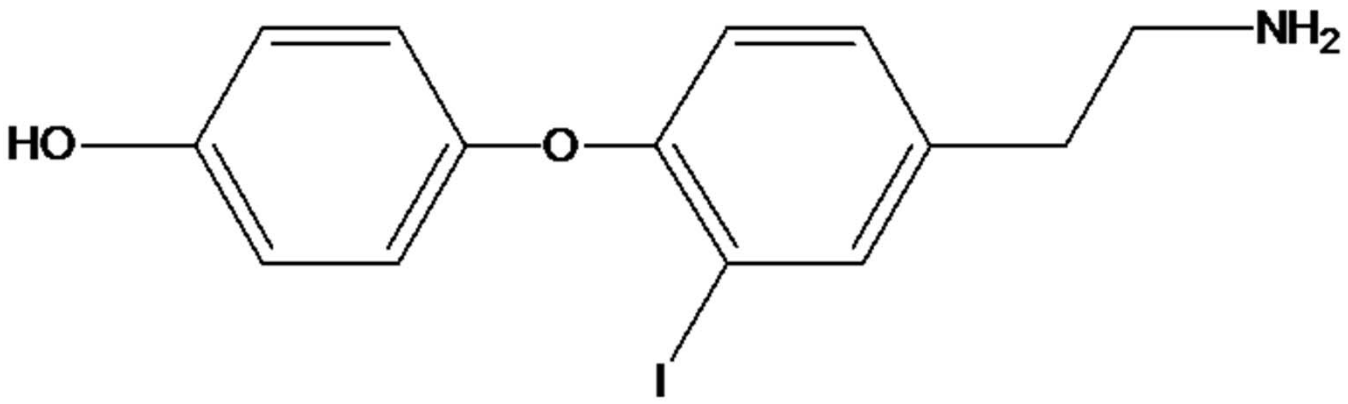
The biology of 3-iodothyronamine

83rd ATA Annual Meeting – Puerto Rico, October 17, 2013

Disclosure

Nothing to disclose

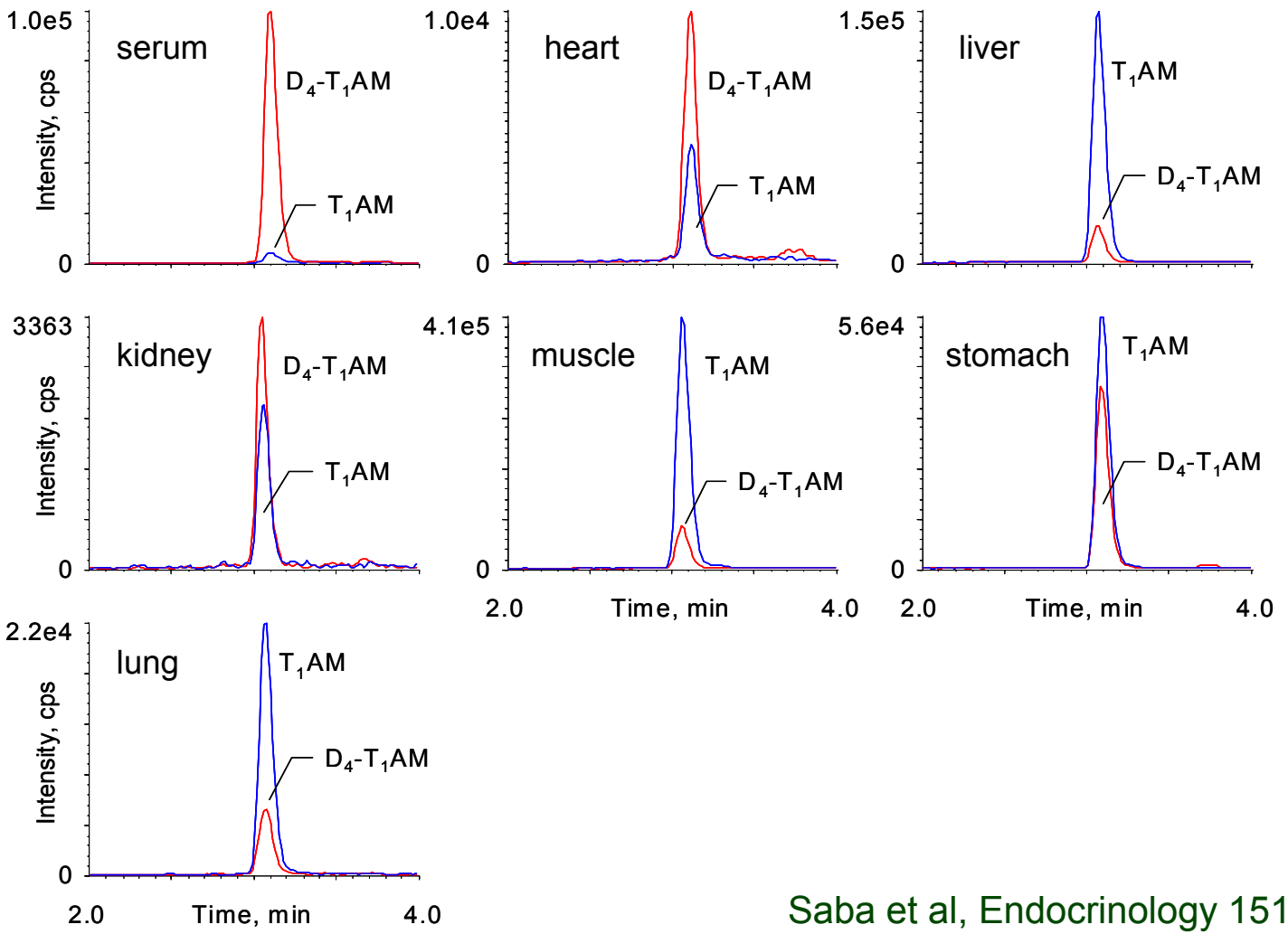
3-Iodothyronamine (T_1AM)



T_1AM as a chemical messenger

- endogenous compound, which
  - found in brain and other tissues
- by acting on specific receptors
  - agonist of TAAR1
  - interacts with amine transporters
  - interacts with mitochondrial targets
  - interacts with apoB-100
- produces functional effects
  - hypothermia
  - decreased cardiac contractility
  - decreased insulin secretion
  - increased gluconeogenesis
  - shift to lipid catabolism
  - neuromodulatory action
  - behavioral effects

T_1AM assay in rat tissues



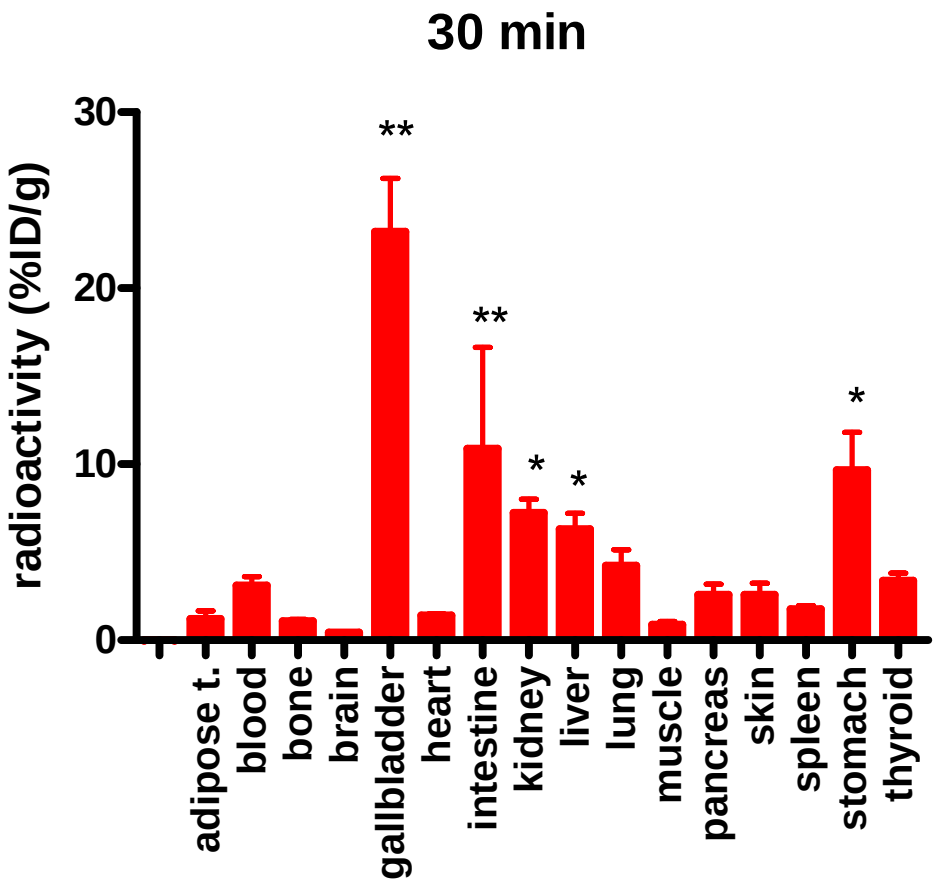
Saba et al, Endocrinology 151:5063, 2010

T_1AM concentration in rat tissues (pmol/g)

	T_1AM	T_3	T_4
Serum (nM)	0.3±0.1	1.4±0.1	49.6±4.8
Heart	6.6±1.4	0.5±0.1	0.7±0.2
Liver	92.9±28.4	4.7±0.8	14.5±3.0
Kidney	36.1±10.4	7.1±0.9	13.0±2.8
Muscle	25.0±6.9	0.8±0.2	1.8±0.4
Stomach	15.5±6.9	3.3±0.7	16.0±9.2
Lung	5.6±1.5	4.4±1.5	24.8±12.2

Saba et al, Endocrinology 151:5063, 2010

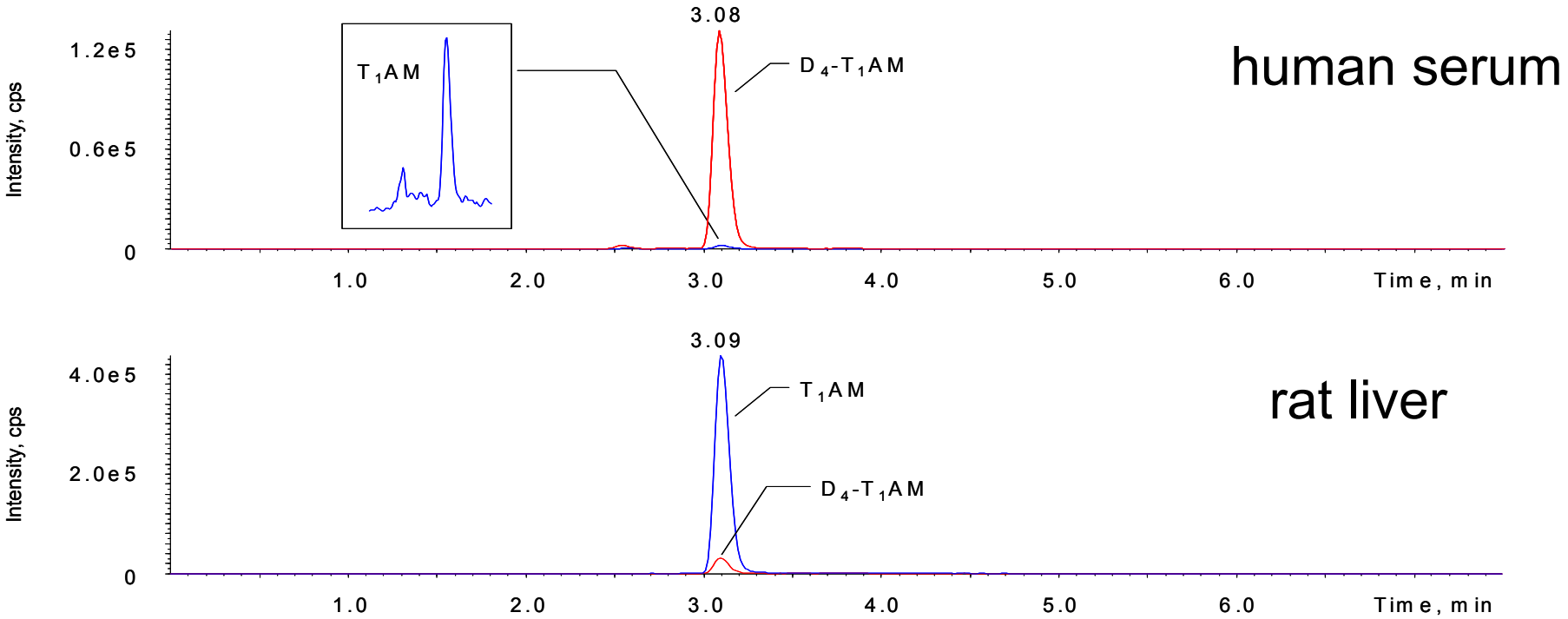
Tissue distribution of [^{125}I]-T_1AM in mouse



* P<0.05 vs blood
** P<0.01 vs blood

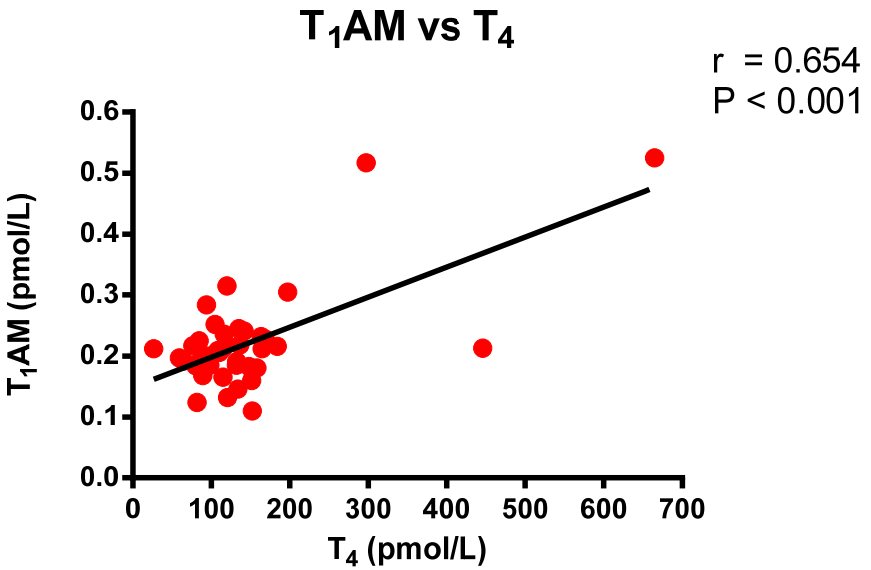
Chiellini et al, J Endocrinol 213:223, 2012

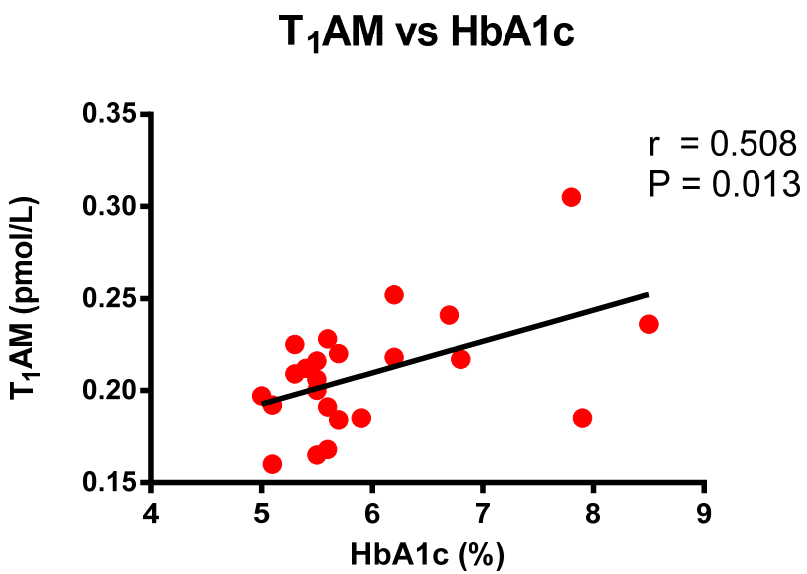
T_1AM in human blood



Saba et al, Endocrinology 151:5063, 2010

T_1AM in human blood





Galli et al, J Clin Endocrinol Metab 97:E69, 2012

T_1AM assay in tissues

Reference	species	tissue	concentration
Scanlan et al, Nat Med 2004	rat	brain	< 1 pmol/g
Chiellini et al, FASEB J 2007	rat	heart	≈ 68 pmol/g
Braulke et al, J Comp Physiol 2008	hamster	blood	6 nM
Ackermans et al, J Endocrinol 2010	rat & human human	blood thyroid	none (<0.25 nM) none (<0.3 pmol/g)
Saba et al, Endocrinology 2010	rat	many	0.3 – 92 pmol/g
Hoefig et al, JCEM, 2011	human	blood	66 nM*
Galli et al, JCEM, 2012	human	blood	0.2 nM
Hackenmuller et al, Endocrinology 2012	mouse	liver	2 pmol/g

** immunological assay*

Messages to take home (1)

- T_1AM can be detected in blood and in most tissues at nanomolar concentrations.

- A few technical issues must still be solved before quantitative correlations between blood T_1AM and other clinical variables can be reliably interpreted.

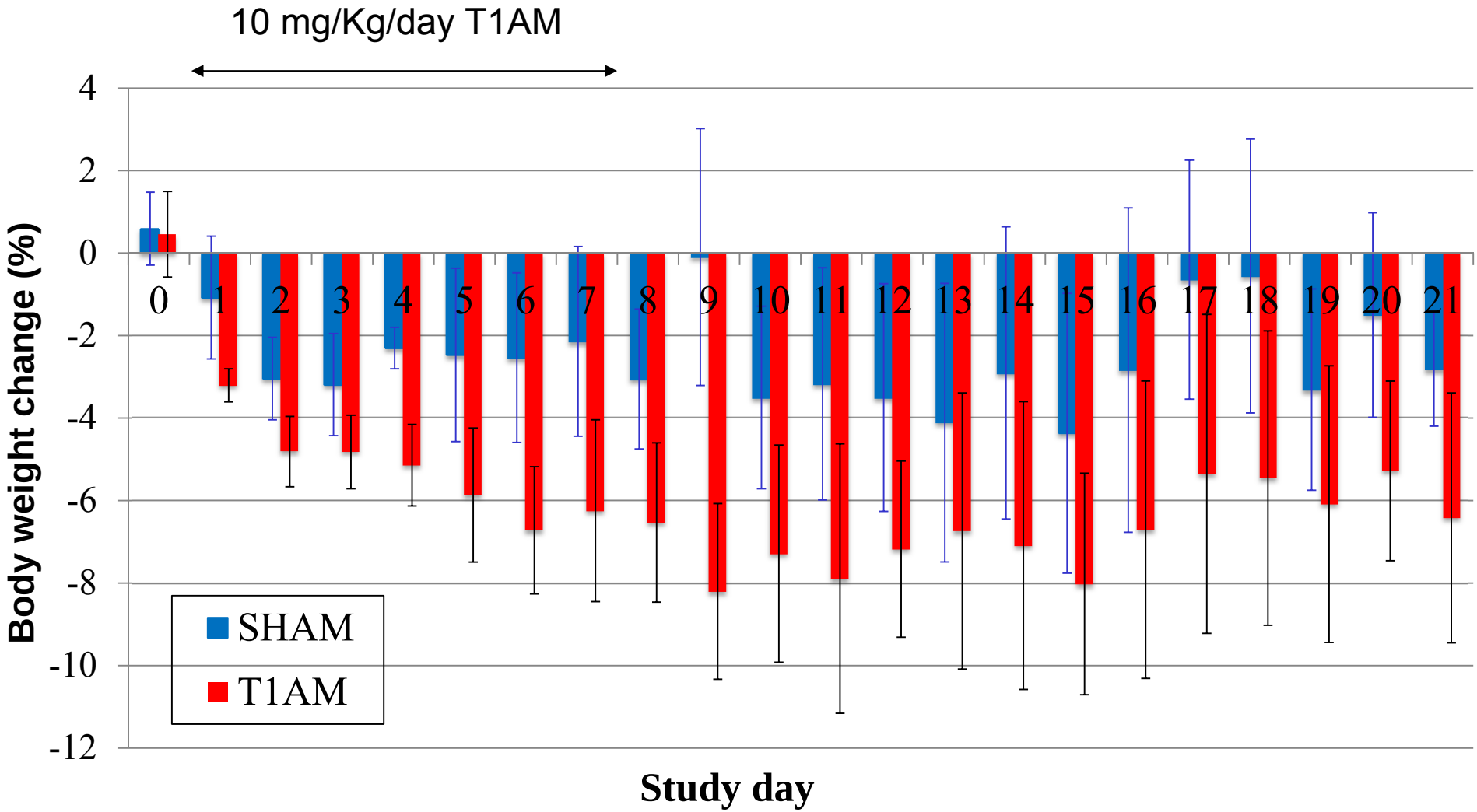
T_1AM as a chemical messenger

- endogenous compound, which
  - found in brain and other tissues
- by acting on specific receptors
  - agonist of TAAR1
  - interacts with amine transporters
  - interacts with mitochondrial targets
  - interacts with apoB-100
- produces functional effects
  - hypothermia
  - decreased cardiac contractility
  - decreased insulin secretion
  - increased gluconeogenesis
  - shift to lipid catabolism
  - neuromodulatory action
  - behavioral effects

Endocrine and metabolic effects of T_1AM

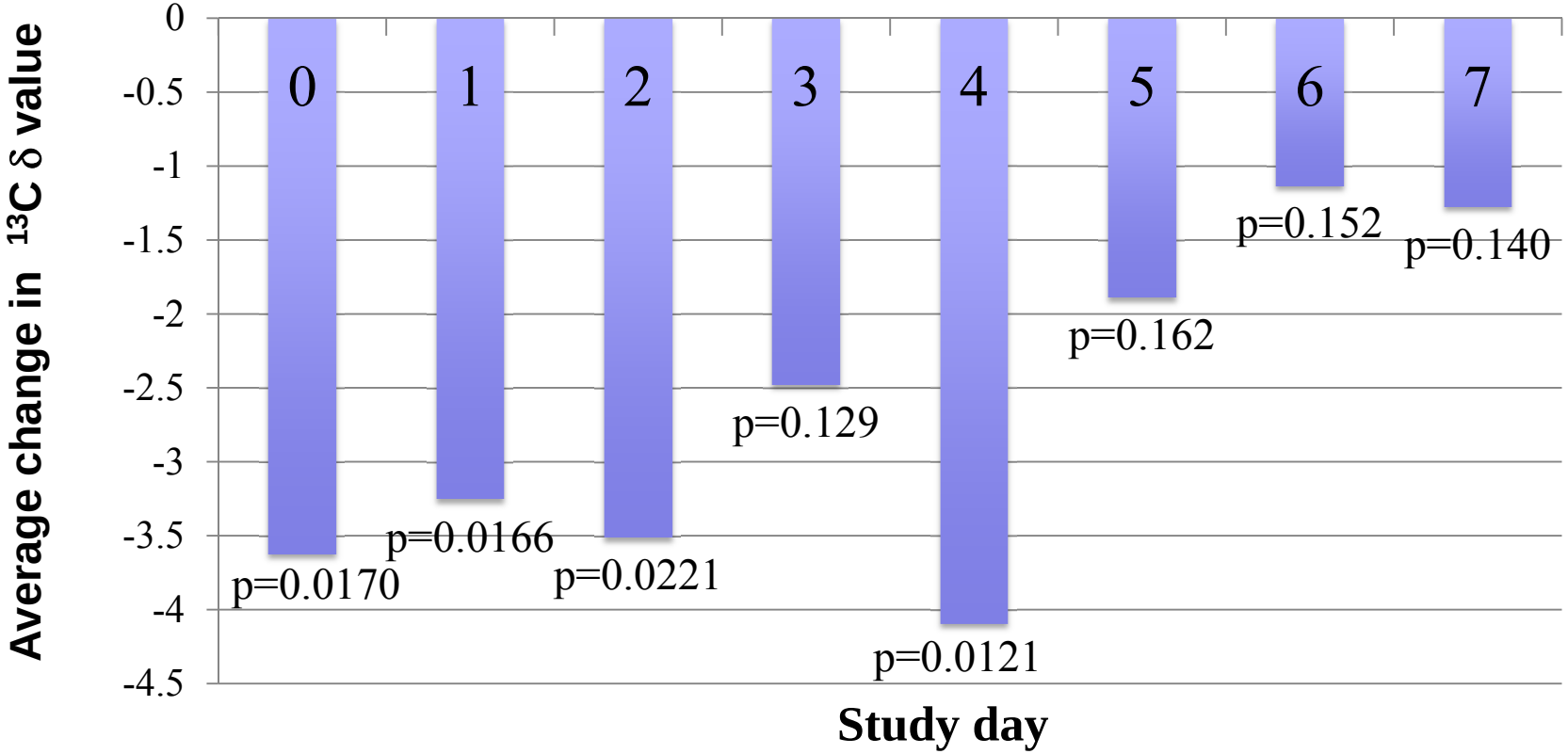
Reference	adm.	dose	effect
Braulke et al, J Comp Physiol 2007	ip	128 μmol/Kg	↓ respiratory quotient, ↓ body fat
Regards et al, J Clin Invest 2007	ip	128 μmol/Kg	↑ glucose, ↓ insulin, ↑ glucagon
Klieverik et al, J Endocrinol 2009	icv	1.2 μmol/Kg	↑ glucose, ↑ glucagon
	ip	128 μmol/Kg	↑ glucose, ↑ glucagon
Manni et al, Br J Pharmacol 2012	icv	3.3 nmol/Kg	↑ glucose
Manni et al, Br J Pharmacol 2013	icv	0.3 nmol/Kg	↑ glucose
Haviland et al, Obesity 2013	ip	25 μmol/kg/day	↓ body weight, lipolysis

Effects of chronic T_1AM treatment on body weight



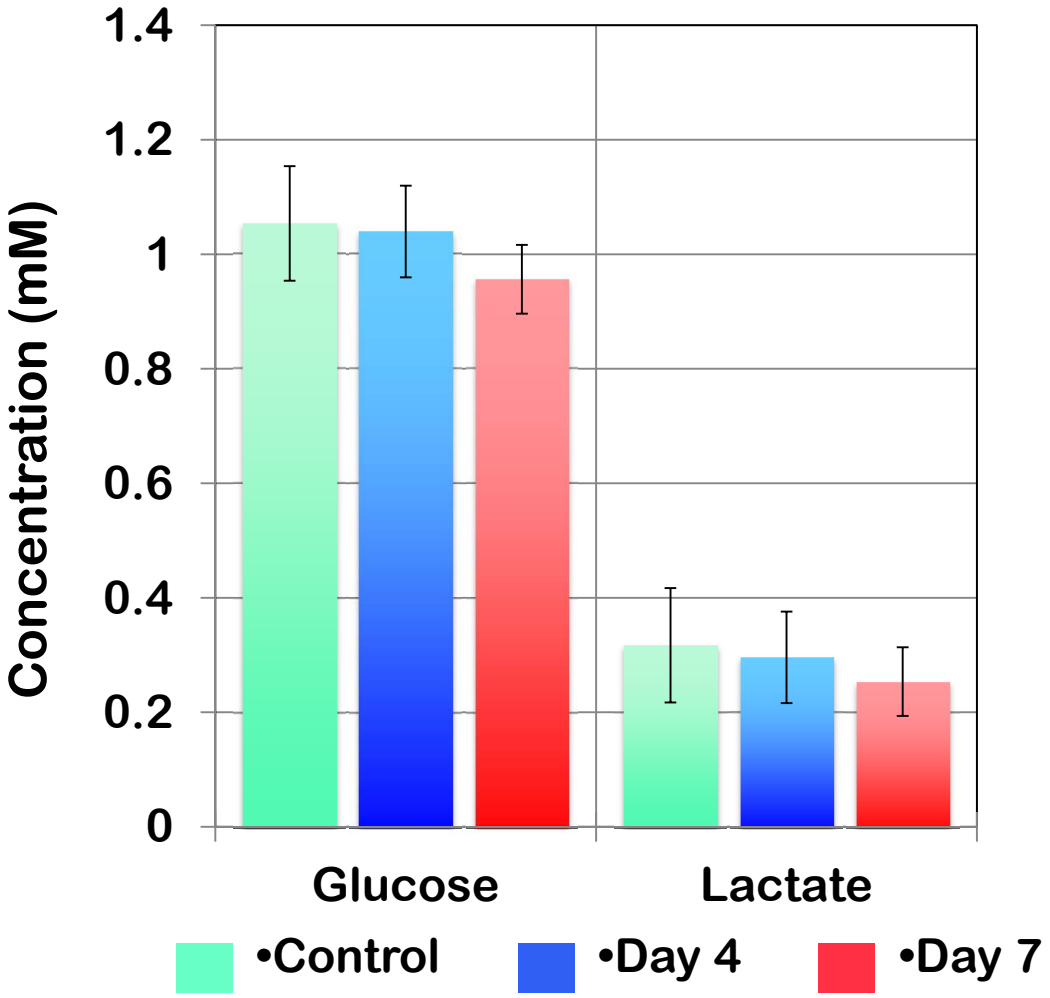
Haviland et al, Obesity, 2013

Effects of chronic T_1AM treatment on lipid metabolism



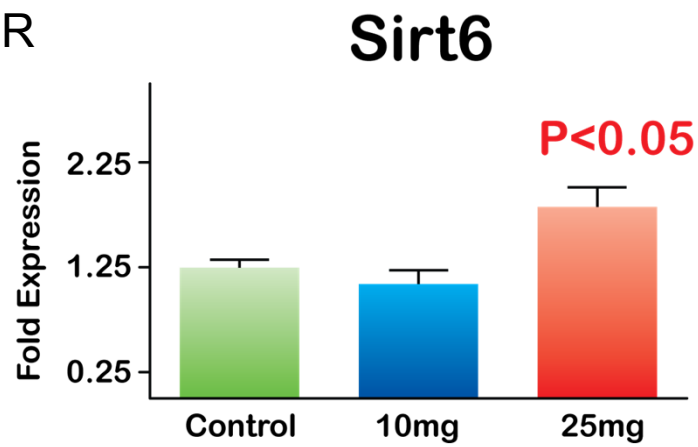
Haviland et al, Obesity, 2013

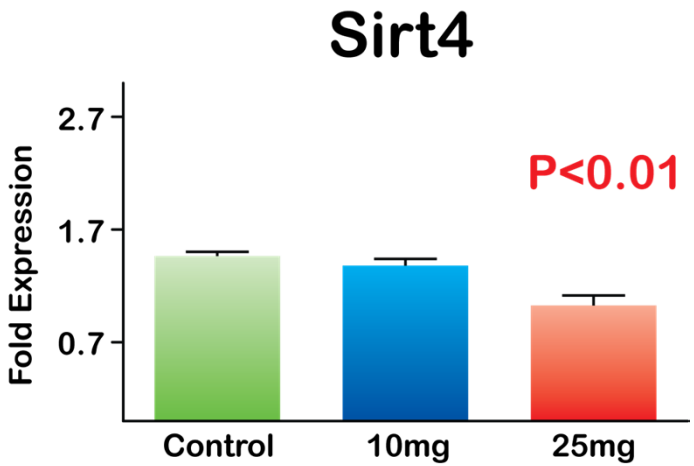
Metabolic effects of chronic T_1AM treatment



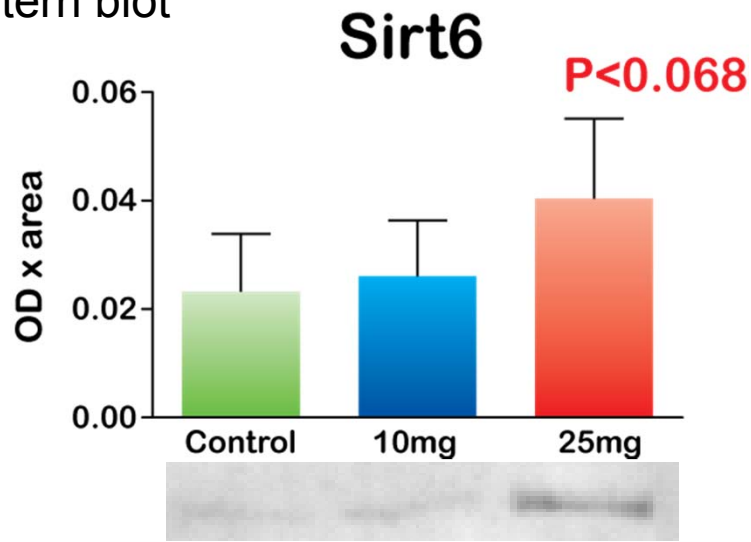
T_1AM and sirtuin expression in liver

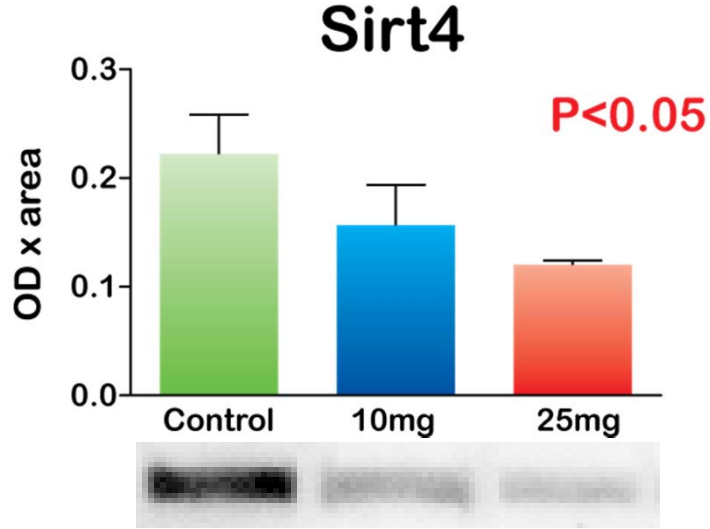
qPCR



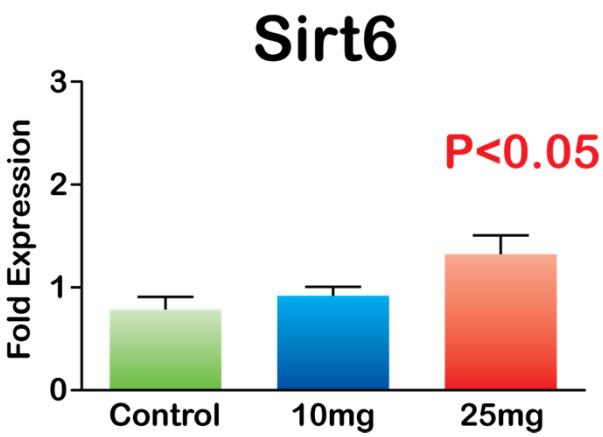


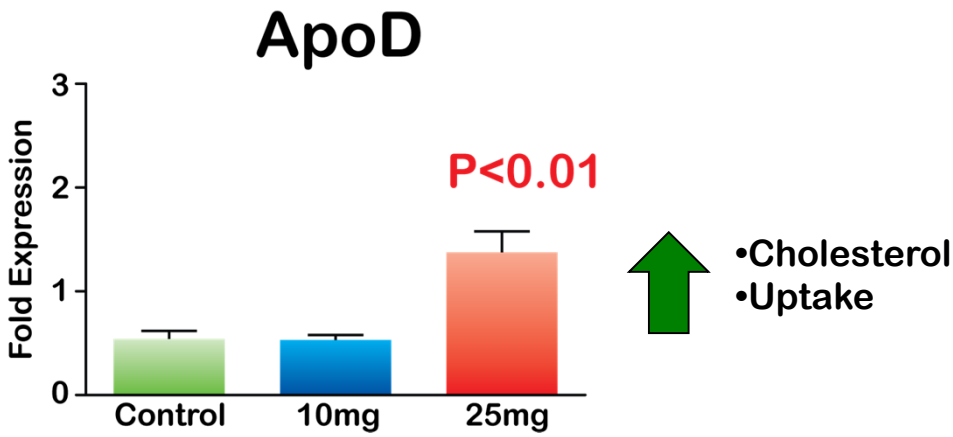
Western blot

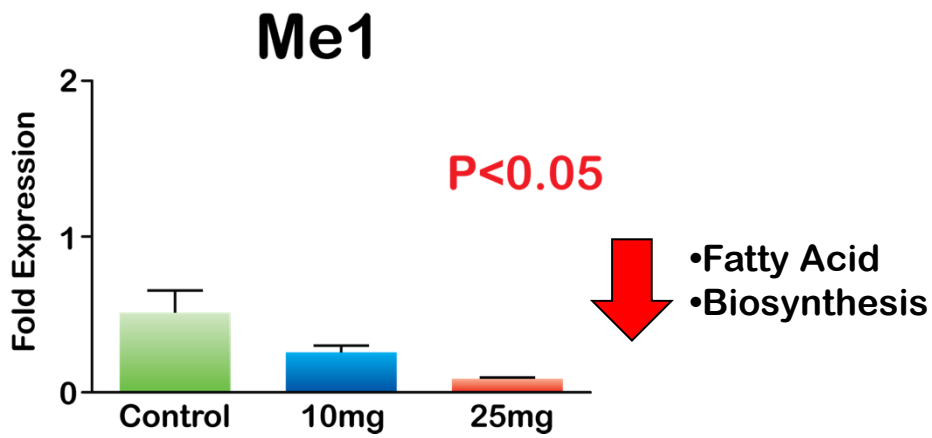


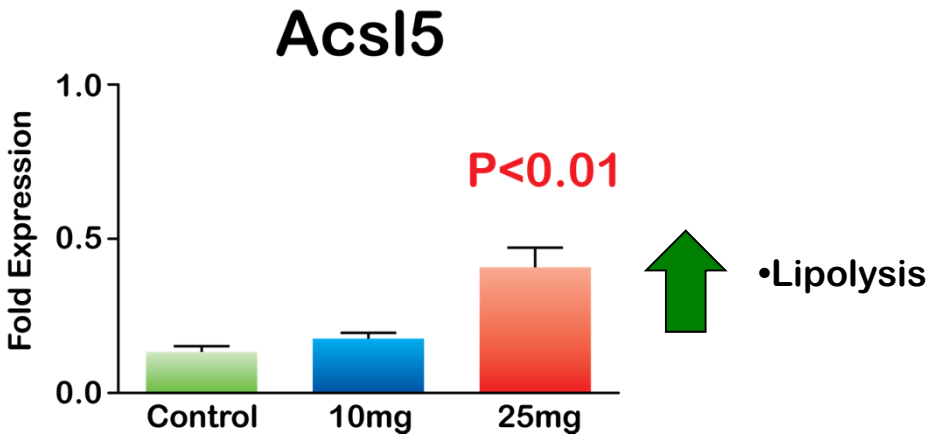


T_1AM and gene expression in adipose tissue









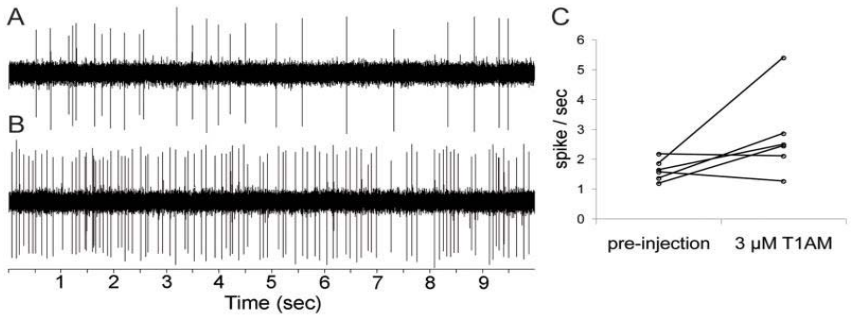
Assay of tissue T_1AM (pmol/g)

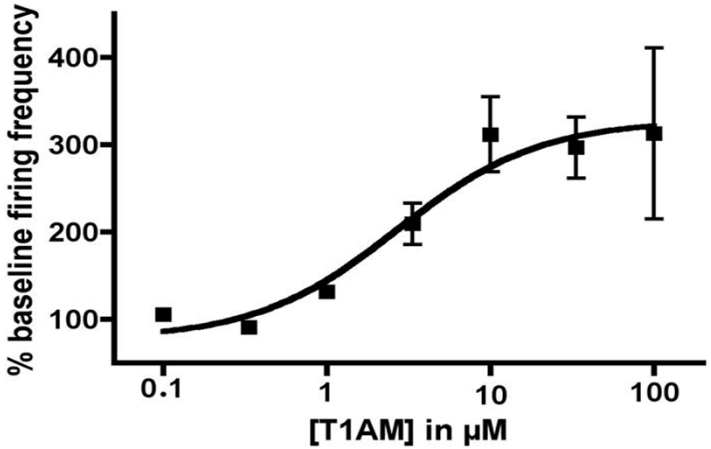
	liver	WAT
control	24±8	0.5±0.2
T_1AM (10 mg/Kg/day)	2041±119	-
T_1AM (25 mg/Kg/day)	8513±1746	14.6±5.5

Messages to take home (2)

- Administration of exogenous T_1AM decreases insulin secretion and/or produces anti-insulin effects.
- Chronic administration of exogenous T_1AM induces lipolysis and decreases body weight. This likely involves complex modulation of gene expression.

Neuromodulatory action of T_1AM



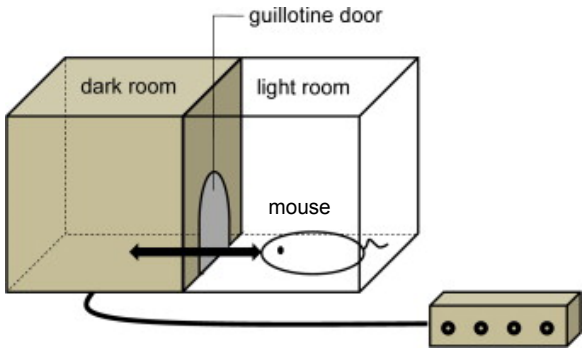


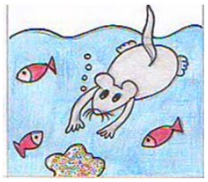
Gompf et al, Brain Res 1351:130, 2010

Behavioral effects of T_1AM

Reference	adm.	dose	effect
Dhillo et al, Diabetes Obes Metab 2009	icv	1.2 nmol/Kg	↑ food intake
	ip	4 nmol/Kg	↑ food intake
Manni et al, Br J Pharmacol 2012	icv	3.3 nmol/Kg	↓ food intake
		51 nmol/Kg	↑ food intake
Haviland et al, Obesity 2013	ip	25 μmol/kg/day	= food intake
James et al, Horm Behav 2013	icv	10 nmol/kg	nREM sleep reduction
Manni et al, Br J Pharmacol 2013	icv	3.3 nmol/Kg	pro-learning effect
		1.0 nmol/Kg	↓ pain threshold

Effect of T_1AM on learning





i.c.v. injection

↓ 15 min

Training

↓ 1 hour

Acquisition

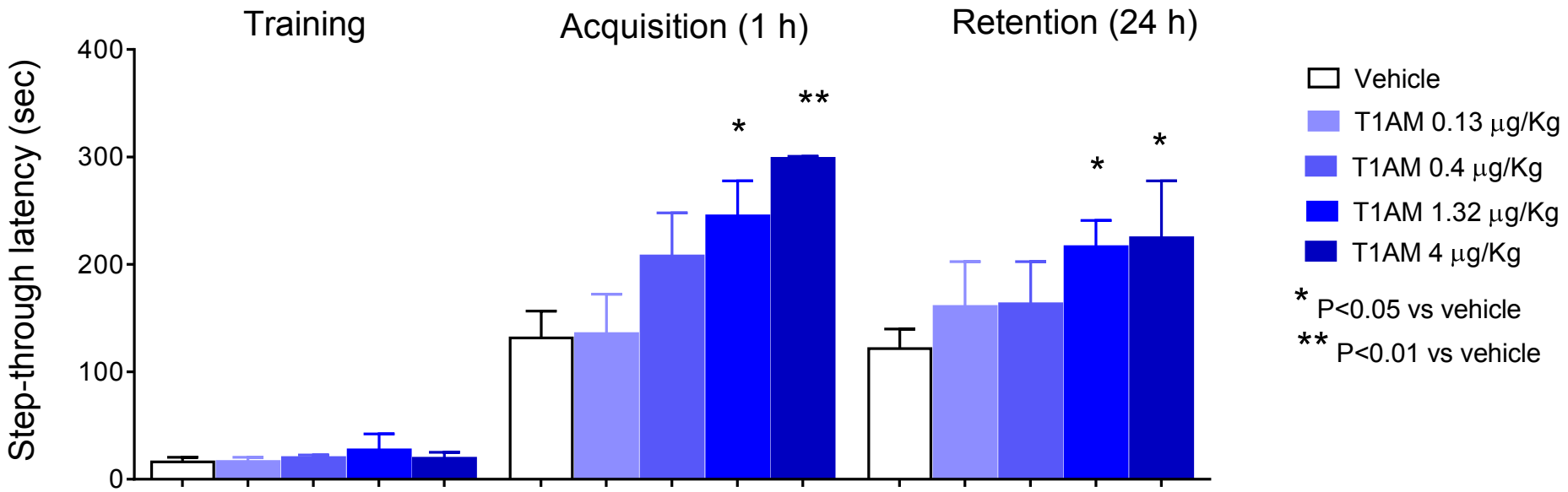
↓ 24 hours

Retention

↓

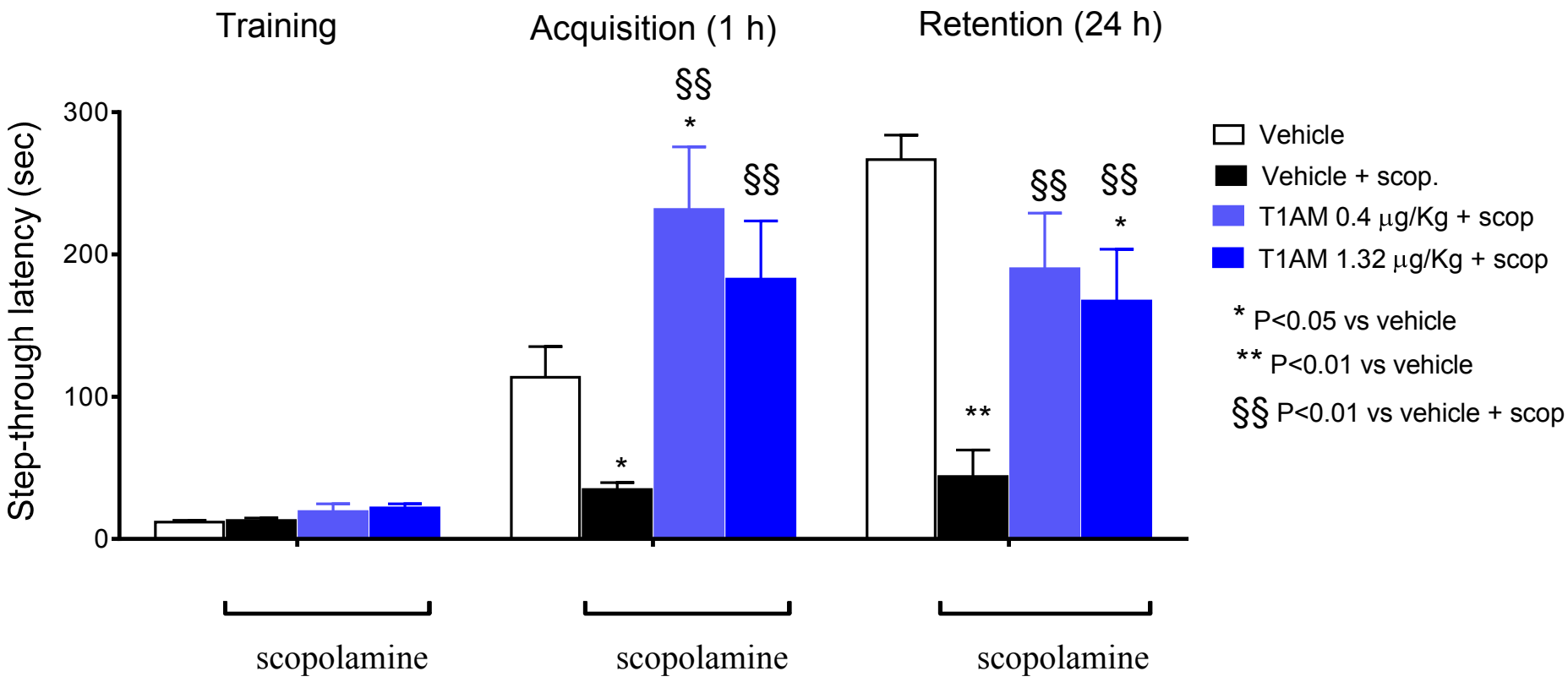
MS assay of T_1AM/TA_1
Western blot for pERK

Pro-learning effect of T_1AM

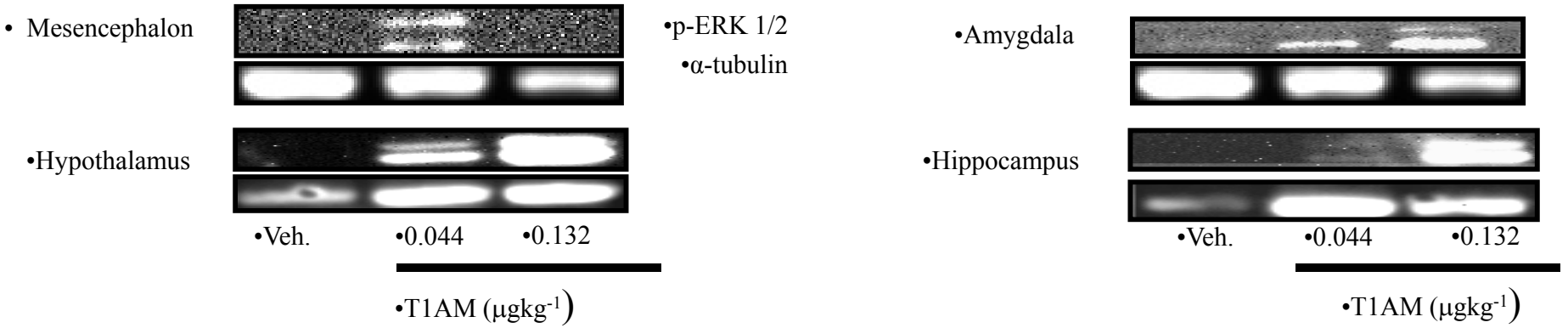


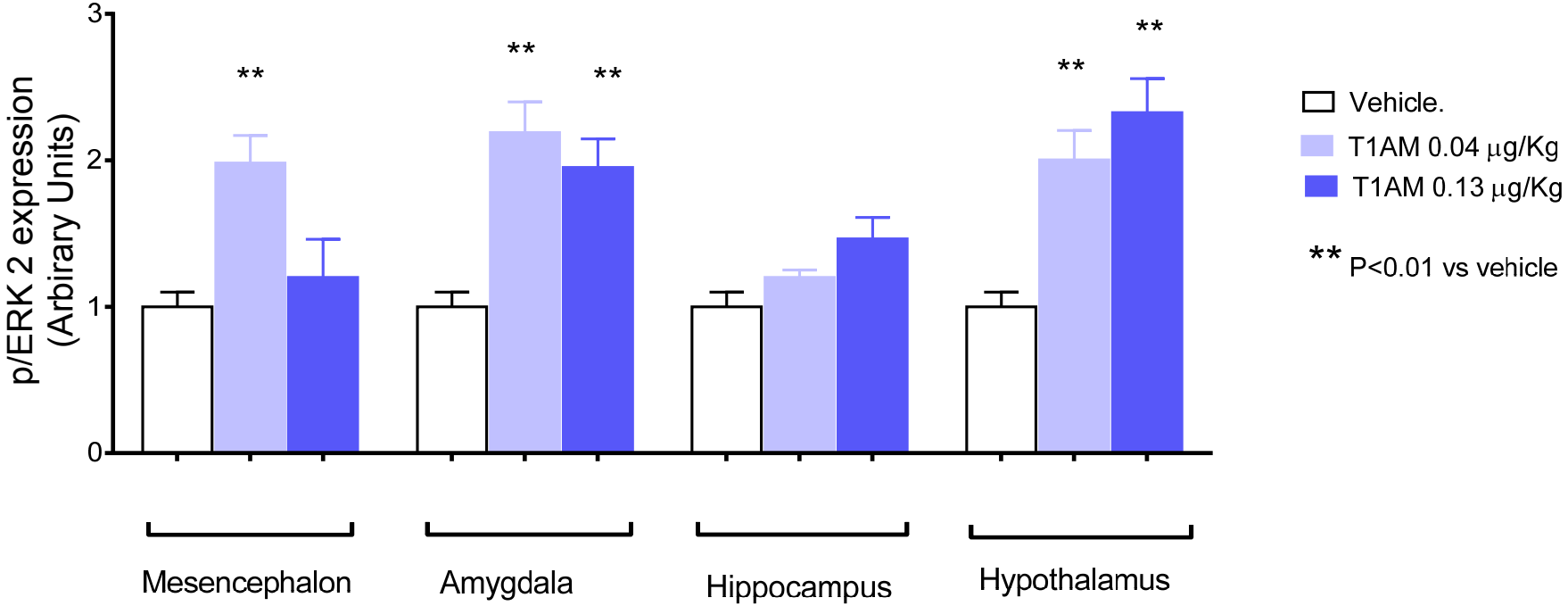
Manni et al, Br J Pharmacol 168:354, 2013

Anti-amnestic effect of T_1AM



ERK activation by T_1AM





Brain assay for T_1AM and TA_1 (pmol/g)

	T_1AM	TA_1
Baseline	48.6±17.7	0.8±0.2
Vehicle	33.6±6.0	0.7±0.3
T_1AM icv (1.32 μg/Kg)	1008.6±313.0	22.2±4.8

Messages to take home (3)

- Intracerebral administration of T_1AM has pro-learning and anti-amnestic effects, at doses increasing endogenous concentration by about one order of magnitude.

- T_1AM might have physiological and/or pathophysiological importance in the regulation of metabolism and of CNS function.