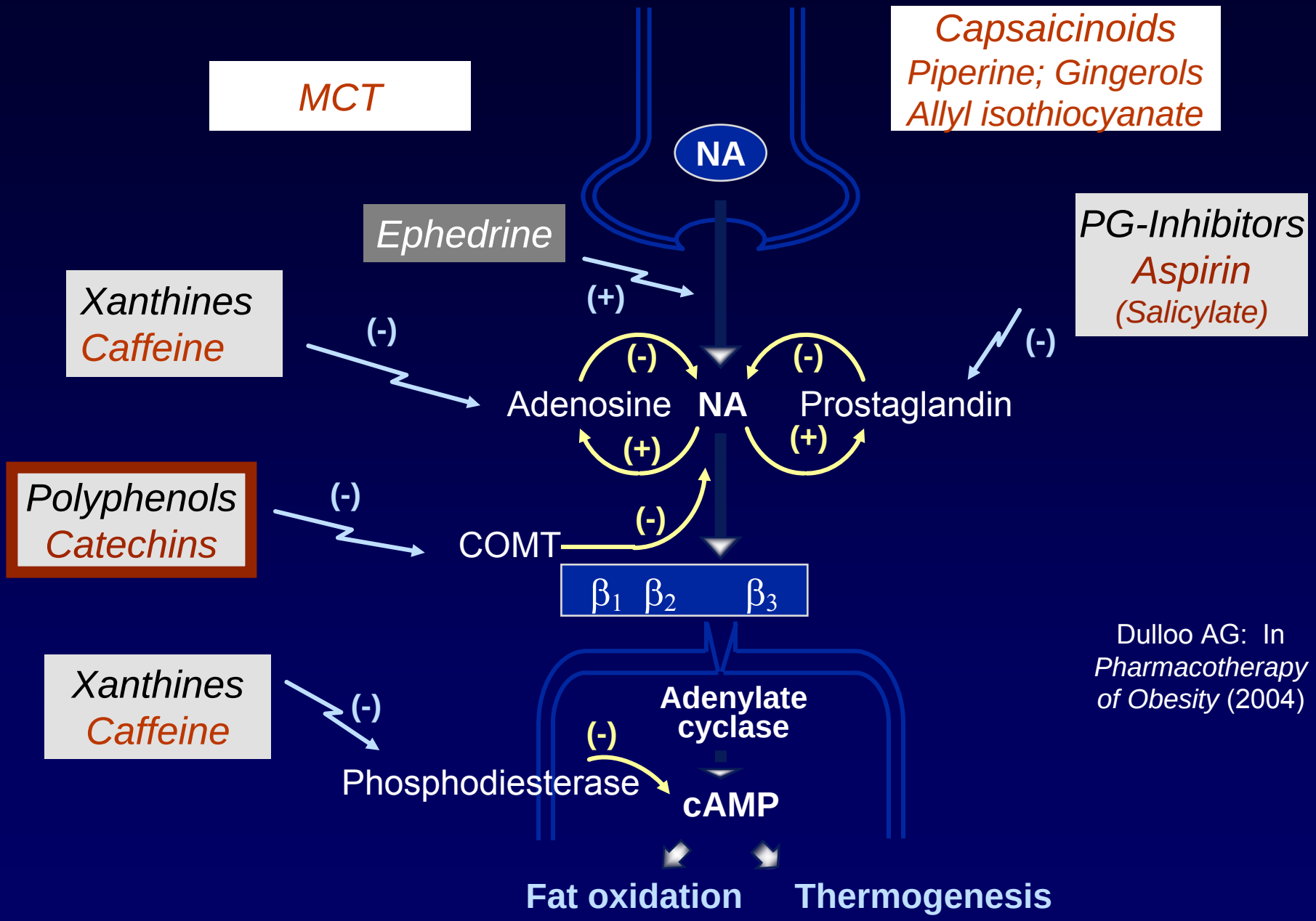
Green tea

Bark of Willow Aspirin



Coconut oil : MCT



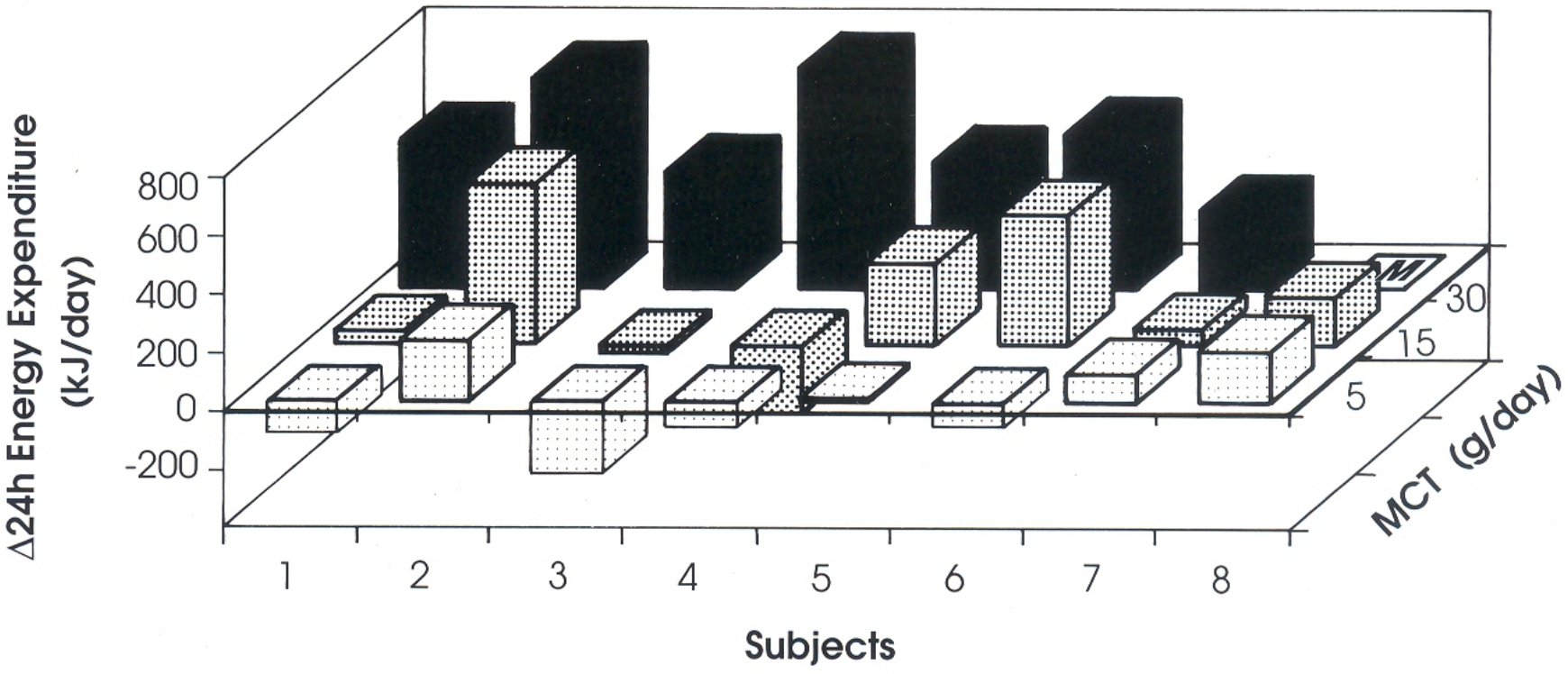


Dulloo AG: In *Pharmacotherapy of Obesity* (2004)

Increased energy expenditure (EE) in humans consuming high-fat diets richer in MCT *(substituting LCT)*

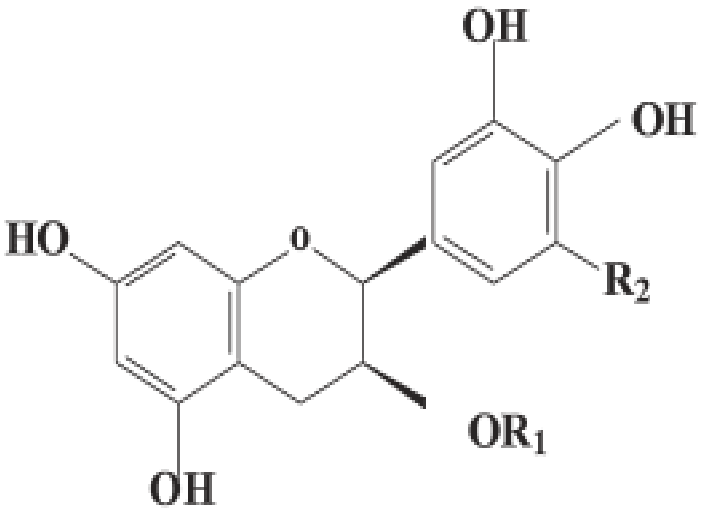
+ 5% daily EE associated with increased 24h urinary noradrenaline excretion

sympathetic activation of thermogenesis



Dulloo et al. Eur J Clin Nutr (1996)

Thé vert et polyphénols



Catechins (catechin-polyphenols)

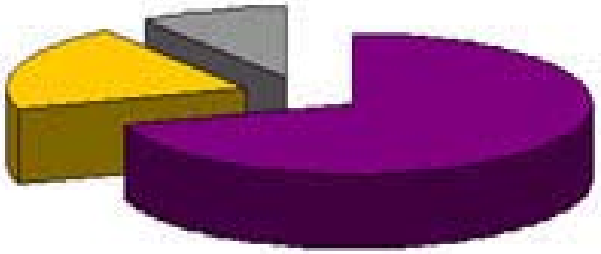
		R_1	R_2
Epigallocatechin gallate	EGCG	Gallate	OH
Epigallocatechin	EGC	H	OH
Epicatechin gallate	ECG	Gallate	H
Epicatechin	EC	H	H

CAMELLIA SINENSIS

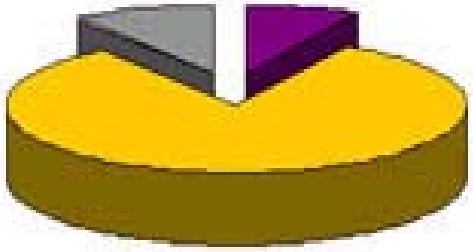
(GREEN TEA EXTRACT)

Total Flavonoids in Tea

Green Tea



Black Tea



Catechins ■ Theaflavins & Thearubigins ■ Flavonols ■

		R_1	R_2
Epigallocatechin gallate	EGCG	Gallate	OH
Epigallocatechin	EGC	H	OH
Epicatechin gallate	ECG	Gallate	H
Epicatechin	EC	H	H

Green tea extract rich in EGCG-catechins

Dulloo *et al.*, *Am J Clin Nutr* (1999), 70: 1040-5

Measurements in a room respirometer

24h energy expenditure, substrate oxidation

urinary catecholamines

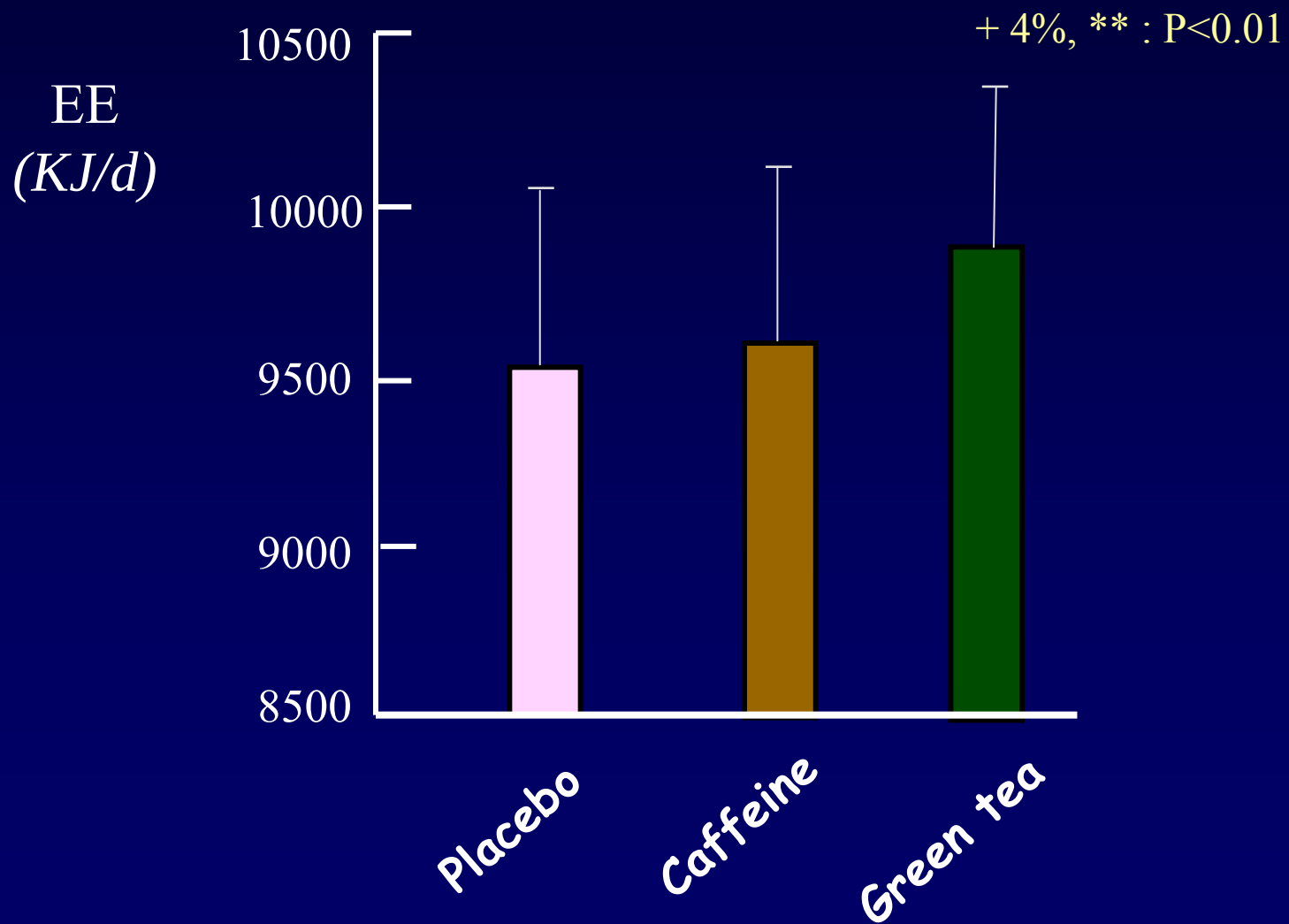
in 10 healthy men (normal weight to overweight)

in response to ingestion (3 x a day) of capsules containing either:

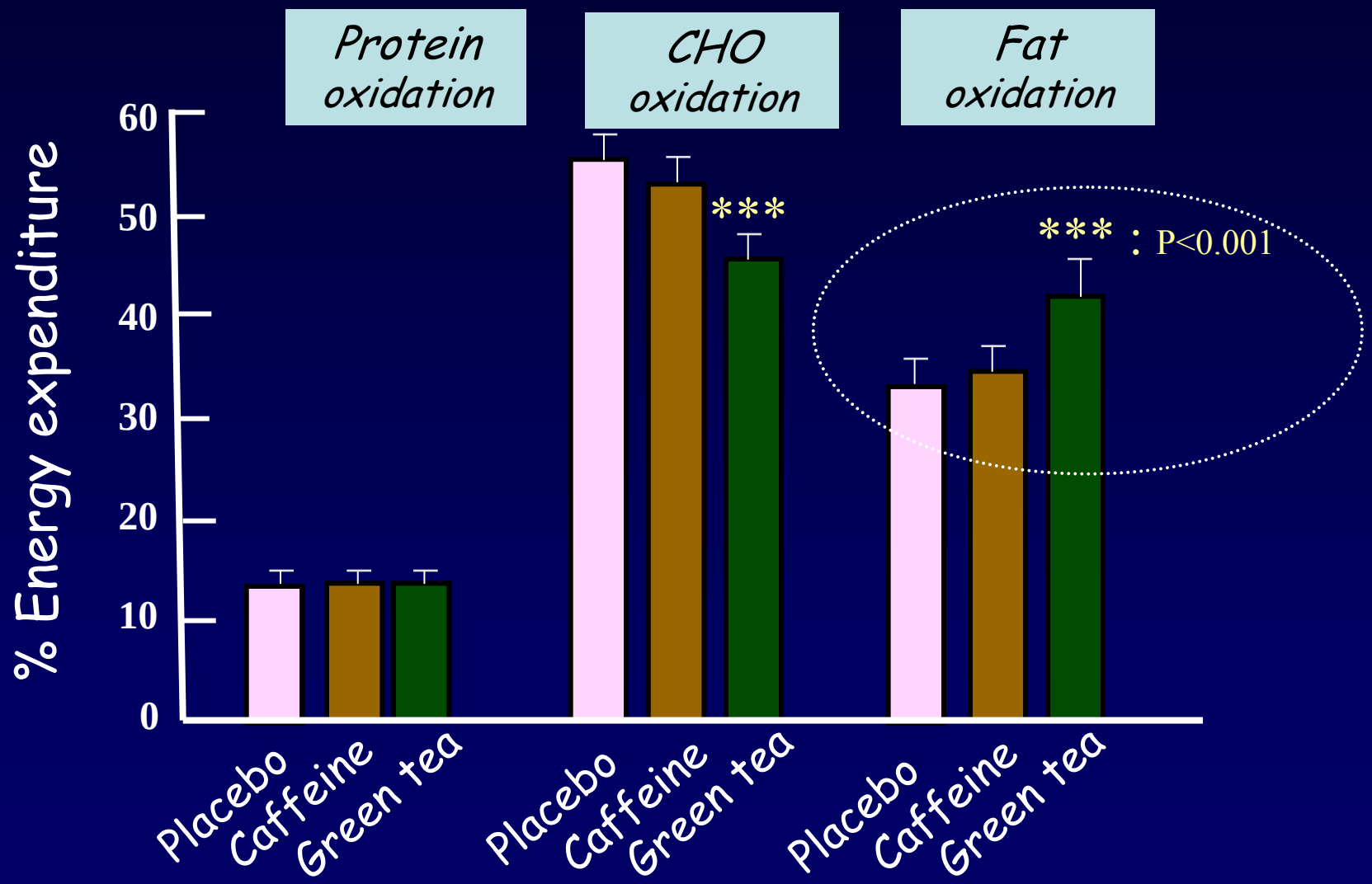
- Placebo
- A Green tea extract
  (*50 mg caffeine* & *90 mg catechin polyphenols*)
- 50 mg caffeine

Daily doses: 150 mg caffeine and 270 mg catechins

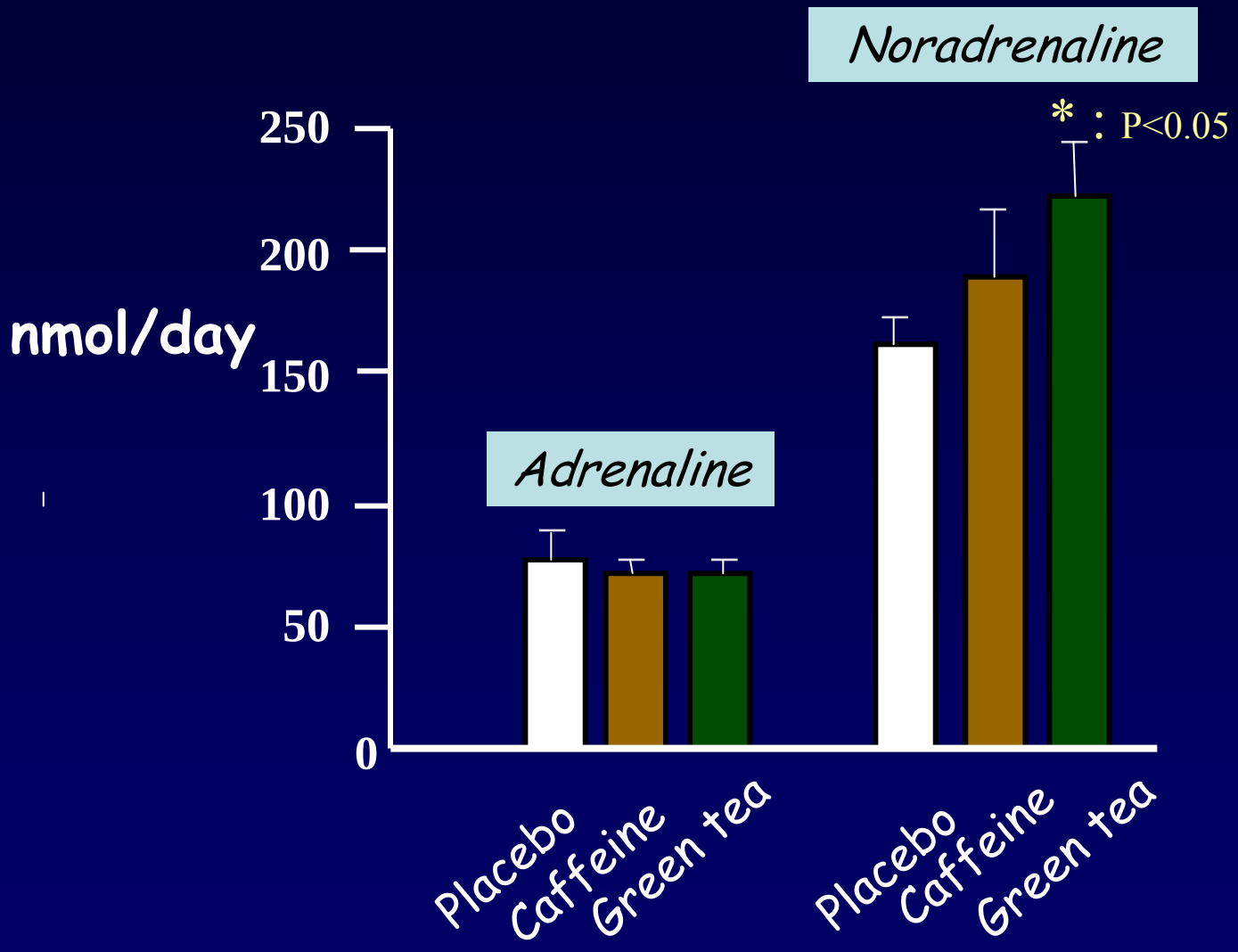
Elevated 24h energy expenditure (kJ) in response to green tea extract but not to caffeine alone



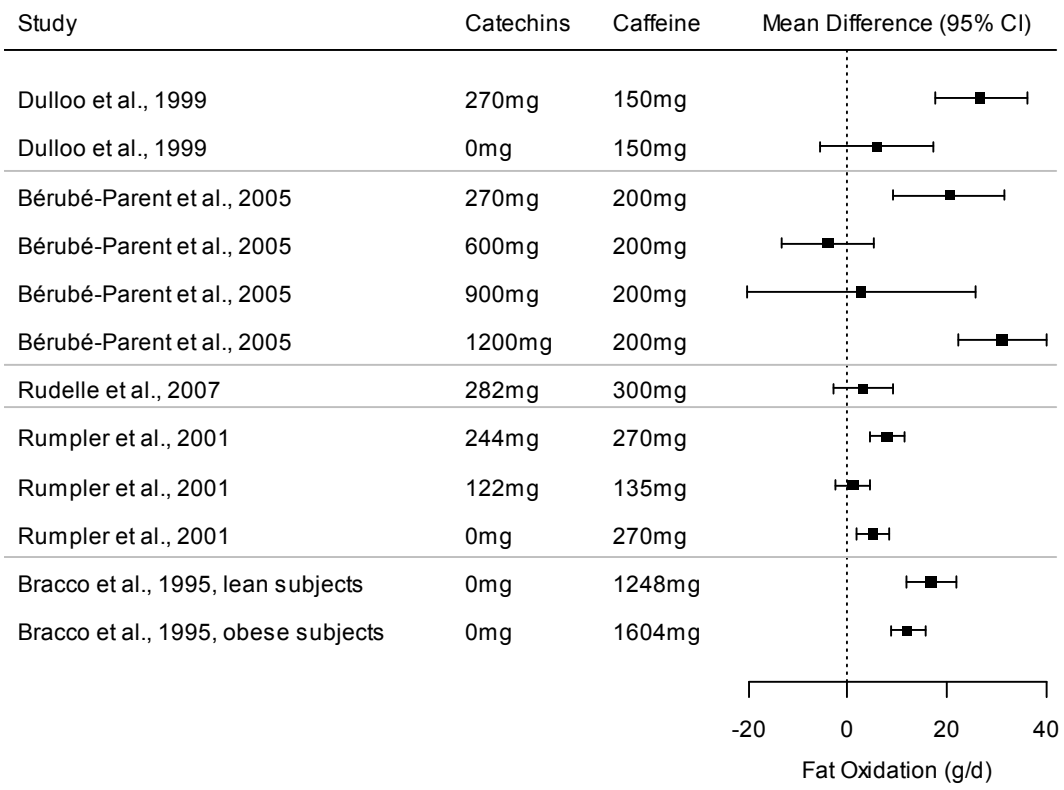
Elevated 24h lipid oxidation in response to green tea extract but not to caffeine alone



Elevated 24h urinary noradrenaline in response to green tea extract but not to caffeine alone

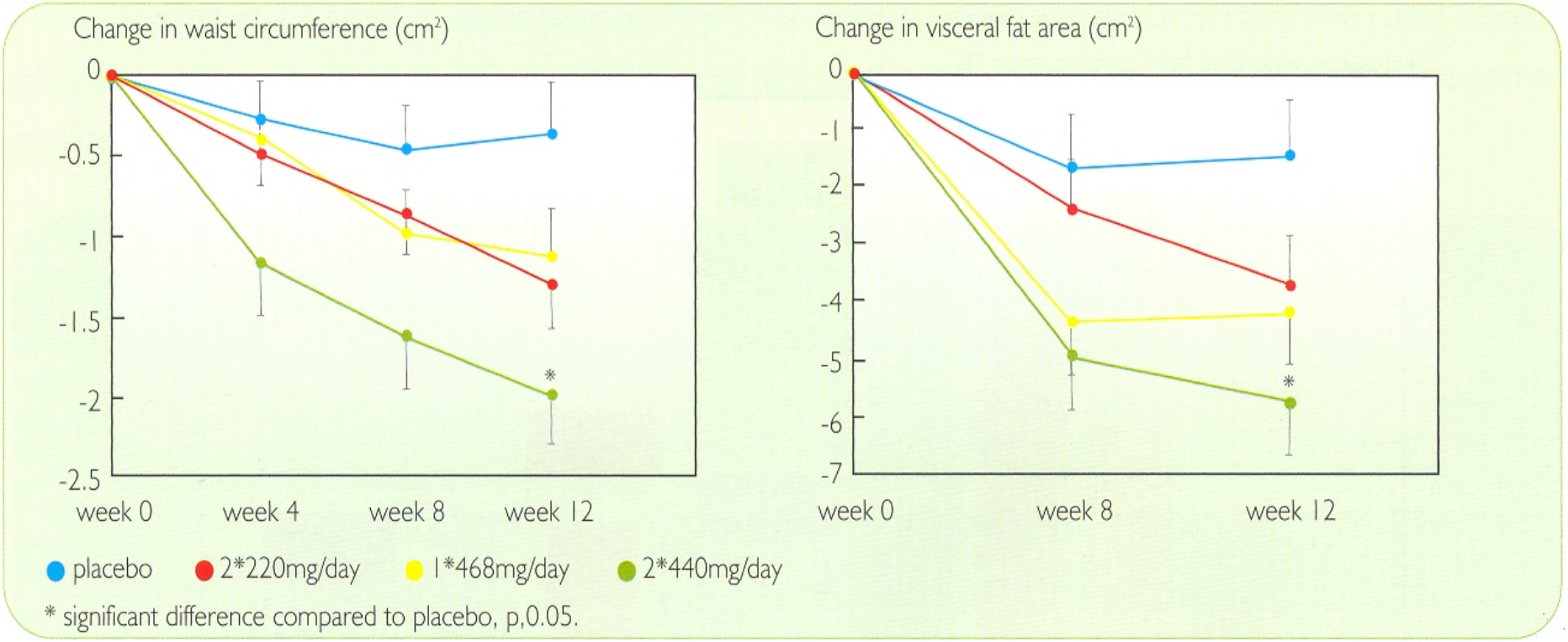


The effects of catechins and caffeine on fat oxidation: a meta-analysis



Hursel, Viechtbauer, Dulloo, Tremblay, Tappy, Rumpler, Westerterp-Plantenga
Obesity Reviews (2011, in press)

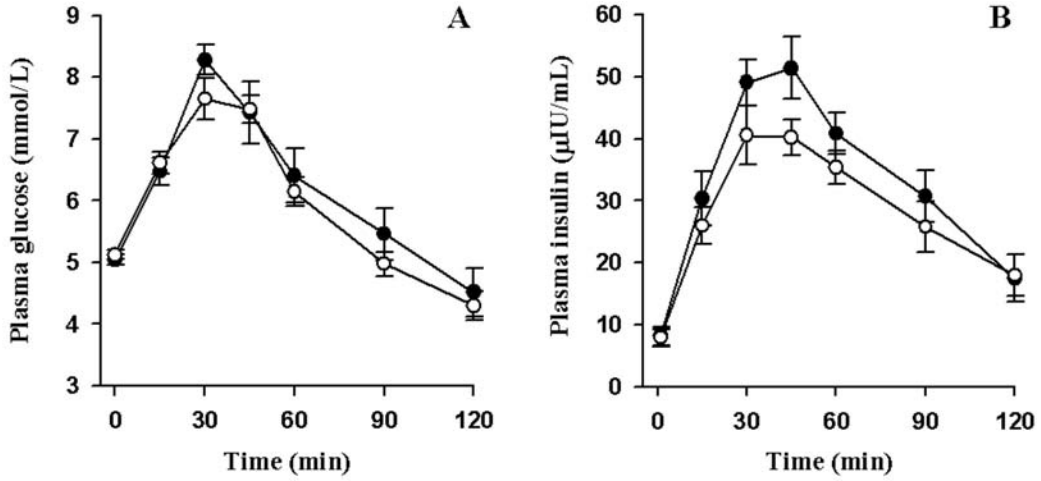
Long-term consumption of green tea rich in catechins is associated with altered body composition and lower abdominal (visceral) fat



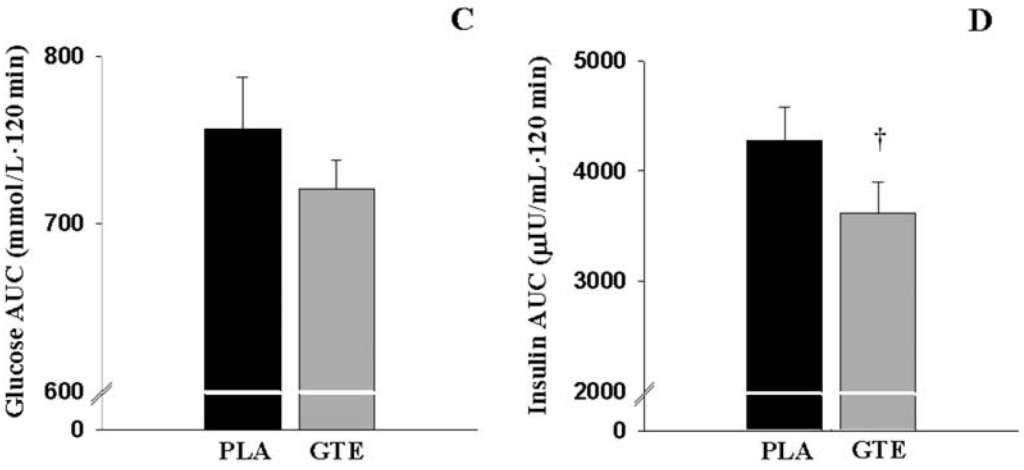
Nagao T et al. *Obesity (Silver Spring).* 2009;17(2):310-7. 2008

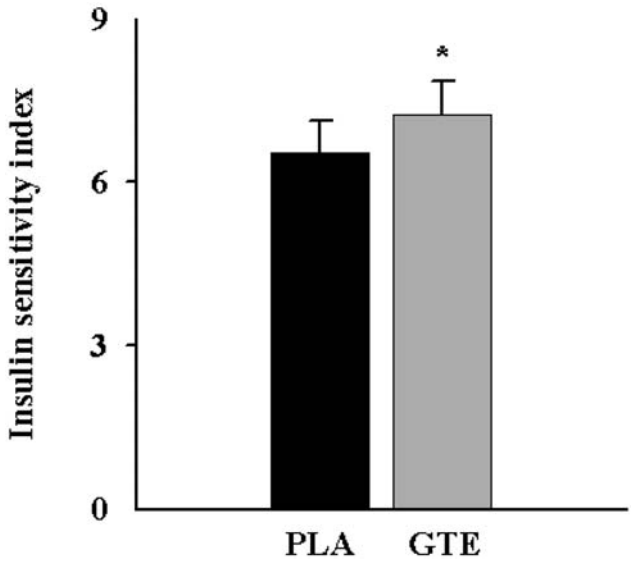
Green tea extract ingestion, fat oxidation & glucose tolerance in healthy humans

Venables M C et al. Am J Clin Nutr 2008;87:778-784



Green tea extract (GTE) (○)

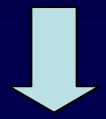




Venables M C et al. Am J Clin Nutr 2008;87:778-784

Mechanisms of action at organ/ tissue level

catechins and caffeine
interact with sympathetically-released NA



stimulate thermogenesis ?

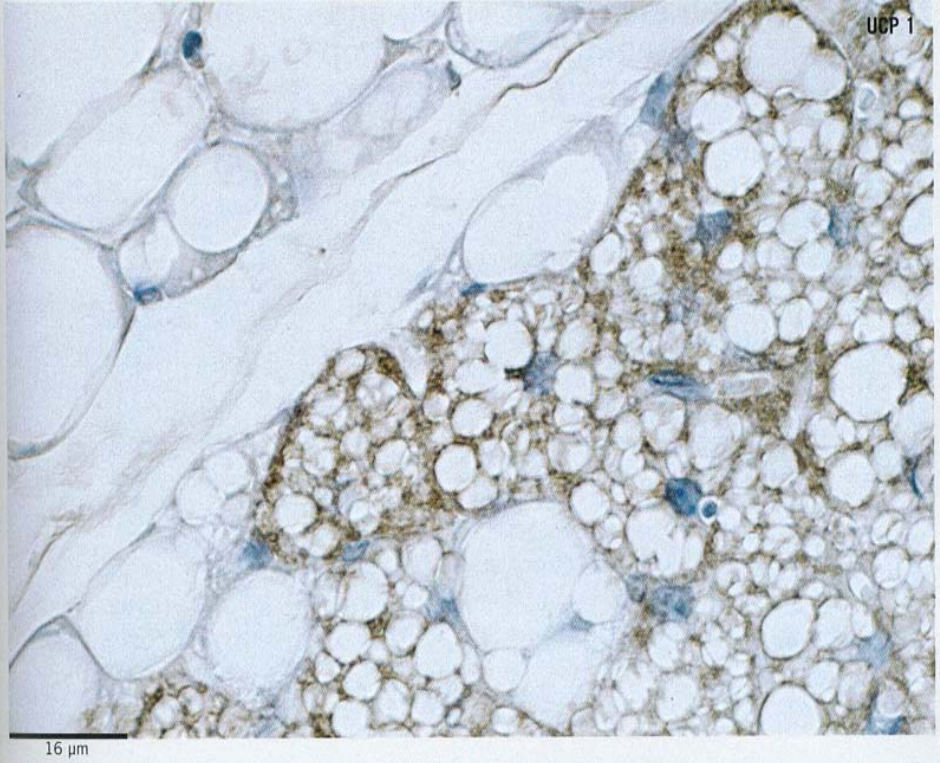
Ex-vivo studies in highy sympathetically innervated

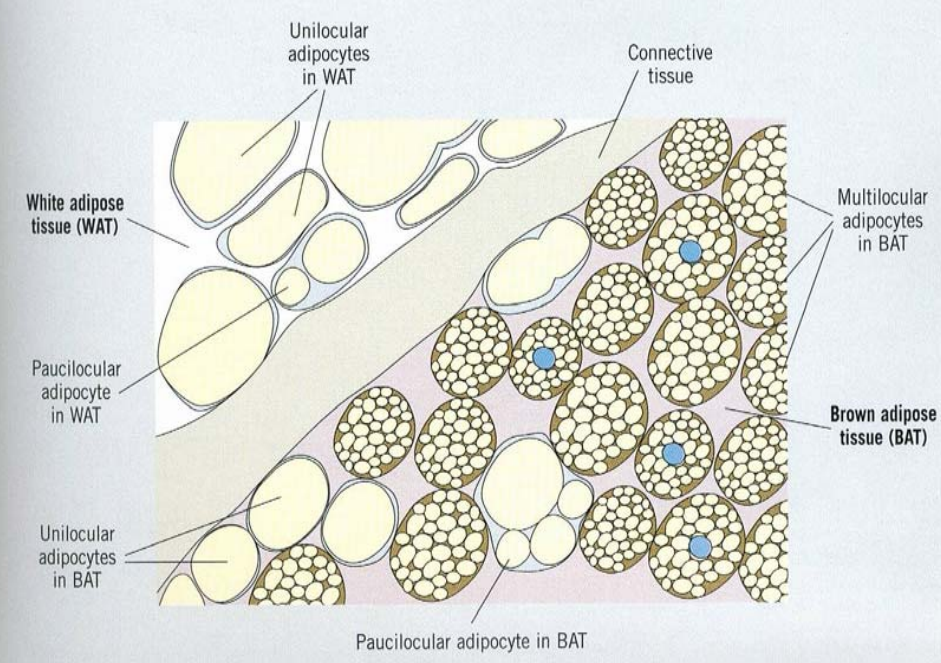
rat interscapular *brown adipose tissue fragments*

WAT & BAT

UCP-1 mitochondrial protein - brown

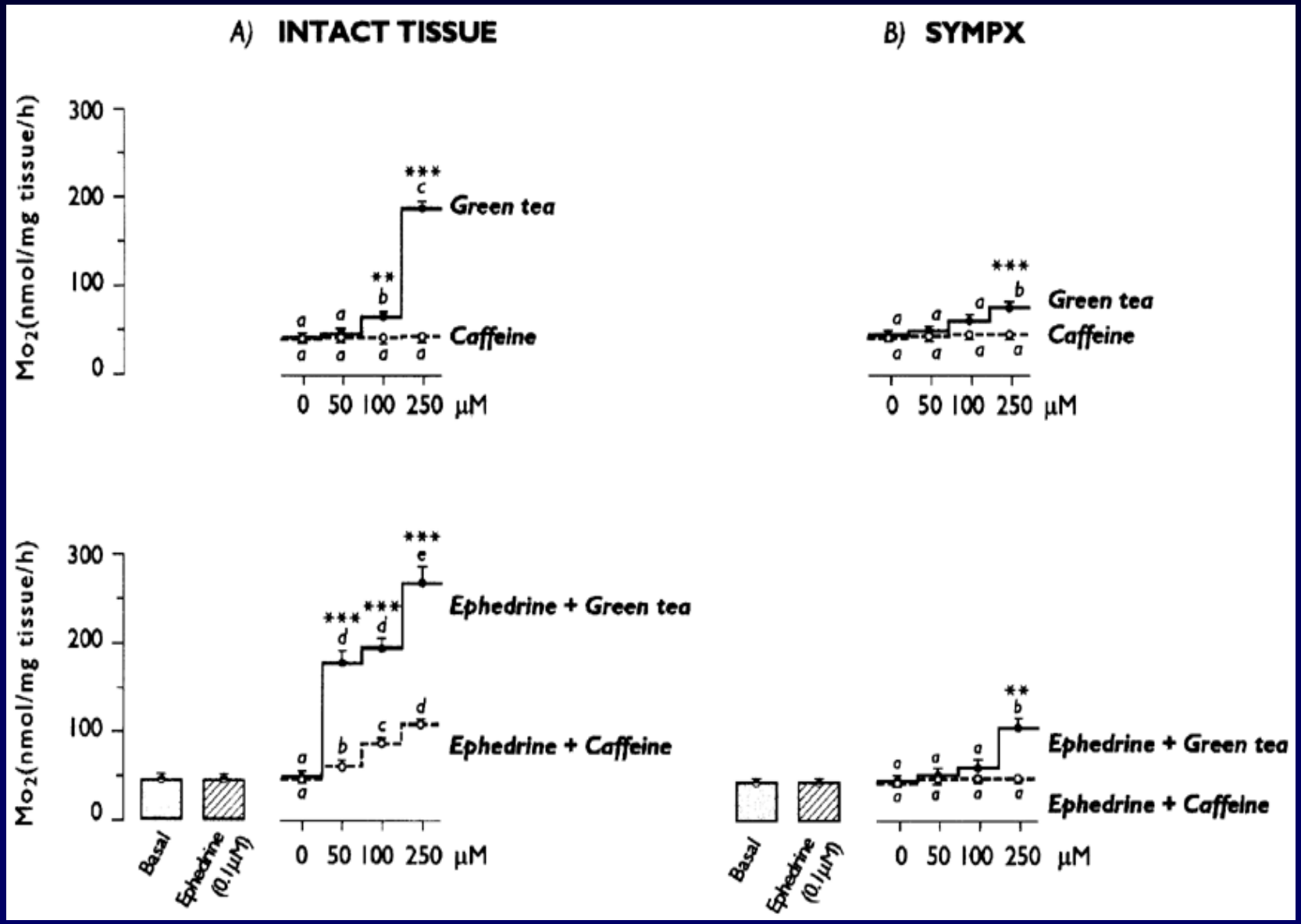
Cinti S: The adipose organ. 1999. Editrice Kurtis, Milano, Italy





Respiration rates (MO2) of rat brown adipose tissue

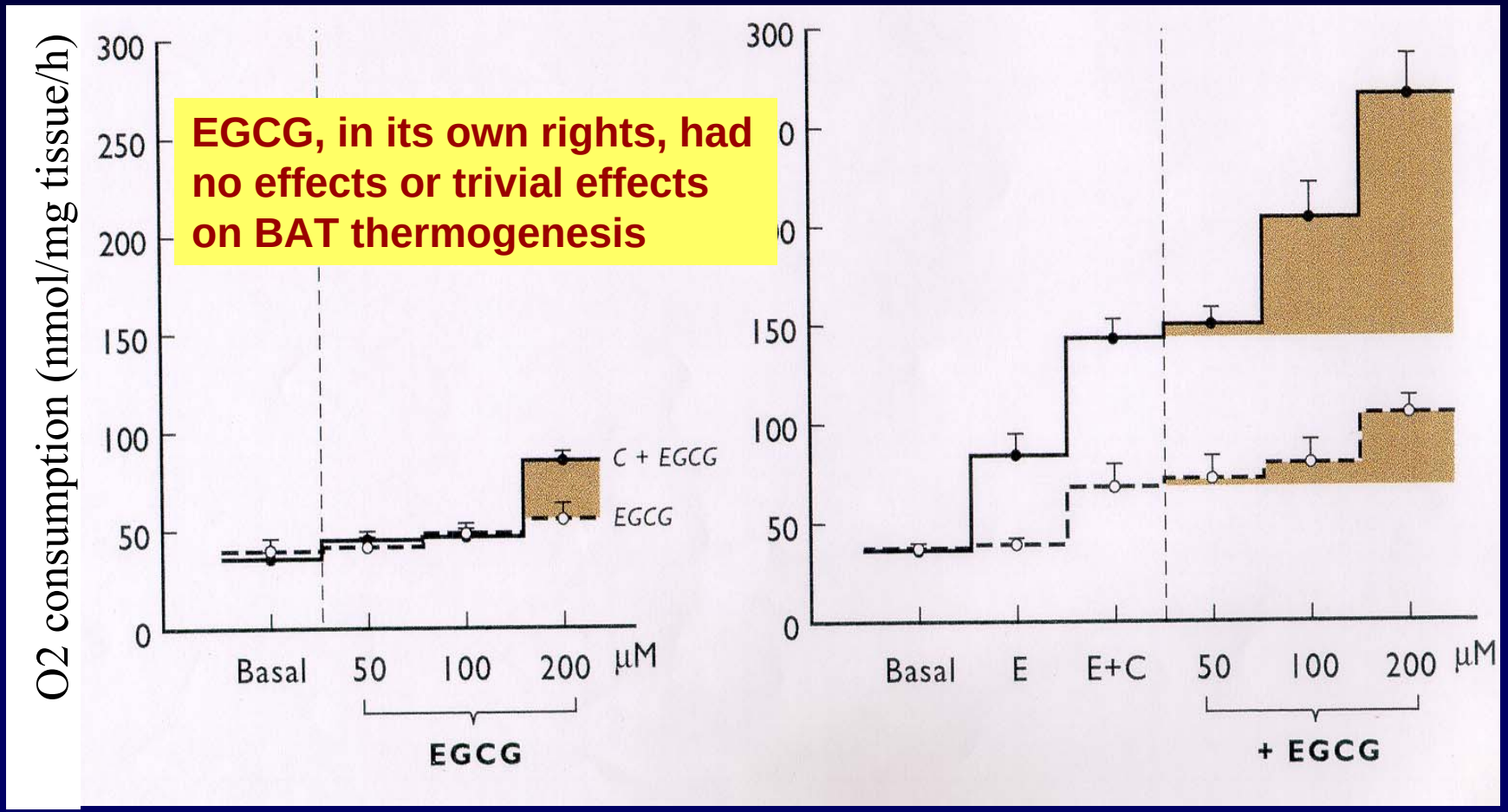
Dulloo, Seydoux,.. Girardier Int J Obesity (2000) 24(2):252-8.



*P<0.05; **P<0.01; ***P<0.001.

Synergistic interactions between EGCG and caffeine on **brown adipose tissue** thermogenesis in vitro

Unstimulated | **Stimulated with ephedrine (E)**



EGCG, in its own rights, had no effects or trivial effects on BAT thermogenesis

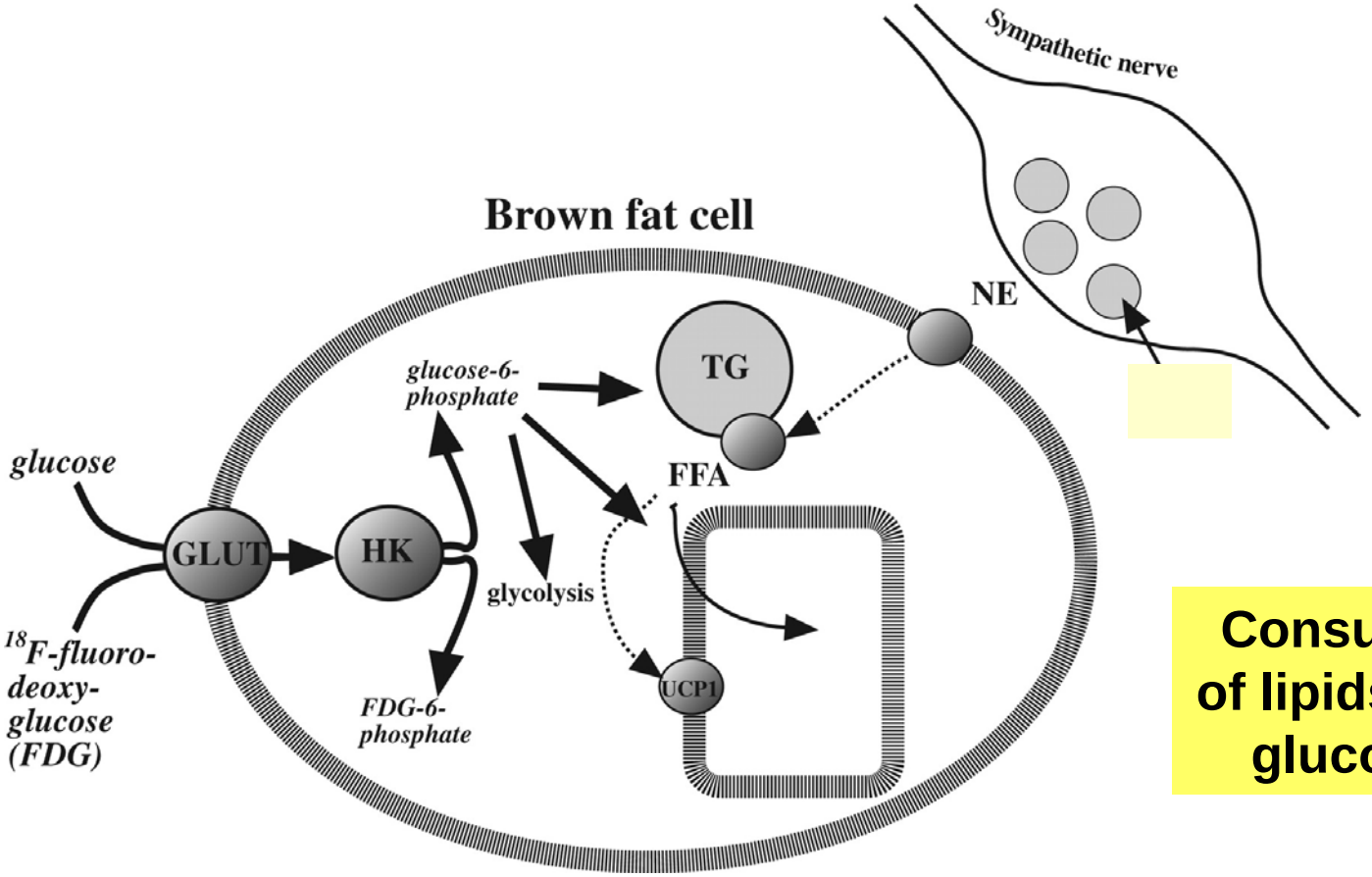
Dulloo et al Int J Obesity (2000) 24(2):252-8.

Unexpected evidence for active brown adipose tissue in adult humans

Jan Nedergaard, Tore Bengtsson, and Barbara Cannon

***Am J Physiol Endocrinol Metab* 293: E444-E452, (2007)**

2-[18F]fluoro-2-desoxy-glucose (FDG) uptake in brown fat cells

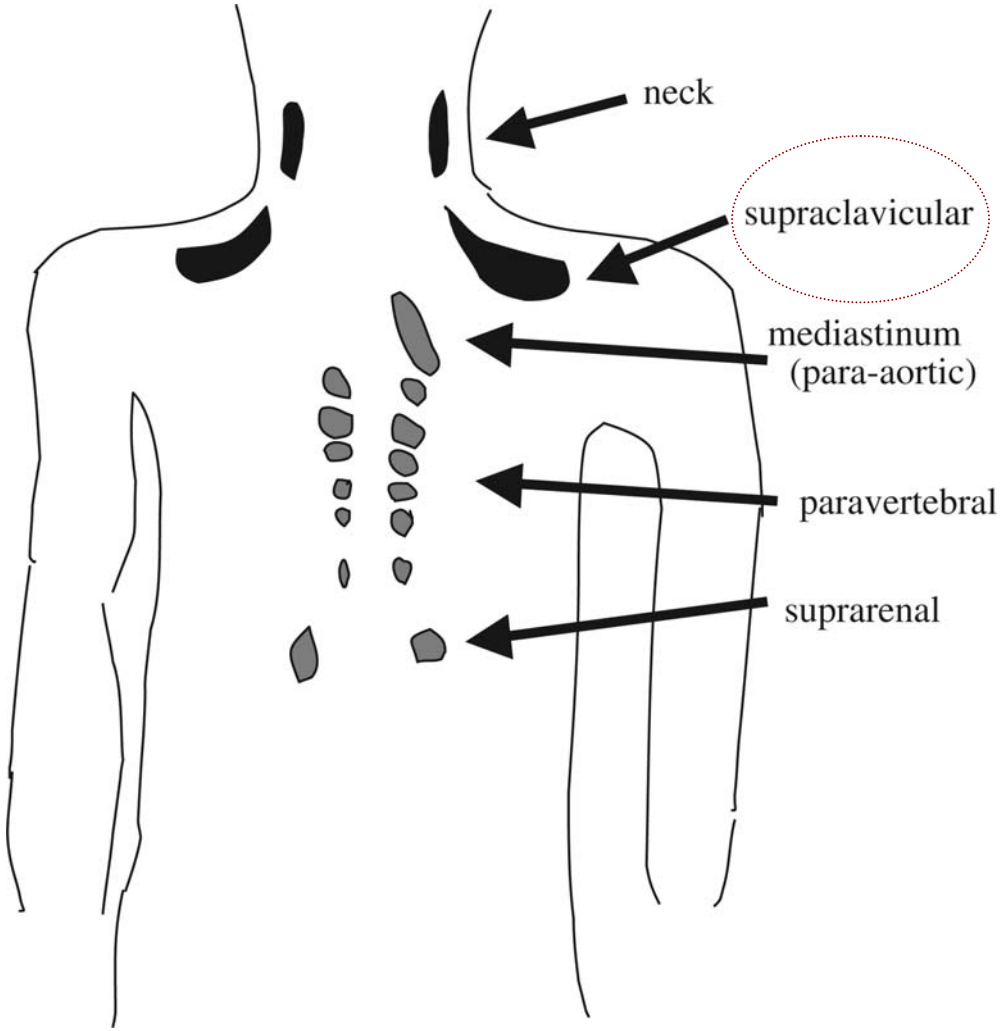


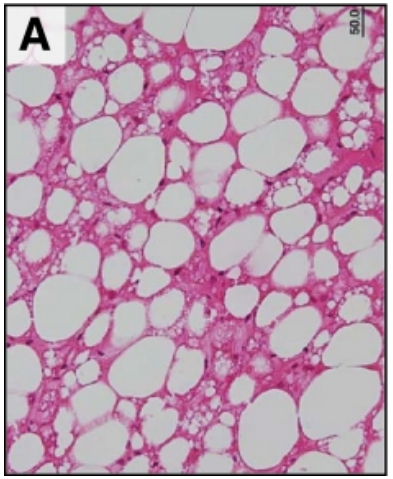
Consumer of lipids and glucose

Nedergaard, J. et al. Am J Physiol Endocrinol Metab 293: E444-E452 2007; doi:10.1152/ajpendo.00691.2006

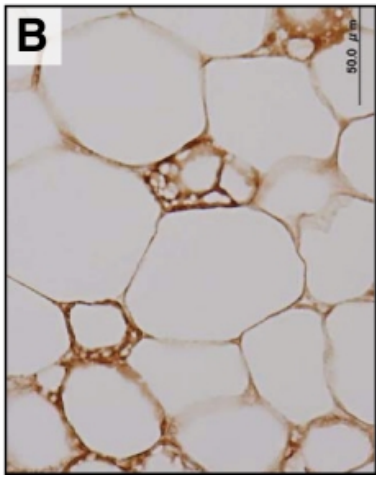
AJP - Endocrinology and Metabolism

Sites of FDG uptake corresponding to brown adipose tissue in adult humans





Stained with Hematoxylin and eosin



Stained with anti-serum against UCP1

www.med.harvard.edu/JPNM/chetan/normals/brown_fat/case.html

Functional brown adipose tissue in adult humans

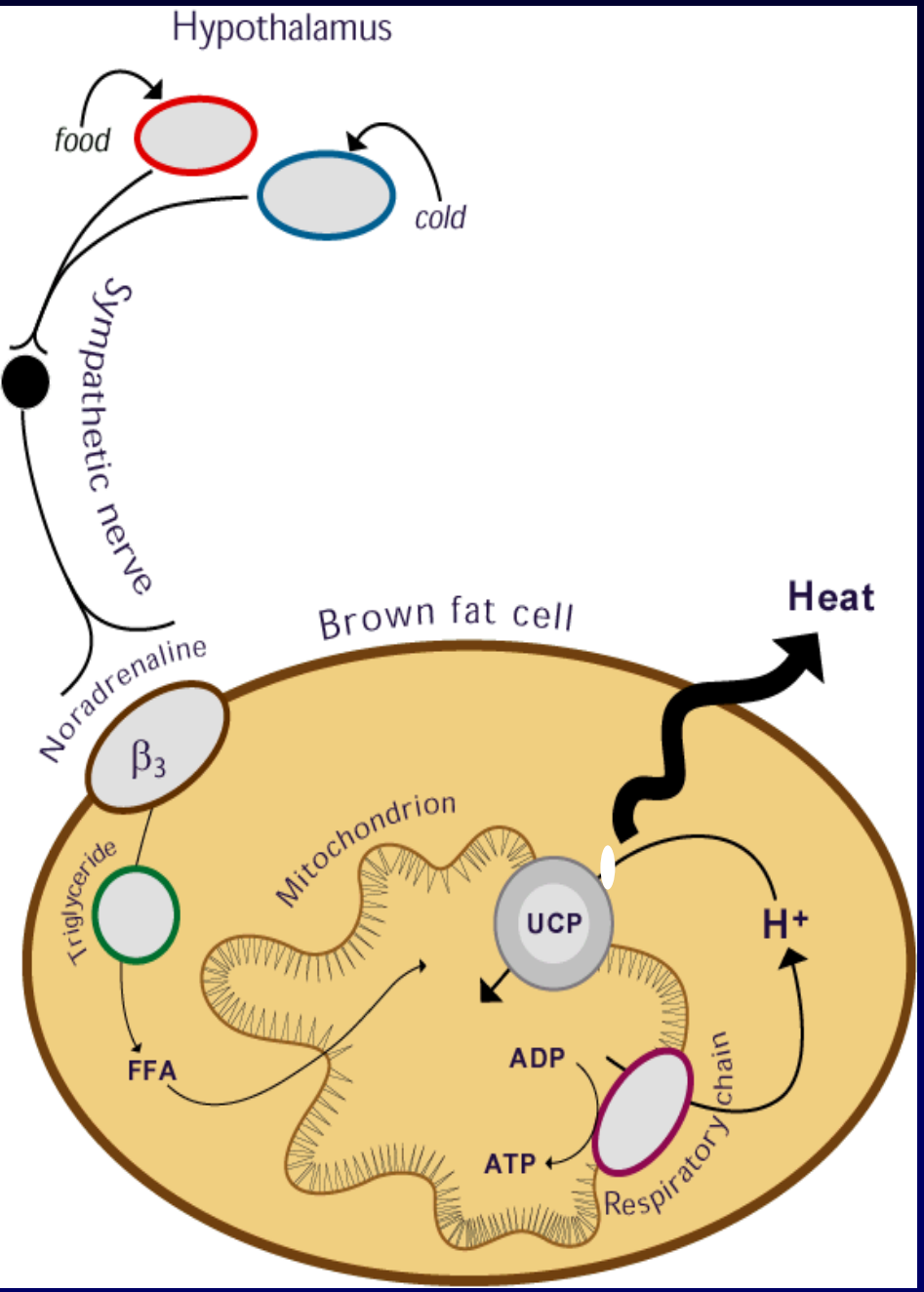
Cold-Activated Brown Adipose Tissue in Healthy Men
van Marken Lichtenbelt et al. *NEJM* (2009) 15: 1500-1508

Identification and Importance of Brown Adipose Tissue in Adult Humans
Cypess et al. *NEJM* (2009) 15: 1509-1517

Functional Brown Adipose Tissue in Healthy Adults
Virtanen et al *NEJM* (2009) 15: 1518-1525

The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue.
Zingaretti et al. *FASEB J.* (2009) May 5. [Epub ahead of print]

High Incidence of Metabolically Active Brown Adipose Tissue in Healthy Adult Humans: Effects of Cold Exposure and Adiposity.
Saito M et al. *Diabetes.* (2009) Apr 28. [Epub ahead of print]



*Adapted from **Nedergaard & Cannon**; In New Comprehensive Biochemistry (**1992**)*

Brown adipose tissue:

The safest target for weight control

in adult humans !

But β3- agonists are ineffective in humans

Need to bypass adrenoceptor system !

Category	Classes	Major Food Sources
Phenolic acids	• Ferulic acid	Dietary fiber – hemicelluloses Many fruits and vegetables, coffee
	• Caffeic acid (Chlorogenic acid)	Mango fruit
	• Condensed tannins	
	• Hydrolyzable tannins: (Gallotannins, Ellagitannins)	Blackberries, raspberries, strawberries, wine, brandy aged in oak barrels
Flavonoids	• Flavones	Sweet red pepper, celery
	• Flavonols (Quercetin)	Tea, onions, many fruits & vegetables
	• Flavanols: (Catechins)	Green tea, chocolate, cocoa
	• Flavanones (Hesperetin)	Oranges, citrus fruits
	• Isoflavones (Genistein)	Soybeans, soy protein-containing foods
	• Anthocyanins (Cyanidin)	Red fruits: cherries, plums, strawberries, raspberries, blackberries, grapes, red and black currants
	• Proanthocyanidins	Apples, pears, grapes, red wine, tea
Lignans	• Enterodiol	Flaxseed, flaxseed oil
Stilbenes	• Resveratrol	Red wine

Adapted from: Scalbert and Williamson, 200

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University of Geneva

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Lucien Girardier
Jean Jacquet

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Philippe Cettour-Rose

Françoise Assimacopoulos-Jeannet