



L'acide lysophosphatidique: obésité, gluco-intolérance et fibrose.

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*Journées Francophones de Nutrition,
Bruxelles, 10-12 Décembre 2014*

• **Déclaration d'intérêts de Mme/M.** :

➤ **Activités de conseil, fonctions de gouvernance, rédaction de rapports**

Non

Société(s) :

➤ **Essais cliniques, autres travaux, communications de promotion**

Non

Société(s) :

➤ **Intérêts financiers (actions, obligations)**

Non

Société(s) :

➤ **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**

Non

Société(s) :

➤ **Réception de dons sur une association dont je suis responsable**

Non

Société(s) :

➤ **Perception de fonds d'une association dont je suis responsable et qui a reçu un don**

Non

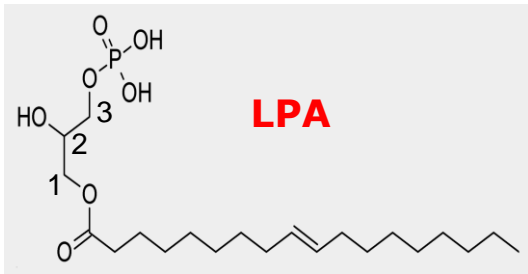
Société(s) :

➤ **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**

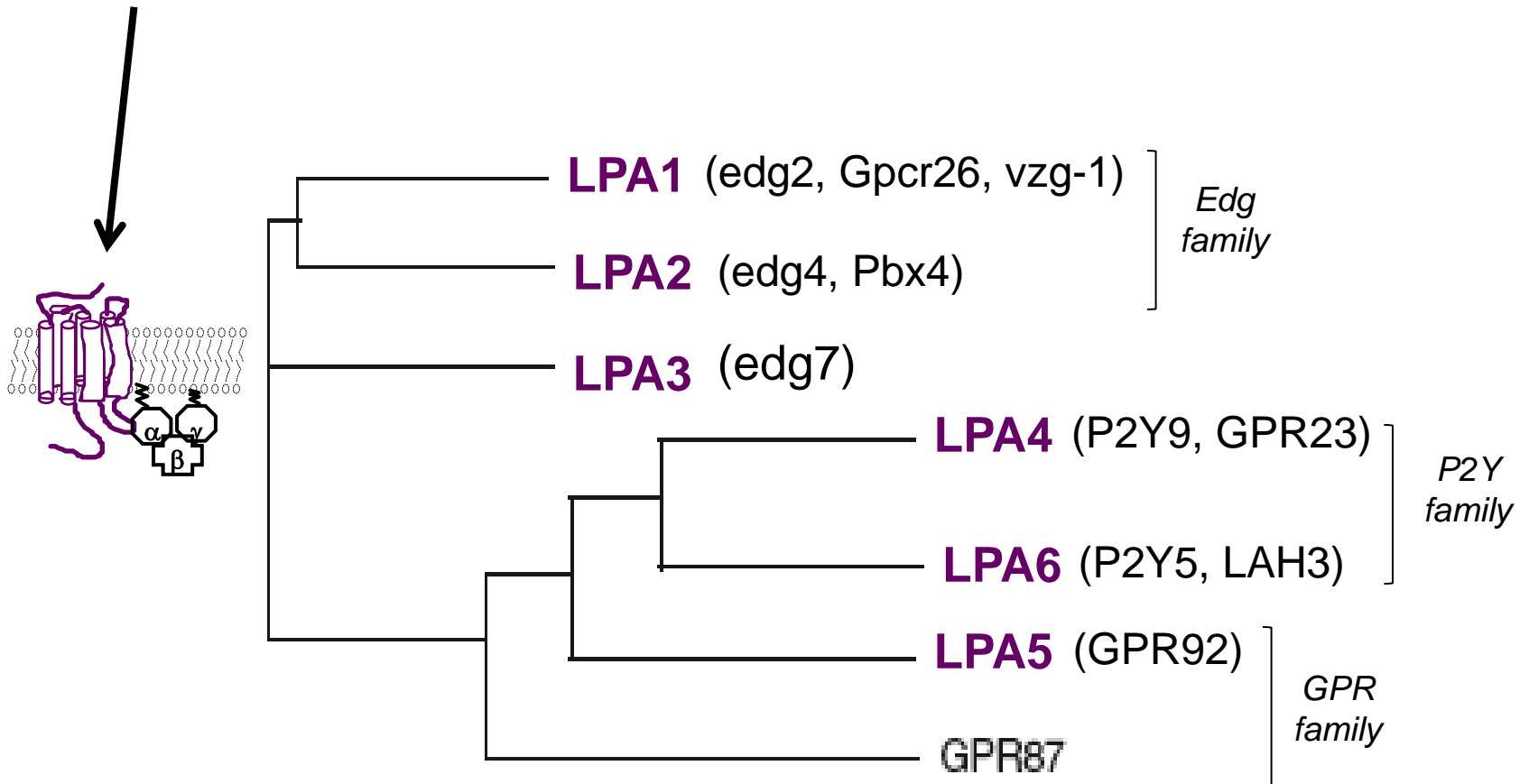
Non

Société(s) :

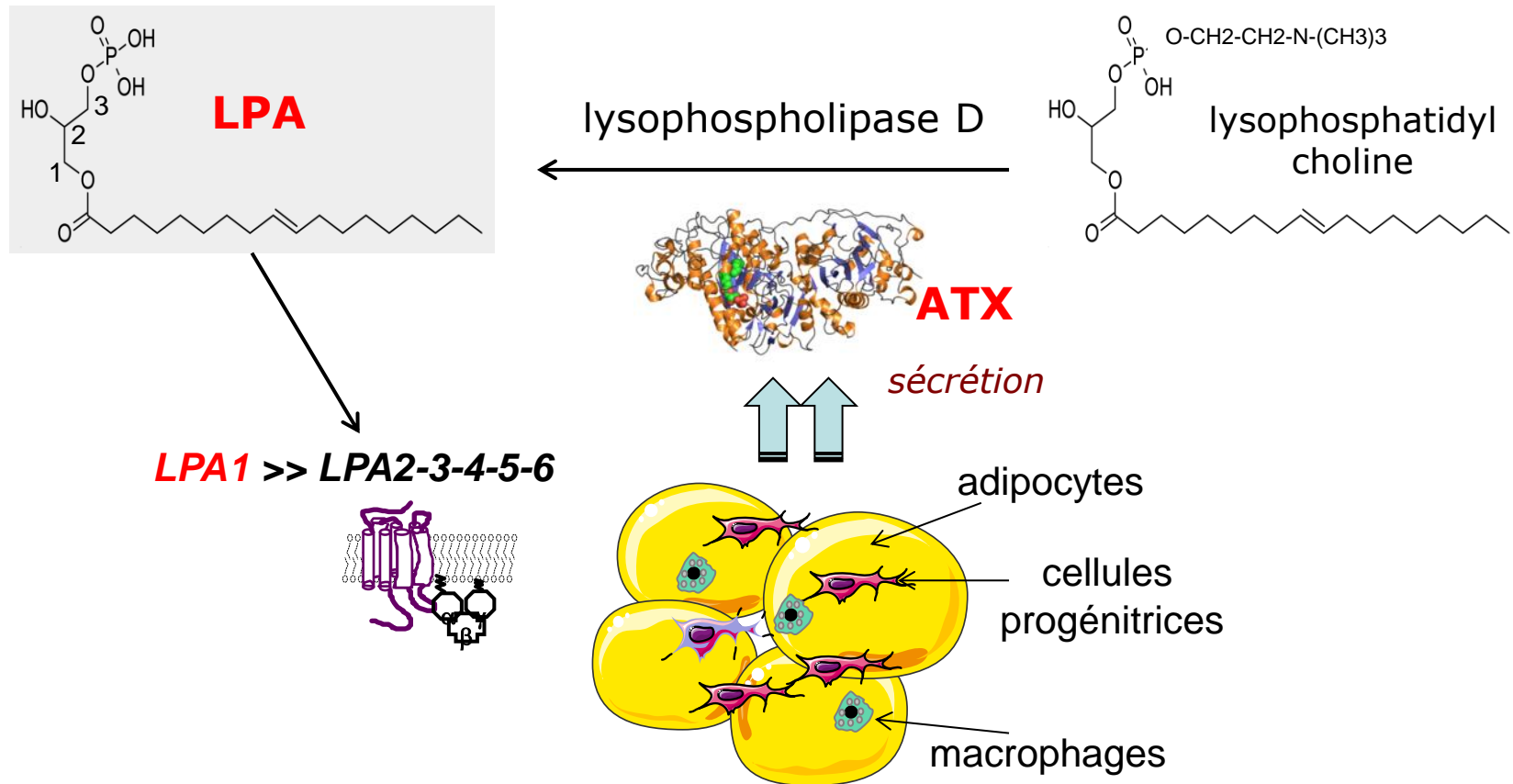
* Effacer l'option inadéquate



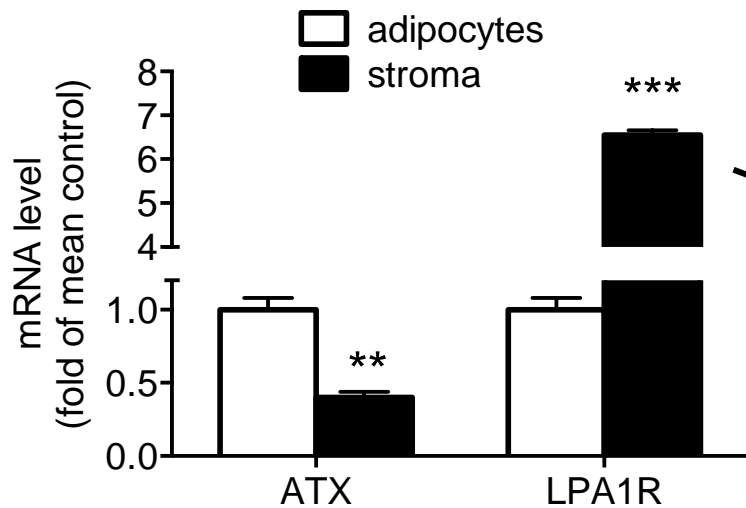
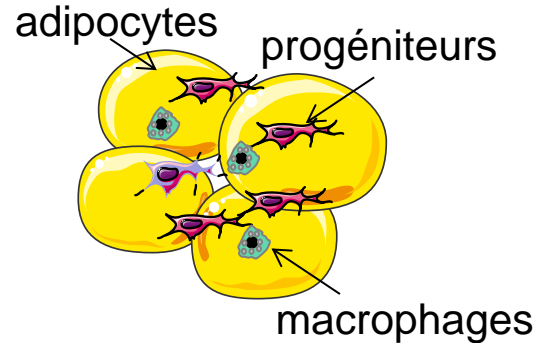
Lipide « bioactif » ligand de récepteurs couplés aux protéines G



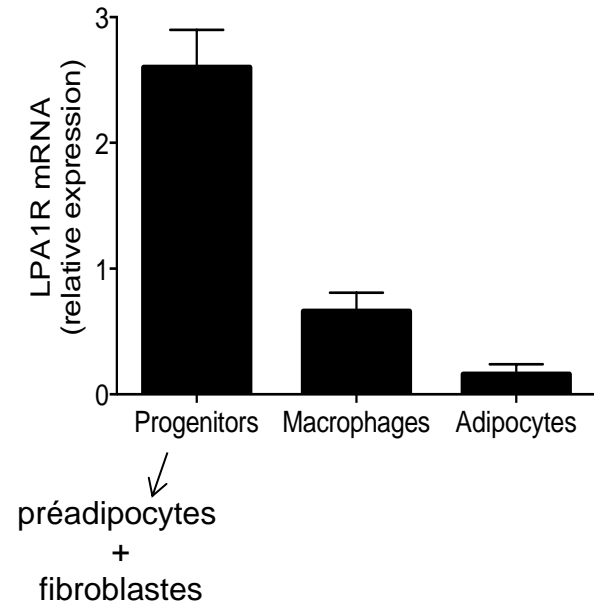
Le LPA est synthétisé par le tissu adipeux *via* la sécrétion d'Autotaxine (ATX)



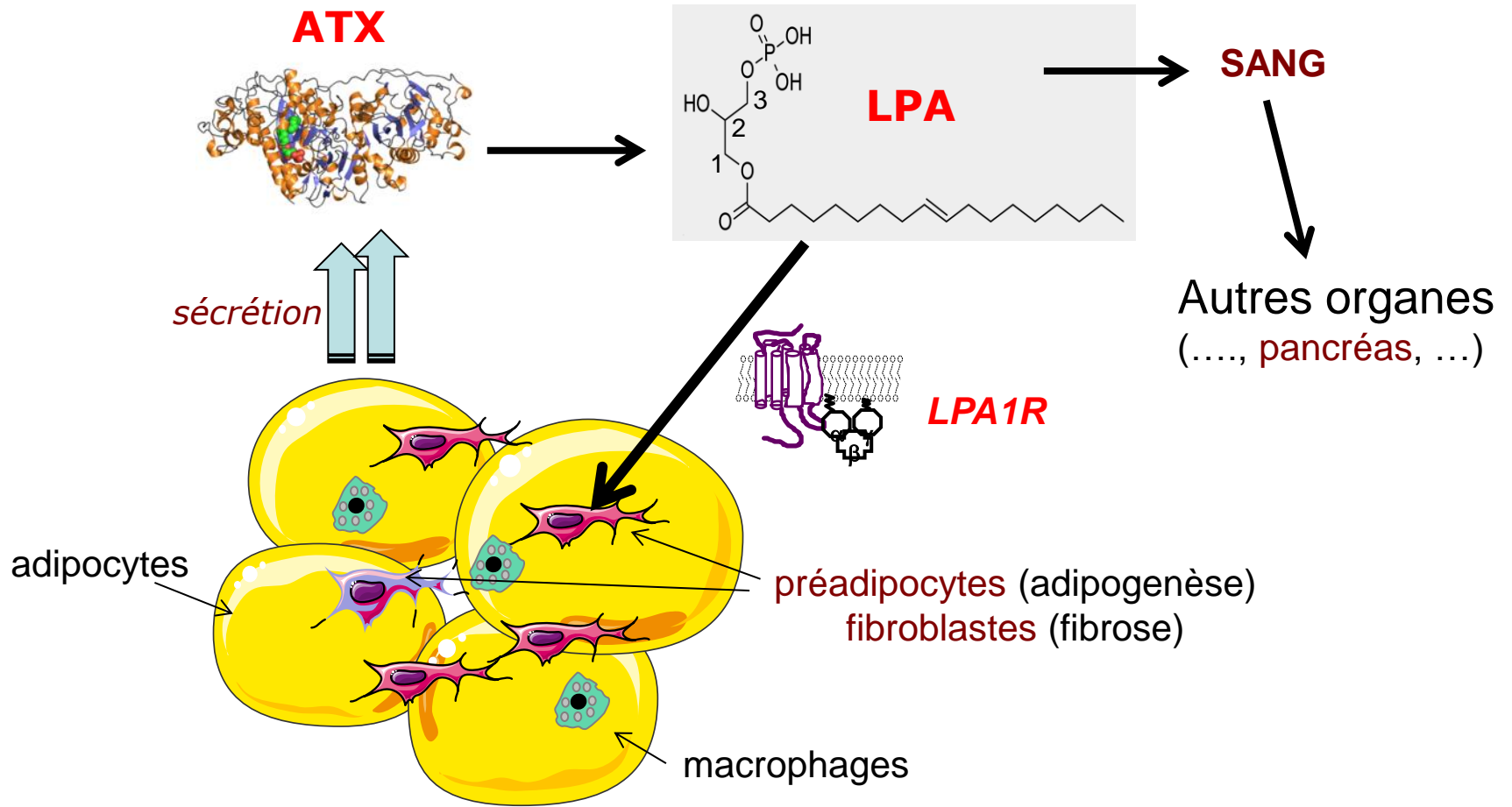
ATX exprimée dans les adipocytes LPA1R exprimé dans les cellules stromales



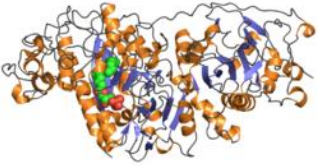
tissu adipeux
humain



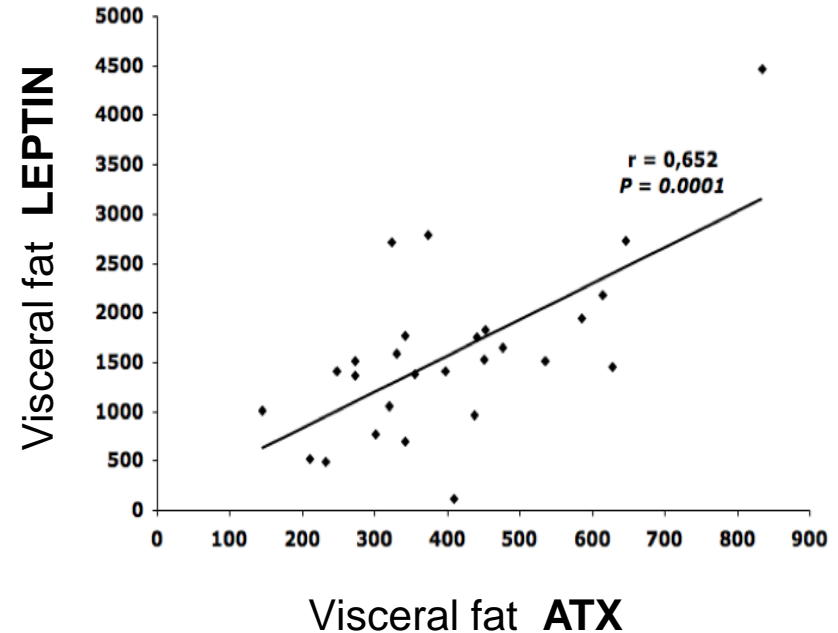
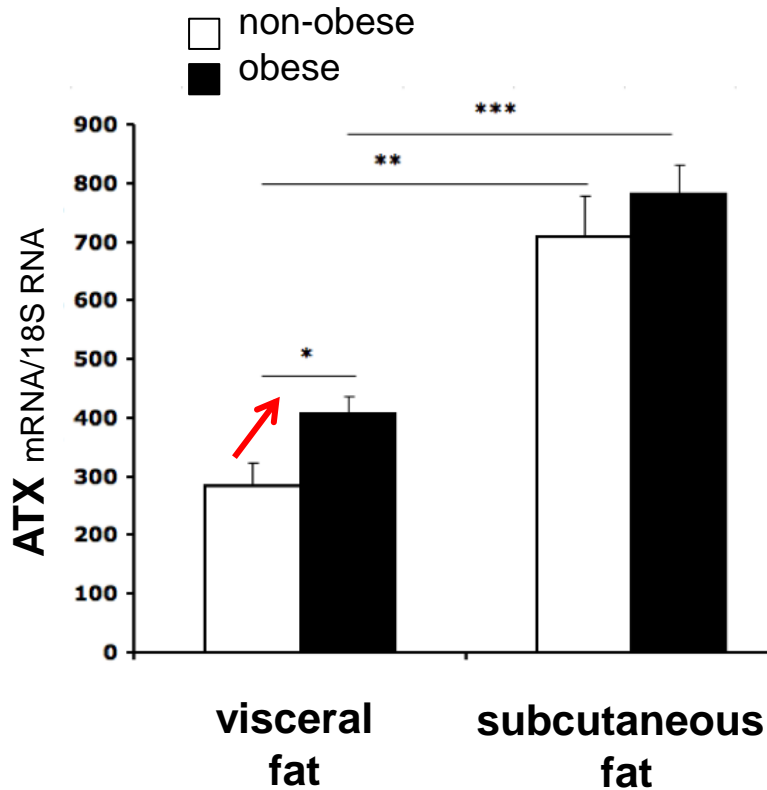
Actions locales et systémiques du LPA



ATX



L'ATX est fortement exprimée dans le tissu adipeux et augmente au niveau viscéral dans l'obésité massive

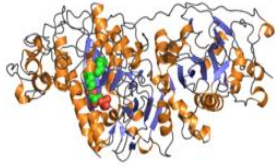


Chirurgie bariatrique.

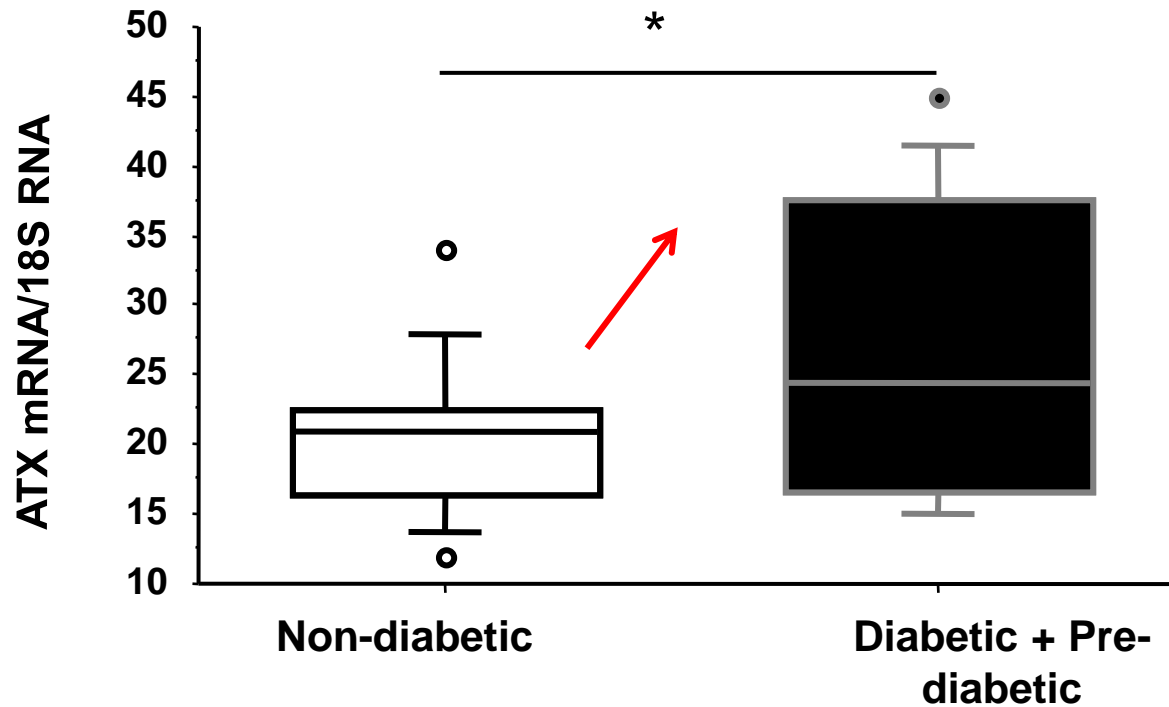
Non obese: BMI < 25 (n=10)

Obese (non-diabetic): BMI > 45 (n=27)

ATX



..... augmentation supplémentaire dans l'obésité massive associée à une gluco-intolérance



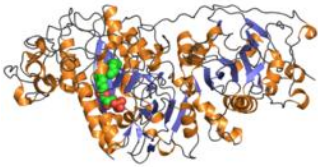
Bariatric surgery

BMI > 45

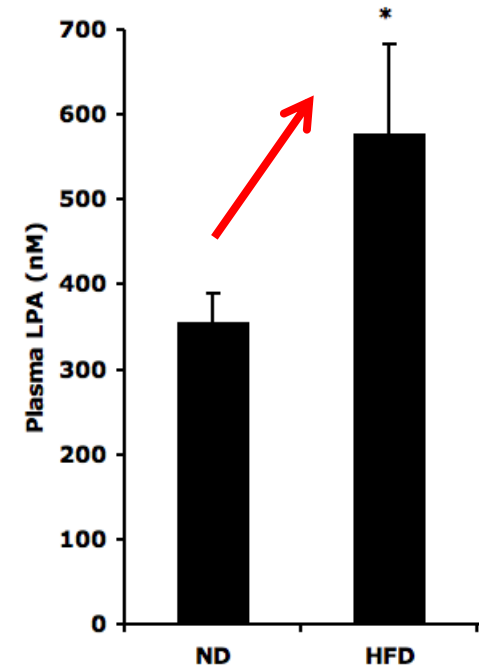
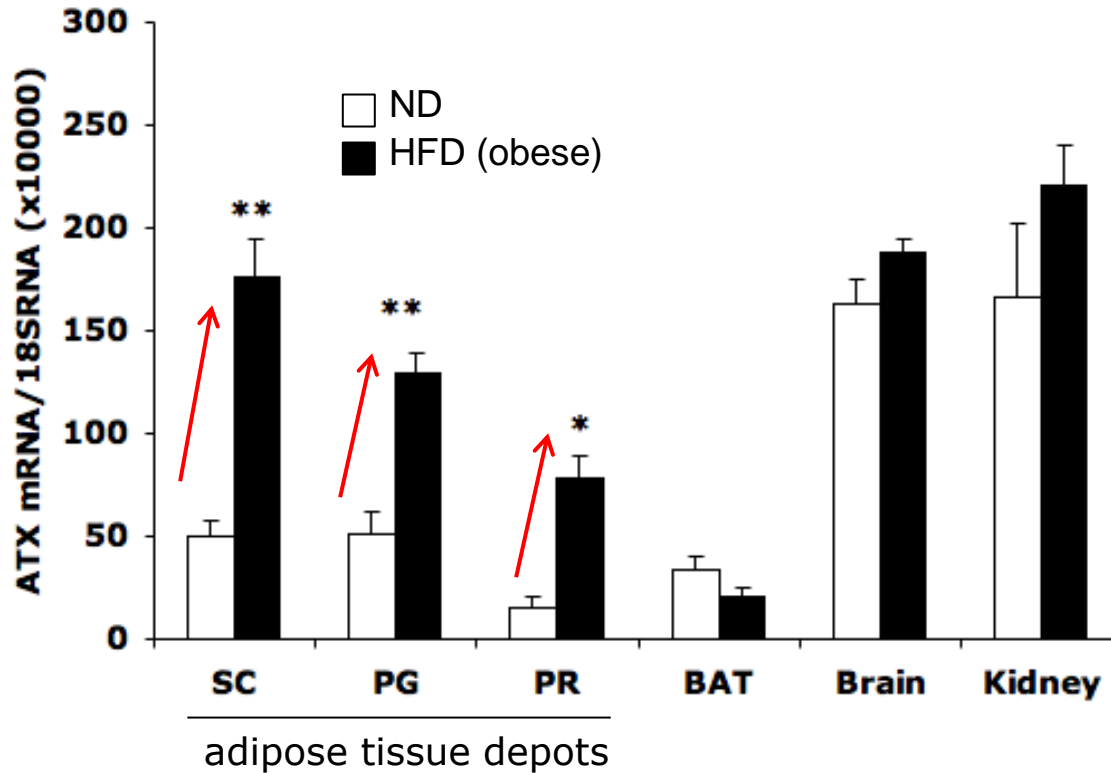
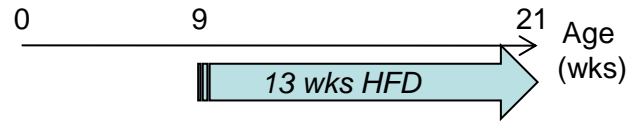
Non-diabetic (n=11): glycaemia <1g/l

Prediabetic/diabetic (n=12): glycemia > 1.3 g/l

ATX

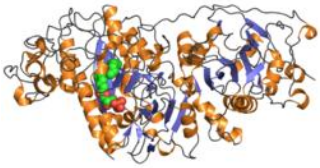


L'ATX adipocytaire augmente chez la souris obèse en régime hyperlipidique



Boucher et al. Diabetologia, 2005
Dusaulcy et al., J Lipid Res. 2011
Rancoule et al. JPB. 2012

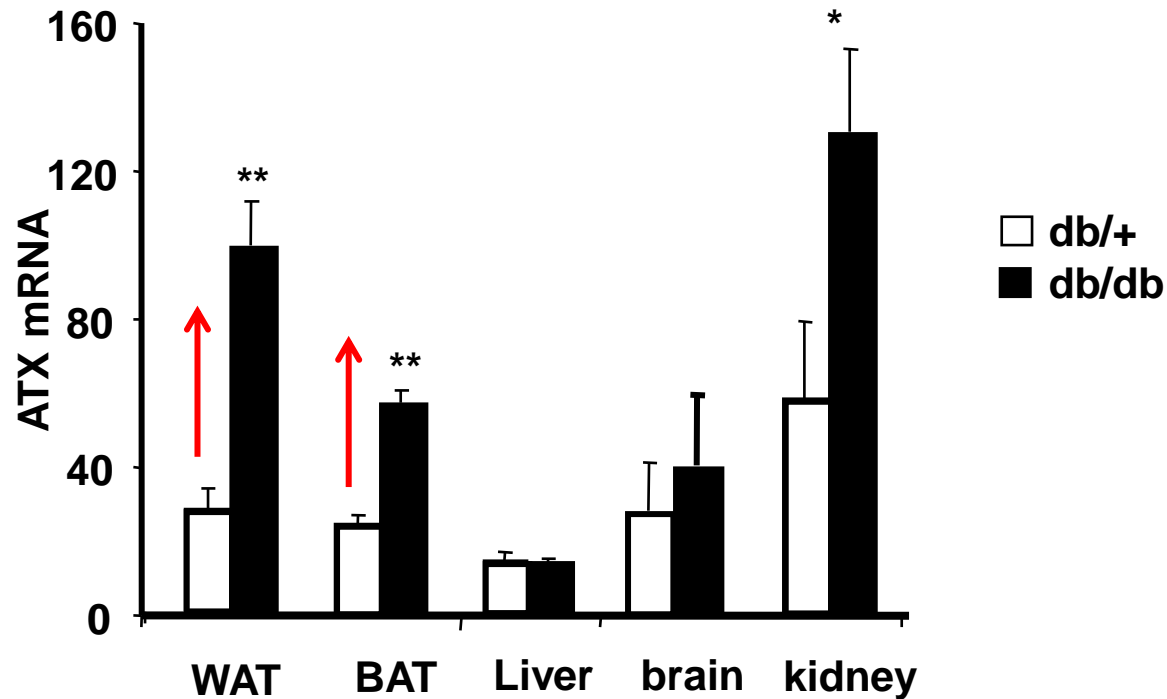
ATX



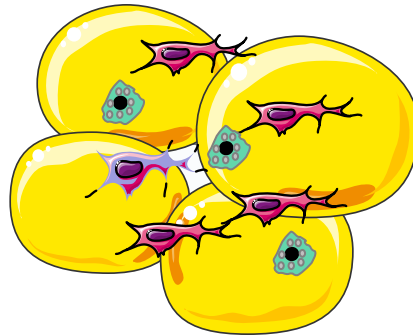
L'ATX augmente dans le tissu adipeux de souris génétiquement obèses/diabétiques db/db

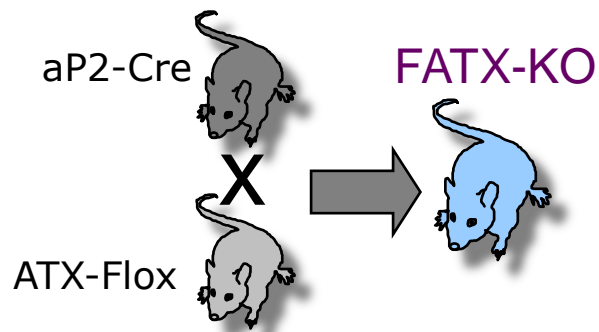


12 semaines

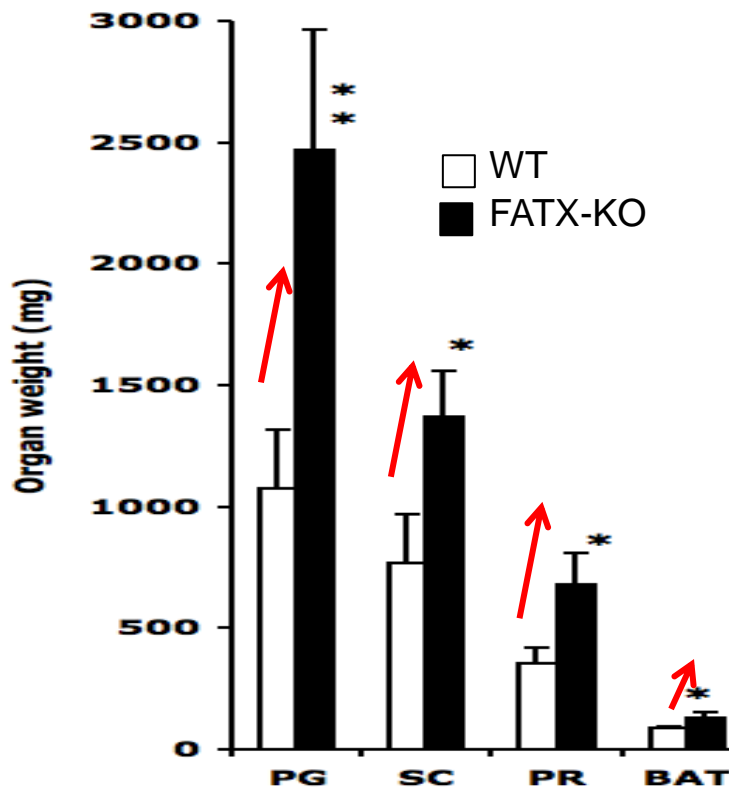
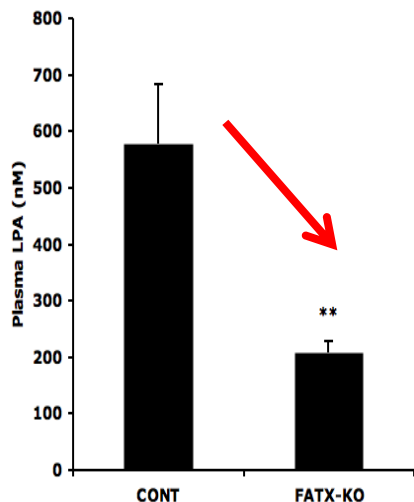
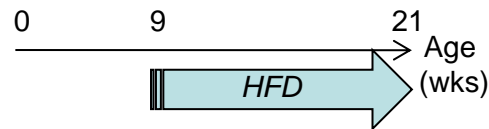


Rôle du LPA dans l'expansion du tissu adipeux

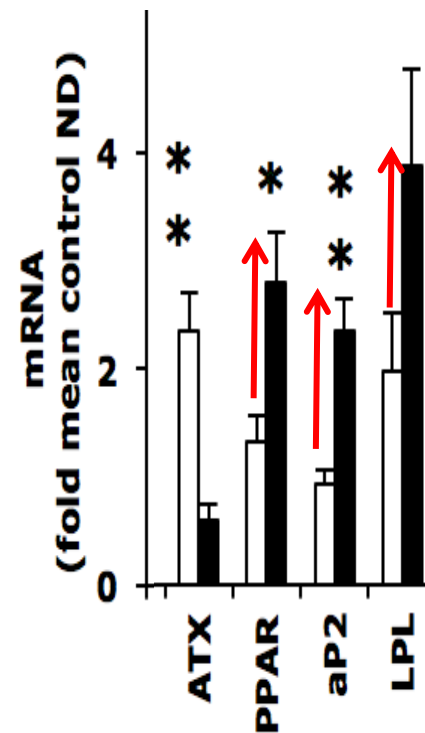


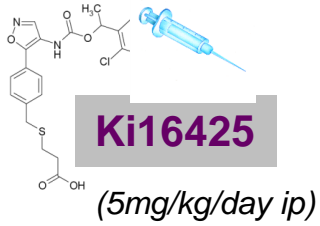


L'inactivation de l'ATX adipocytaire amplifie l'obésité nutritionnelle.



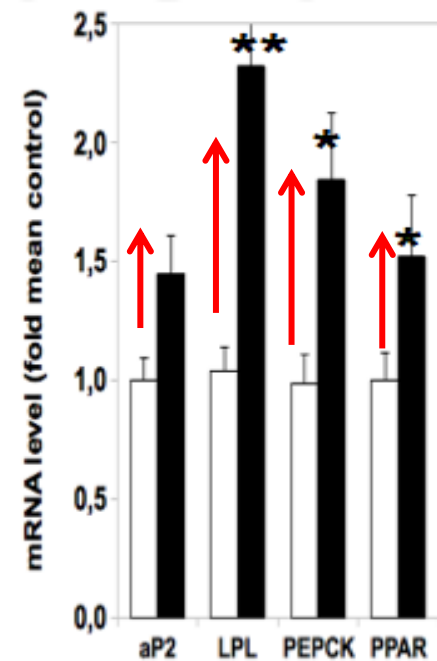
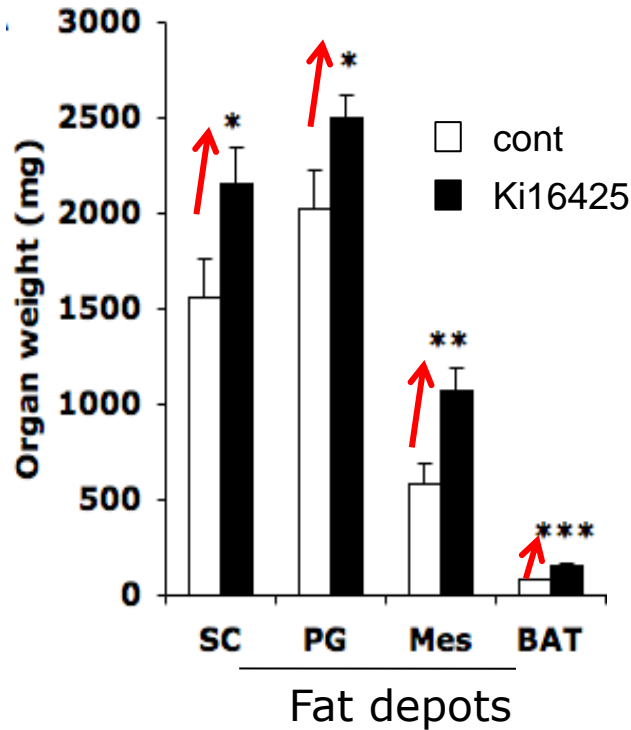
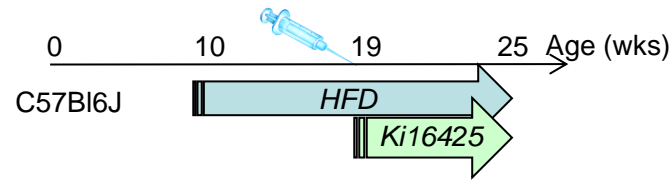
Fat depots

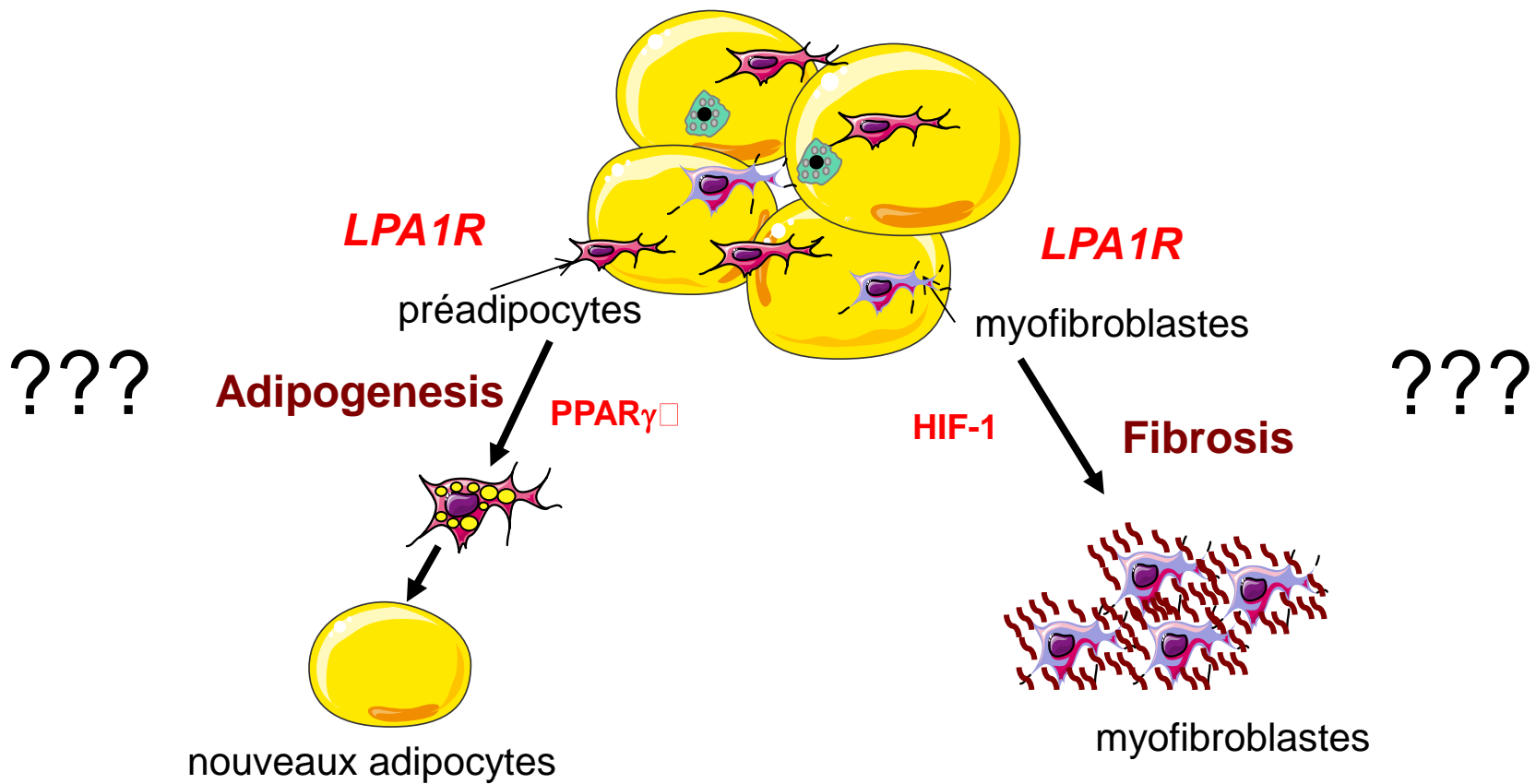




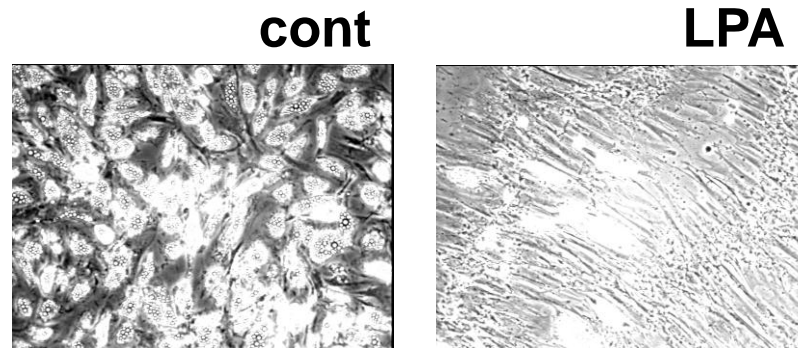
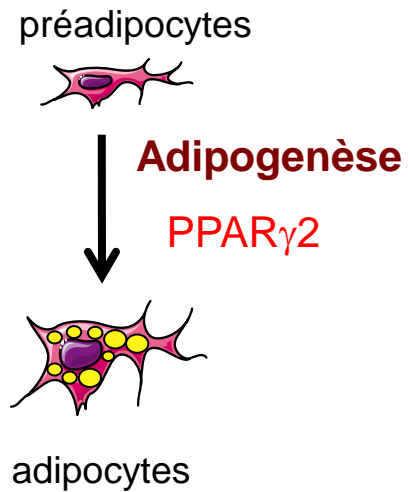
Le blocage pharmacologique des LPA1R amplifie l'obésité nutritionnelle.

antagoniste LPA1/3R



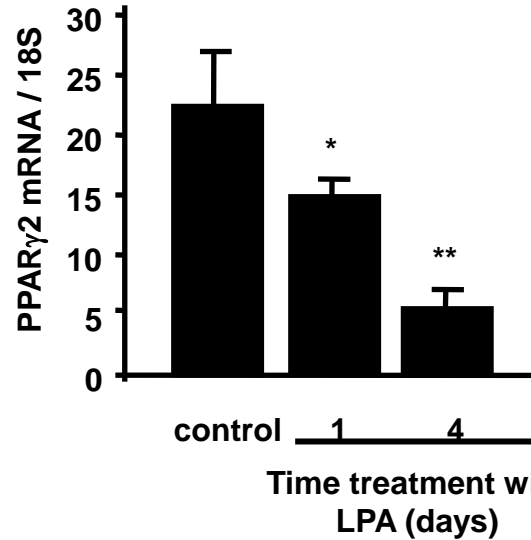


Le LPA inhibe l'adipogénèse *in vitro*



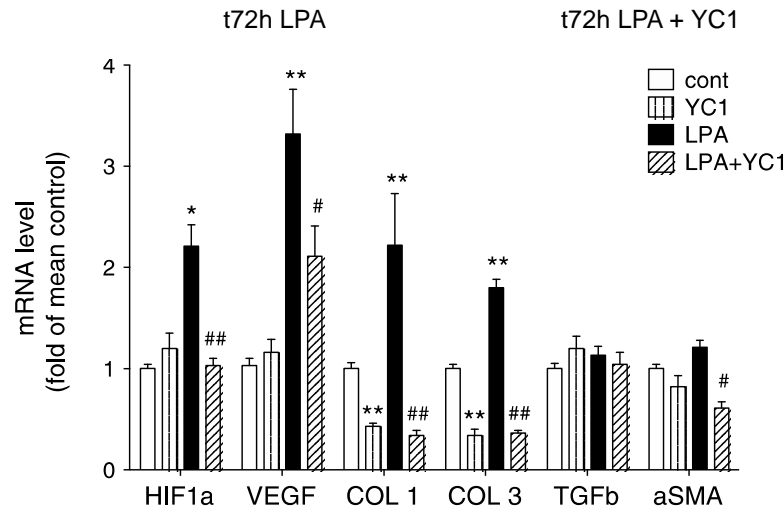
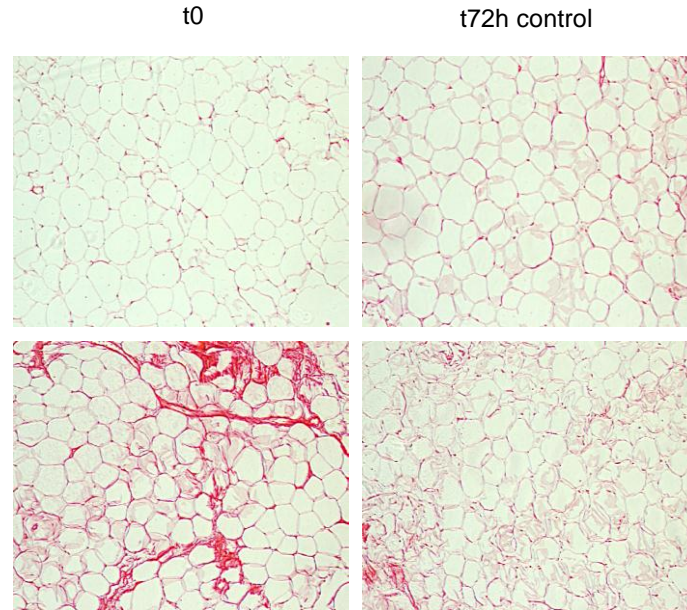
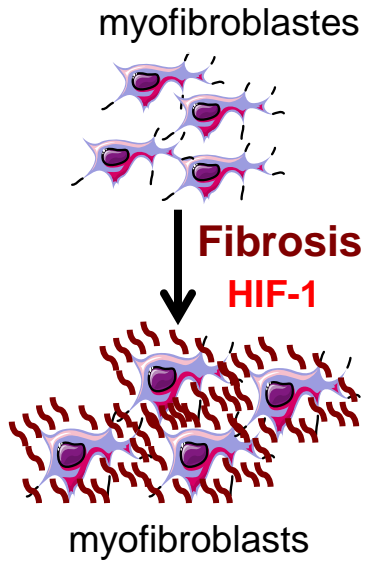
SGBS preadipocytes

Simpson-Golabi-Behmel syndrome

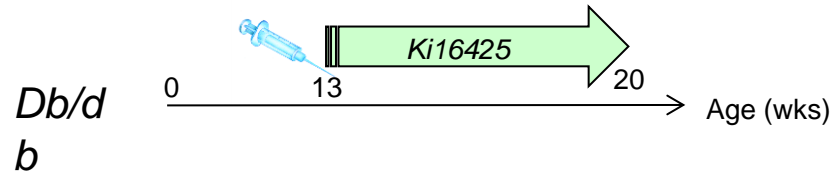


3T3F442A preadipocytes

Le LPA augmente la fibrose du tissu adipeux *in vitro*



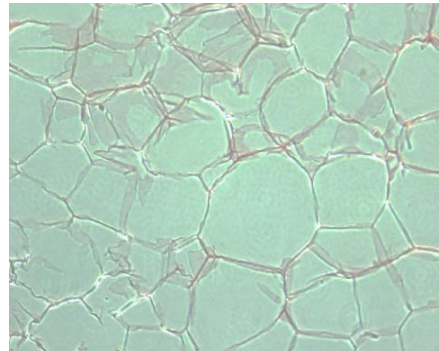
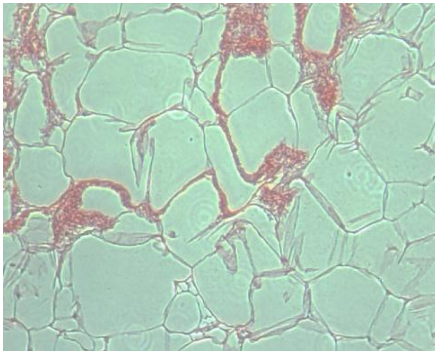
Le blocage pharmacologique des LPA1Rs diminue la fibrose du tissu adipeux chez la souris db/db



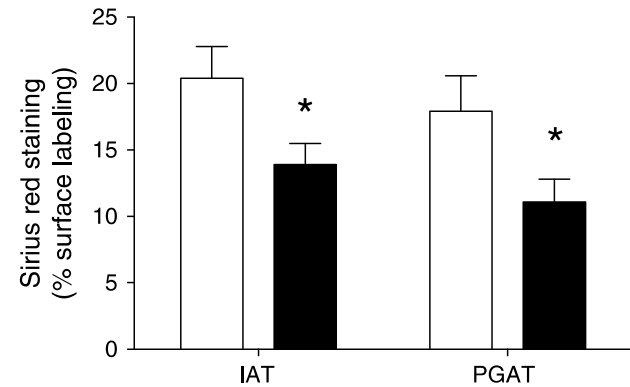
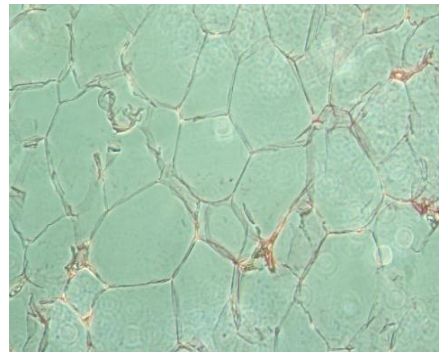
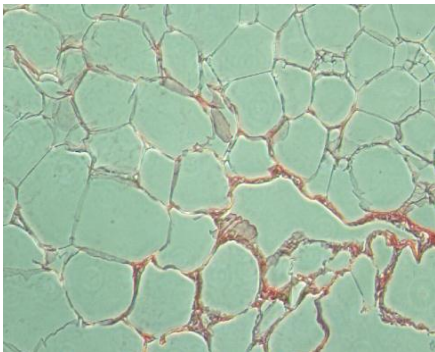
cont

Ki16425

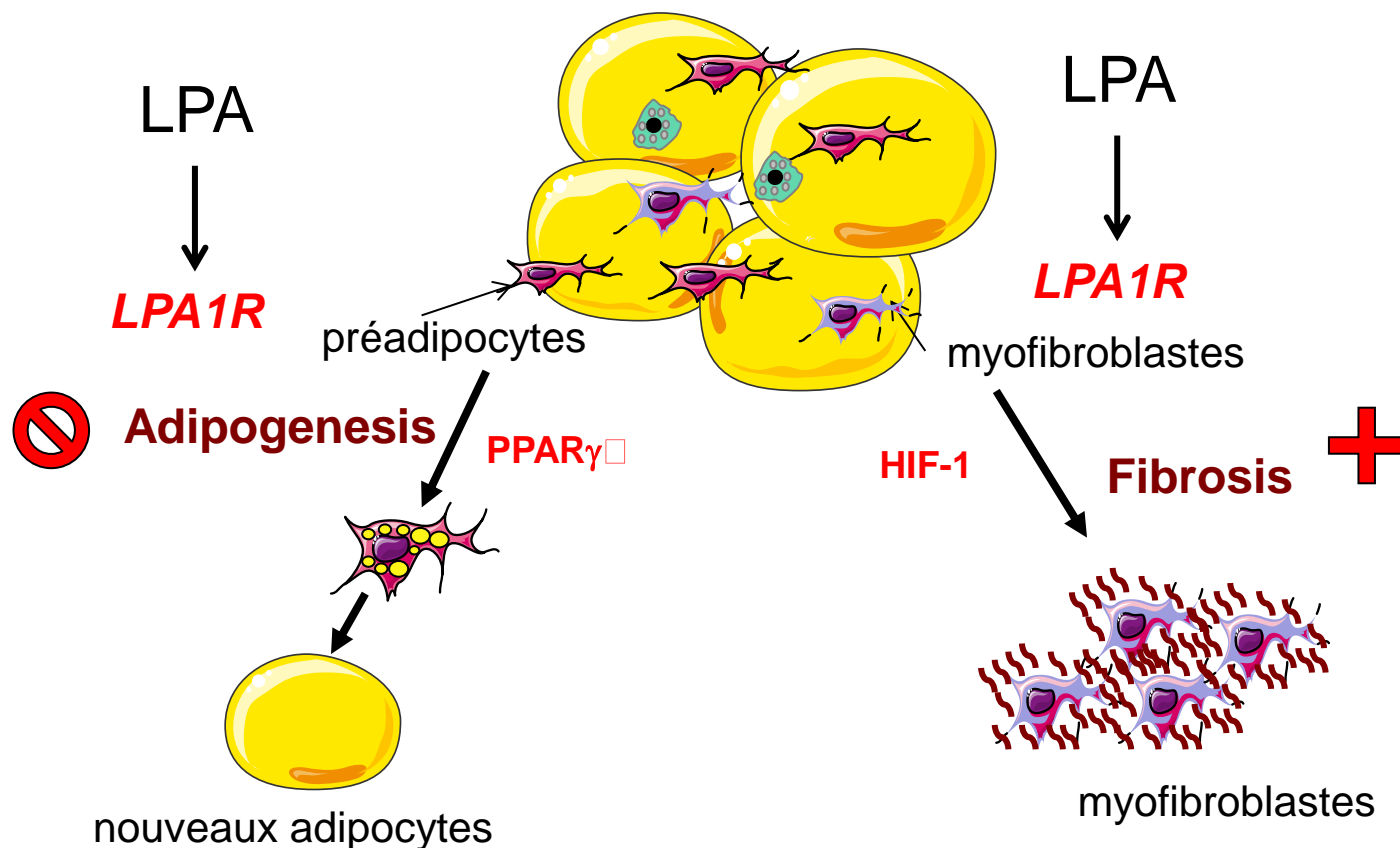
IAT



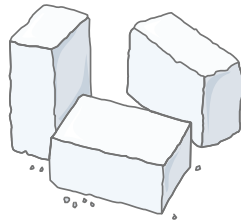
PGAT



Conclusion #1- Le LPA s'oppose à l'expansion du tissu adipeux associée à l'obésité nutritionnelle vraisemblablement *via* ses effets anti-adipogénique & pro-fibrosant .

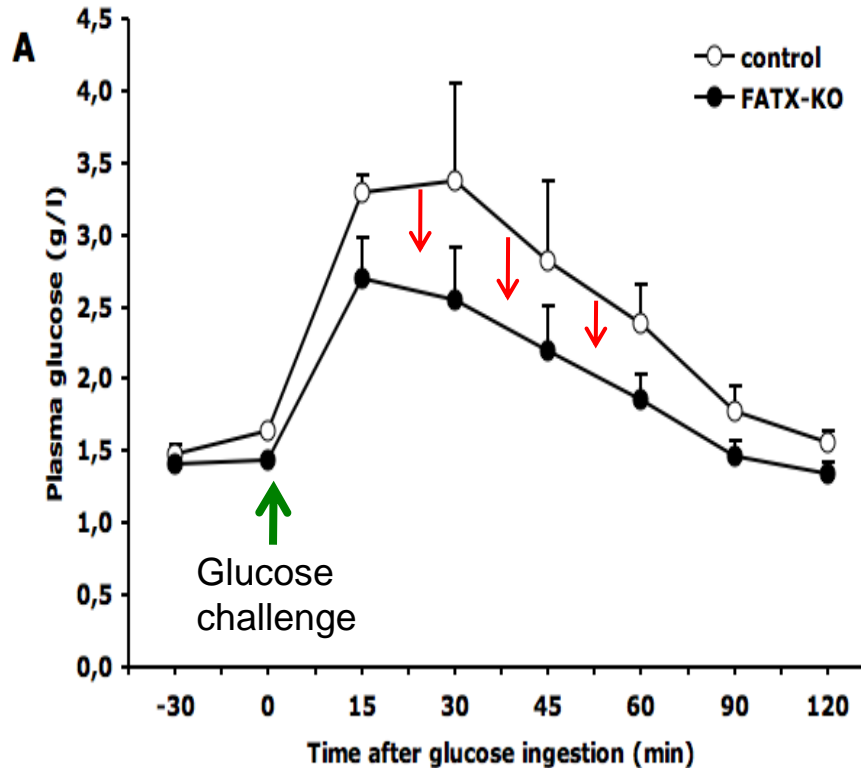
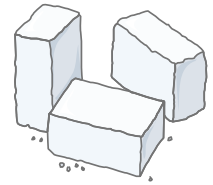
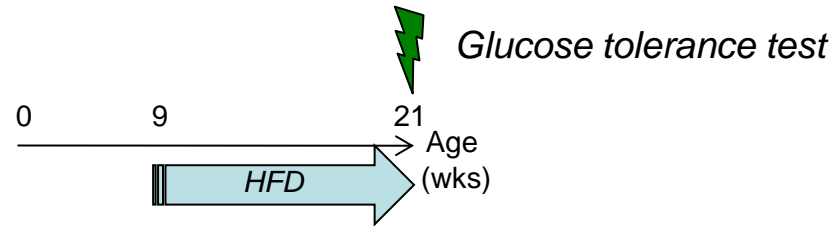


Rôle du LPA dans l'intolérance au glucose

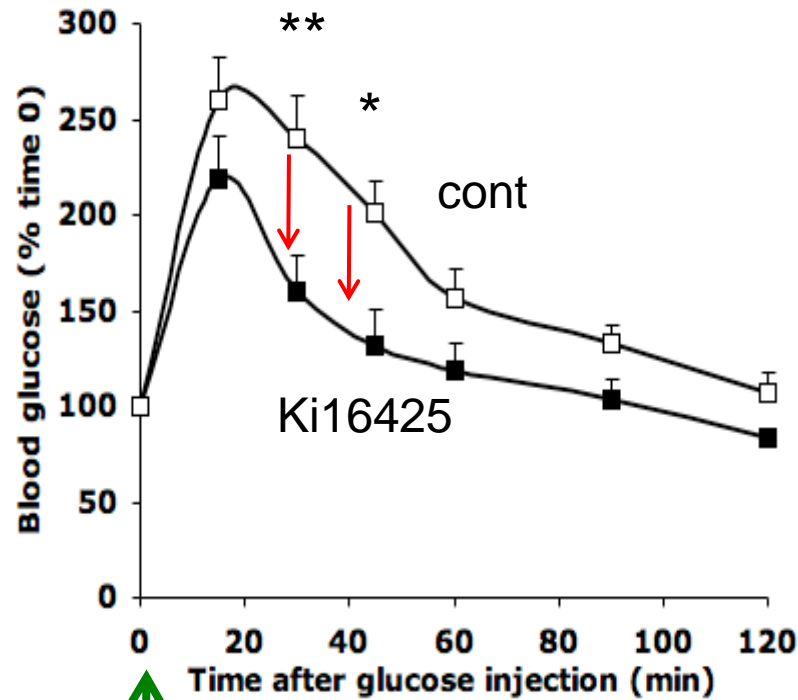
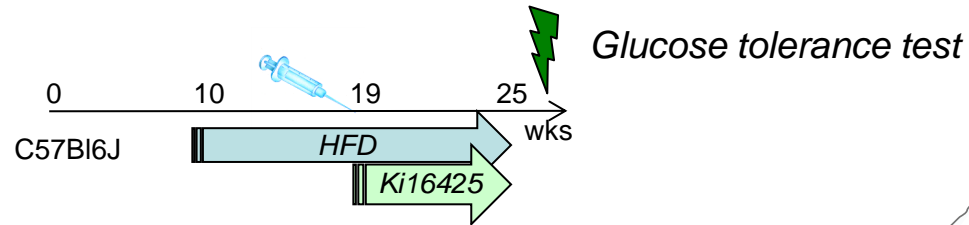
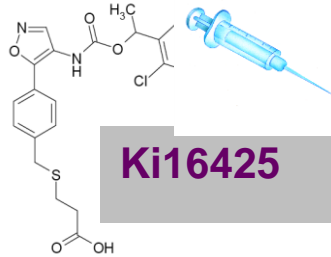


L'inactivation d'ATX adipocytaire améliore la tolérance au glucose des souris obèses

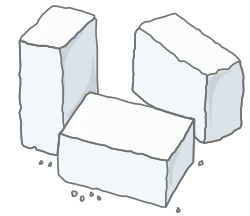
FATX-KO



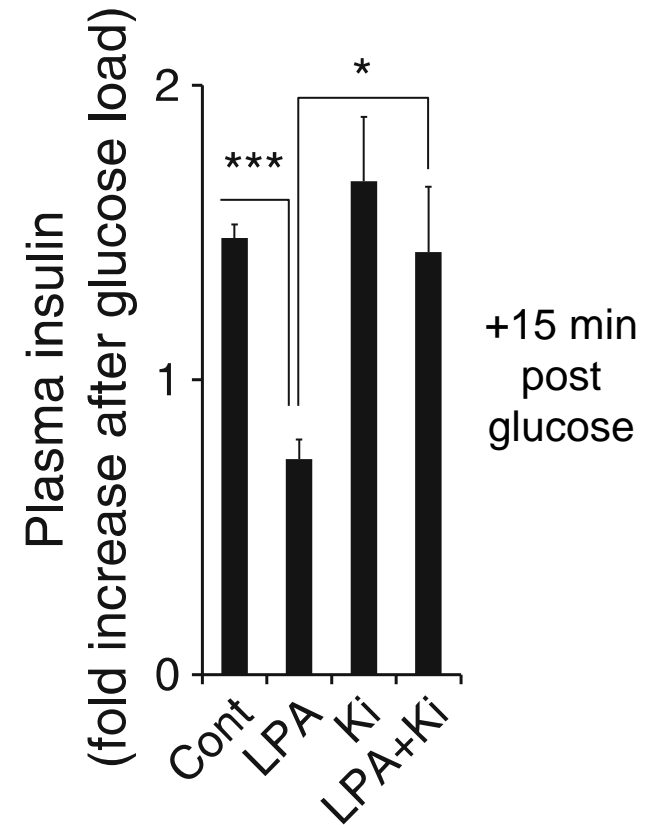
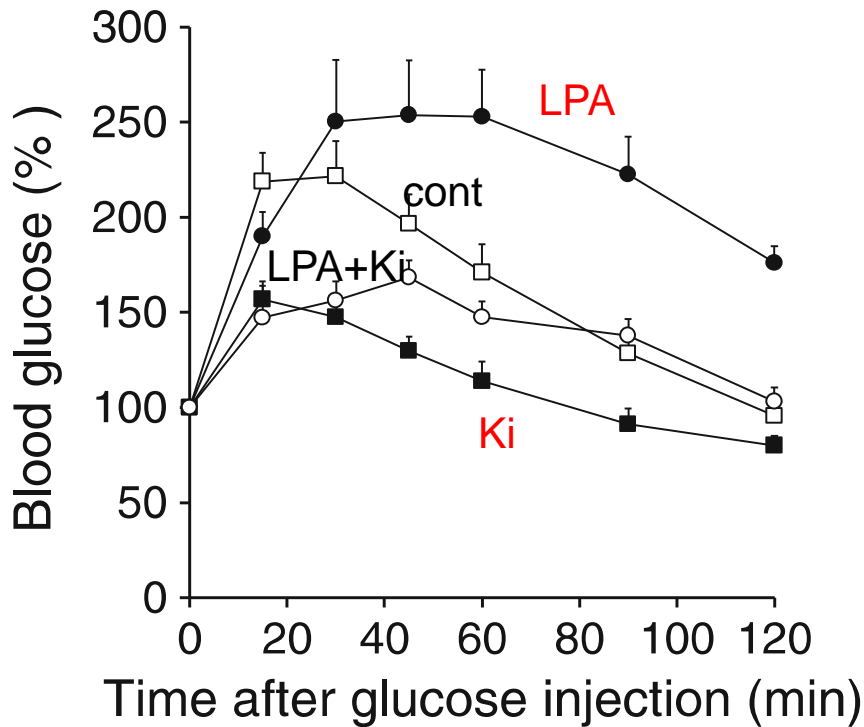
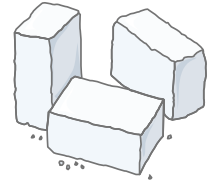
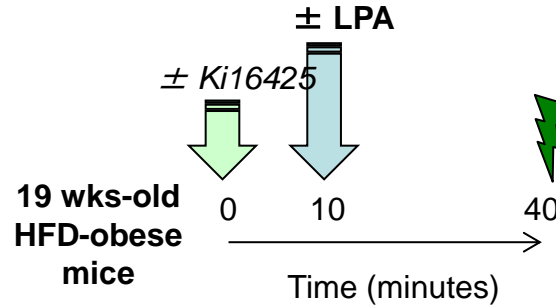
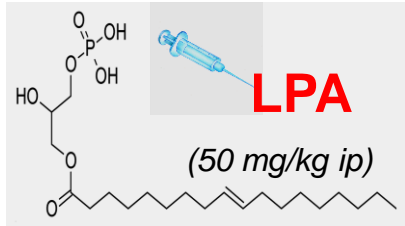
Le blocage des LPA1R améliore la tolérance au glucose des souris obèses



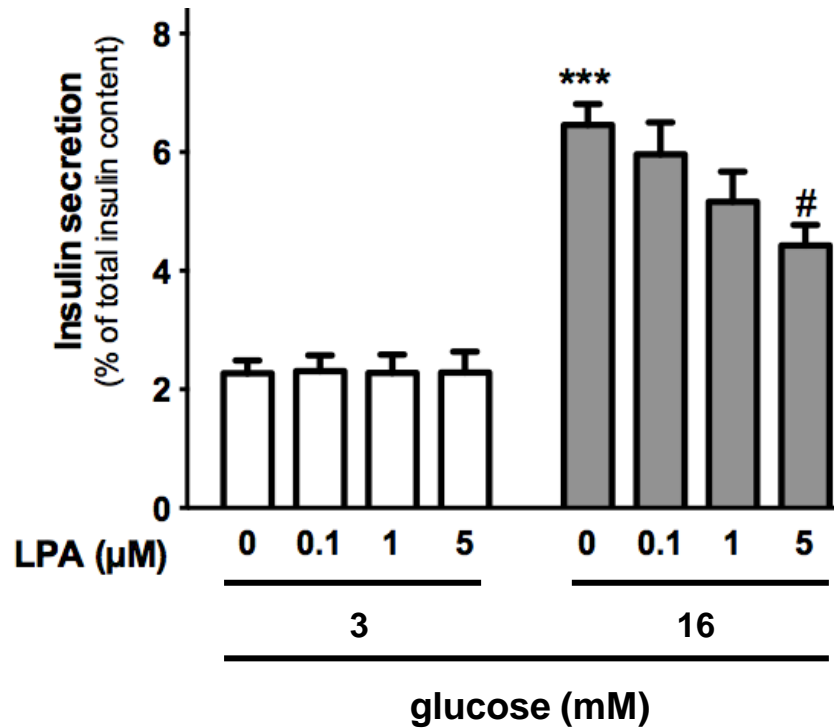
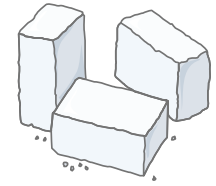
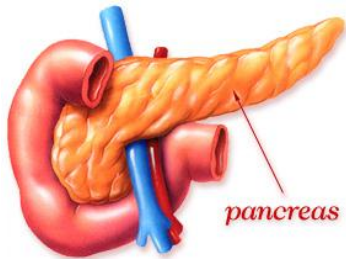
Glucose challenge



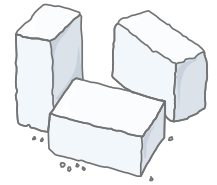
LPA détériore la tolérance au glucose et réduit l'hyperinsulinémie post-glucose



Le LPA inhibe la sécrétion d'insuline par les îlots pancréatiques isolés



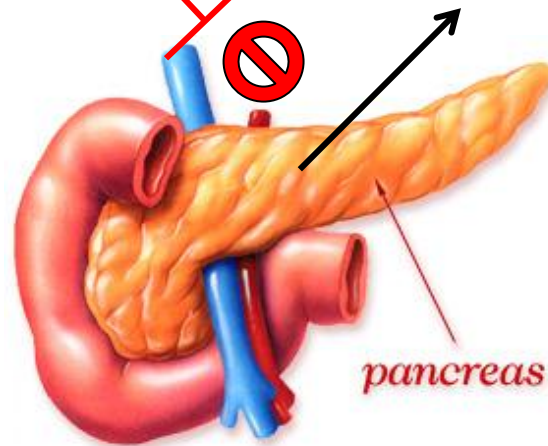
Conclusion #2- le LPA détériore la tolérance au glucose en inhibant la sécrétion d'insuline.

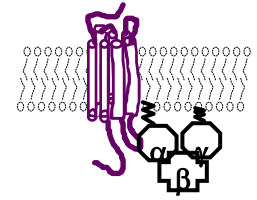
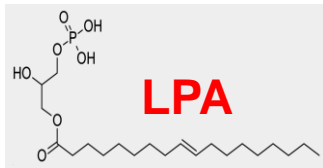


LPA

LPA1R

Insulin → utilisation du glucose





Conclusions - Perspectives

- L'obésité augmente la production de LPA adipocytaire: relation avec l'inflammation ?
- Paradoxe ?
- Le LPA freine l'expansion du tissu adipeux: inhibition adipogenèse + activation fibrose.
- Le LPA inhibe la tolérance par un effet pancréatique.
- Blocage pharmacologique du LPA1R:
 - Avantages: améliore la tolérance au glucose, augmente la sensibilité à l'insuline, réduit la fibrose (antidiabétique ?)
 - Inconvénient: favorise la prise de poids
 - Comparaison avec autres antidiabétiques (thiazolidinediones,.....)



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Estelle Wanecq

Jean-Philippe Pradère

Jérémie Boucher

Stéphane Gesta

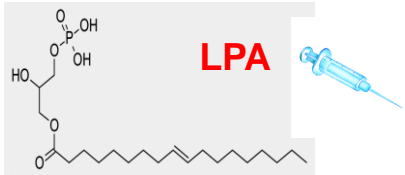
Céline Pagès

Danièle Daviaud

Marie-Françoise Simon

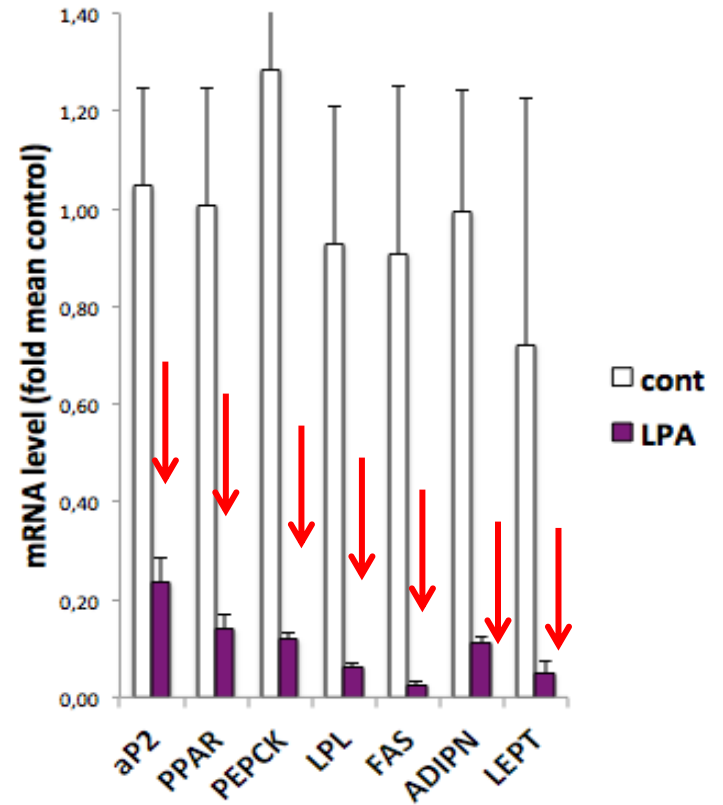
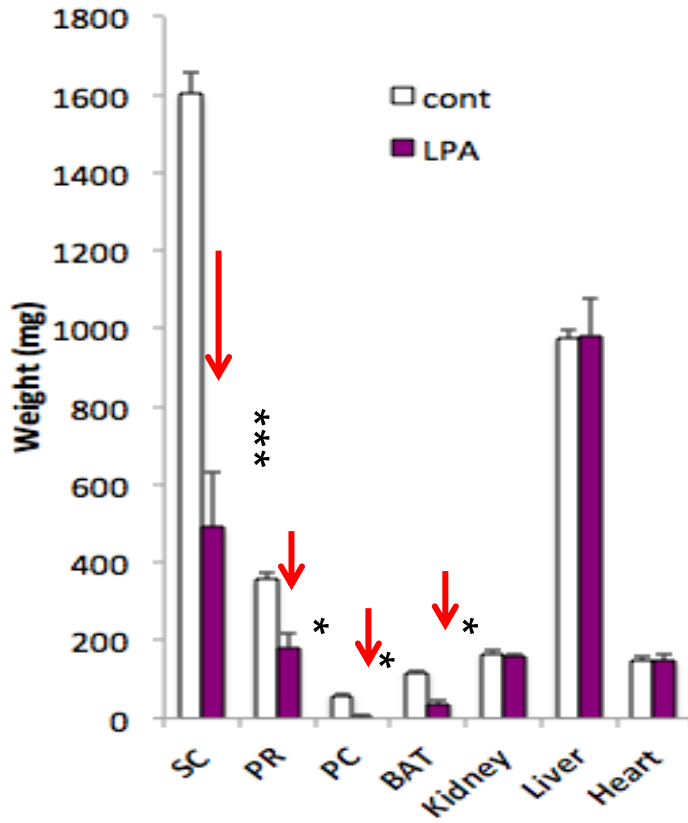
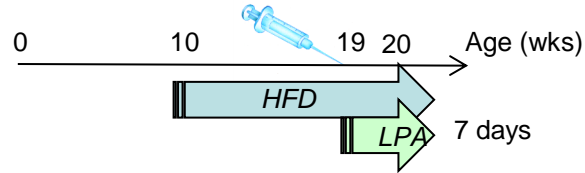
Collaborations

- **Attané C** (Prentki's lab Montreal)
- **Quilliot D** (Nancy Hospital)
- **Moolenaar W** (The Netherlands Cancer Institute)
- **Chun J** (Scripps Research Institute)
- **Boutin JA** (IdRS, Suresnes)

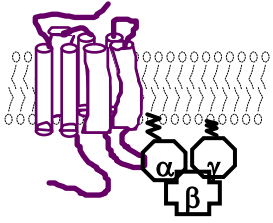


50 mg/kg/day ip

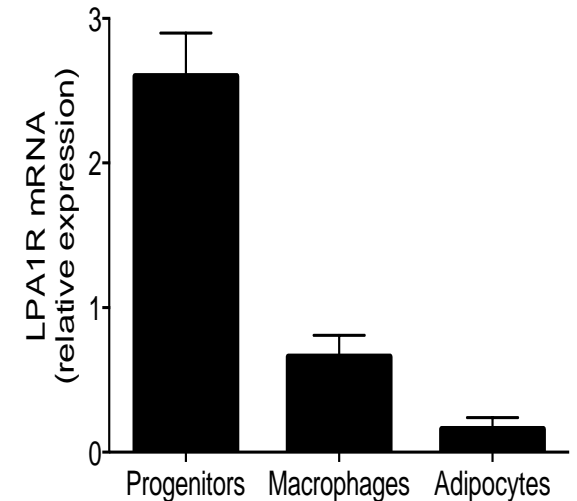
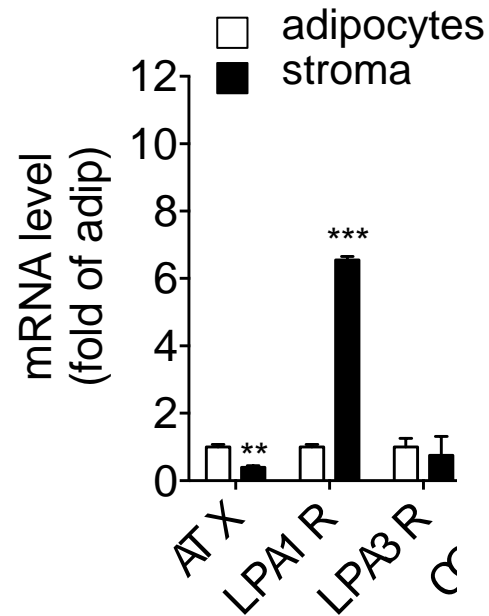
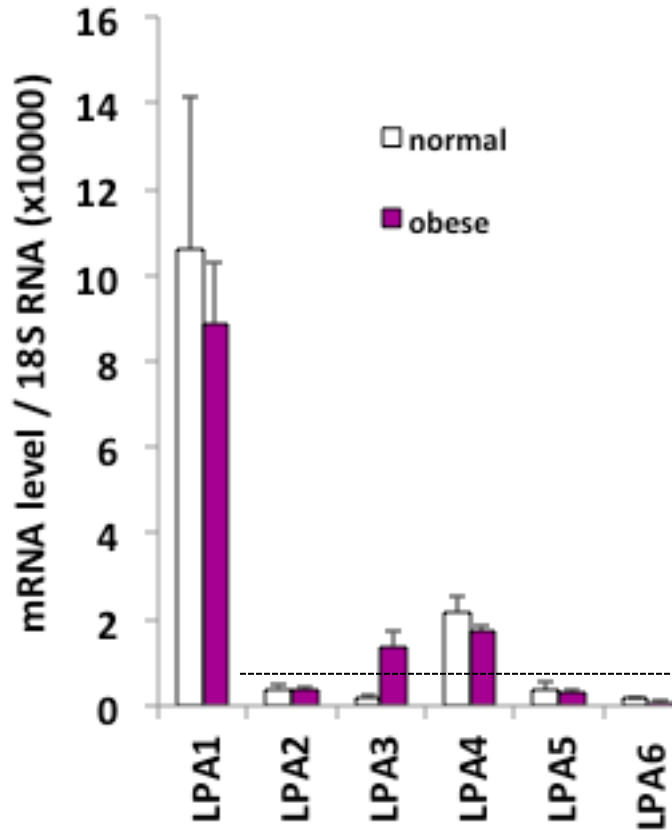
L'injection de LPA réduit l'obésité nutritionnelle.

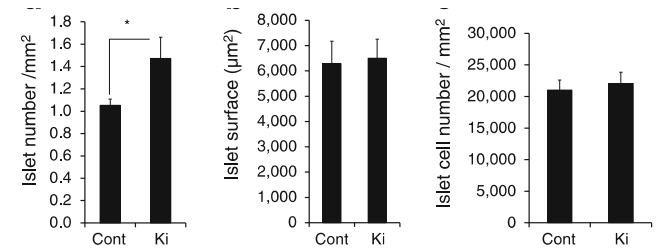
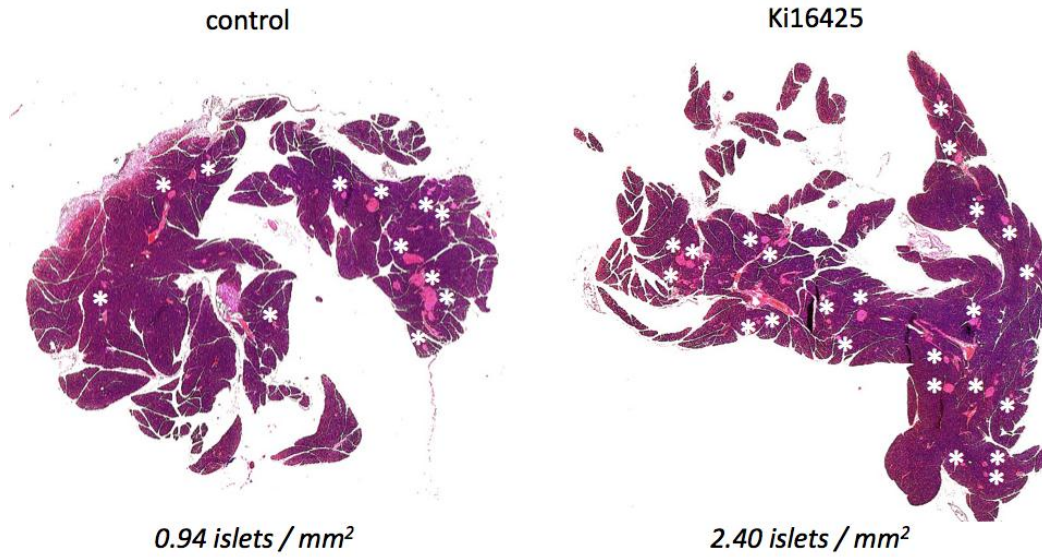
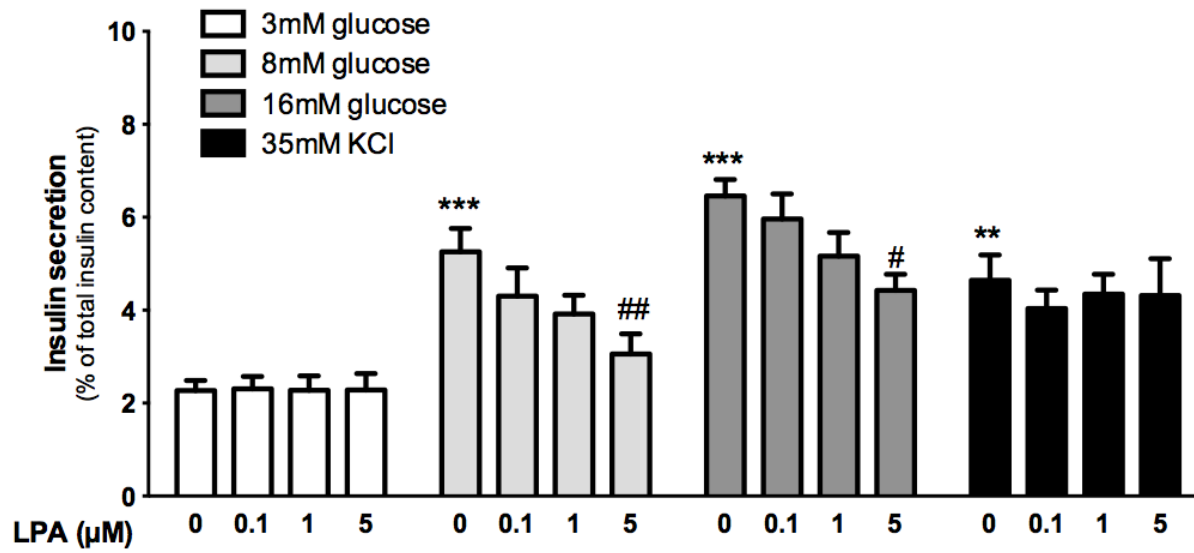


Rancoule et al. (unpublished)



Le sous-type LPA1R est majoritaire dans le tissu adipeux (cellules progénitrices)





Pro-fibrotic activity of lysophosphatidic acid in adipose tissue: *In vivo* and *in vitro* evidence

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Anne Bouloumié ^{a,b}, Dominique Langin ^{a,b,c}, Jean-Loup Bascands ^{a,b},
Philippe Valet ^{a,b}, Jean Sébastien Saulnier-Blache ^{a,b,*}

^a Institut National de la Santé et de la Recherche Médicale (INSERM), UMR1048, Toulouse Cedex 4, France

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Gene expression in inguinal (IAT) and perigonadal (PGAT) adipose tissue and liver of 13-week-old lean db/m and obese/diabetic db/db mice.

	IAT		PGAT		liver	
	db/m	db/db	db/m	db/db	db/m	db/db
Organ weight (mg)	273 ± 48	3476 ± 172***	295 ± 84	2345 ± 80***	1125 ± 103	2008 ± 59***
<i>Gene expression [mRNA level/β-actin mRNA ($\times 10^5$)]</i>						
Col I	184 ± 44	395 ± 37**	221 ± 53	396 ± 35**	3.1 ± 0.3	24.4 ± 5.2**
Col III	1152 ± 320	2622 ± 305**	361 ± 74	669 ± 89*	47 ± 7	204 ± 53*
Col IV	149 ± 20	446 ± 66**	268 ± 47	331 ± 57	6.7 ± 1.1	18.7 ± 3.7**
Fbn	134 ± 40	312 ± 24*	272 ± 94	465 ± 54*	3754 ± 696	8357 ± 1137**
TGF β	28 ± 3	45 ± 5*	40 ± 7	49 ± 4	4.7 ± 0.7	16.0 ± 1.7***
CTGF	10 ± 2	44 ± 7***	32 ± 5	33 ± 1	8.6 ± 1.9	42.7 ± 7.7***
aSMA	244 ± 39	444 ± 47**	638 ± 62	326 ± 34*	13.3 ± 4.1	34.2 ± 3.0**
MCP1	3.8 ± 0.3	19 ± 5*	11 ± 4	23 ± 3*	1.0 ± 0.3	2.2 ± 0.3**
F4/80	12 ± 2	25 ± 2**	25 ± 4	42 ± 5*	10.0 ± 0.5	13.0 ± 1.2*
ATX	258 ± 44	668 ± 58***	252 ± 20	309 ± 40	314 ± 63	584 ± 53**
LPA1R	37 ± 5	25 ± 2*	154 ± 18	31 ± 6***	4.8 ± 2.5	13.0 ± 1.5**
LPA2R	2.8 ± 1.3	1.6 ± 0.2	14 ± 5	4.2 ± 0.7*	2.3 ± 0.6	0.6 ± 0.2*
LPA3R	1.7 ± 0.2	1.9 ± 0.4	3.5 ± 0.3	0.8 ± 0.2***	0.4 ± 0.1	3.1 ± 0.6**
LPA4R	4.2 ± 0.8	12 ± 1*	19 ± 2	11 ± 1	0.3 ± 0.1	0.3 ± 0.1
LPA5R	1.7 ± 0.1	7 ± 1*	4.9 ± 0.3	15 ± 4*	1.3 ± 0.3	0.9 ± 0.3

Characteristics of db/m (n = 6) vs db/db (12) mice: body weight (23.4 ± 1.3 vs 40.5 ± 0.8 g, p < 0.001); plasma glucose (145 ± 10 vs 286 ± 36 mg/dl, p < 0.01). * p < 0.05, ** p < 0.01, *** p < 0.001.

Morphometric parameters and plasma composition of db/db mice after treatment with Ki16425.

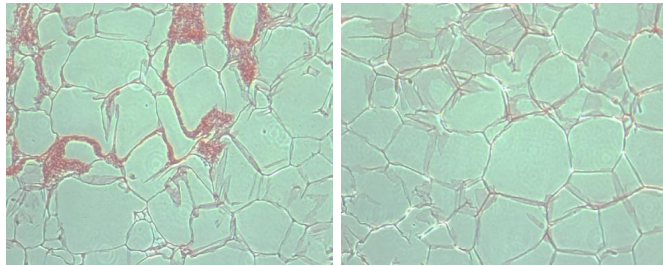
	Control (n = 12)	Ki16425 (n = 12)
ITT (AUC)	13778 ± 312	11985 ± 457 *
Fasting plasma insulin (pg/ml)	8351 ± 270	7581 ± 212 *
Fasting blood glucose (mg/dl)	324 ± 27	278 ± 31
Plasma glycated Hg %	5.8 ± 0.3	6.0 ± 0.2
Body weight (g)	39.9 ± 1.0	37.3 ± 1.1
IAT weight (mg)	3476 ± 172	3061 ± 173
PGAT weight (mg)	2345 ± 80	2123 ± 84
Liver weight (mg)	2008 ± 59	1879 ± 97
Cumulative food intake (cumulative g/g body weight)	6.38 ± 0.20	6.84 ± 0.27
ALT (U/L)	79.2 ± 6.5	84.8 ± 10.7
AST (U/L)	87.2 ± 6.2	94.3 ± 13.9
Creatinin (µmol/L)	16.7 ± 1.5	17.5 ± 1.6
Plasma triglycerides (mmol/L)	2.9 ± 0.4	2.8 ± 0.3

Db/db mice were treated for 7 weeks with Ki16425 (5 mg/kg/day ip) before analysis. Values are means ± SEM of 12 mice per group. *p < 0.05, **p < 0.01, comparing indicated values.

cont

Ki16425

IAT



PGAT

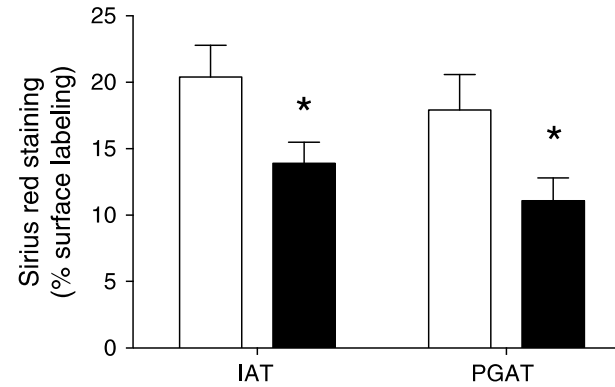
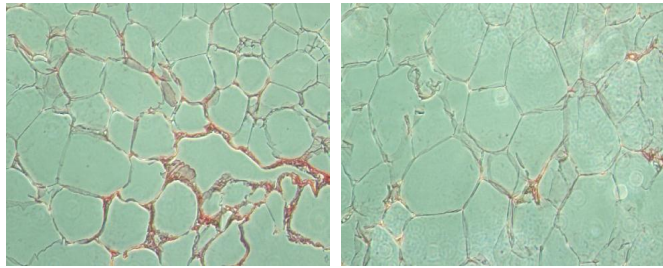
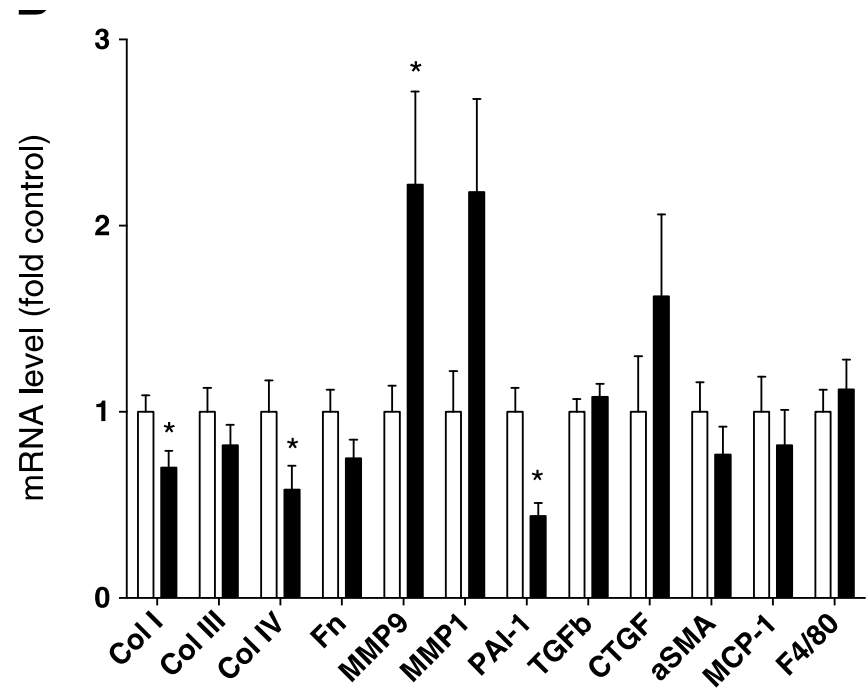
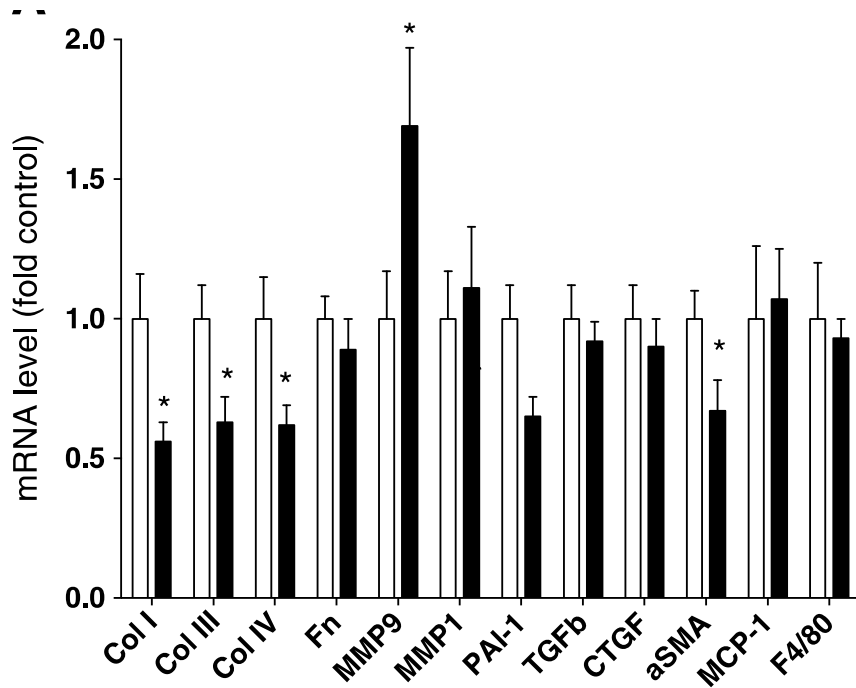
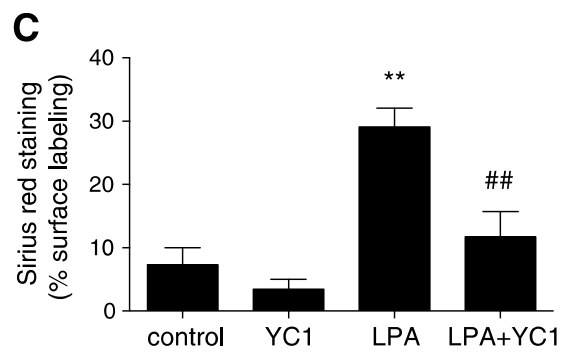
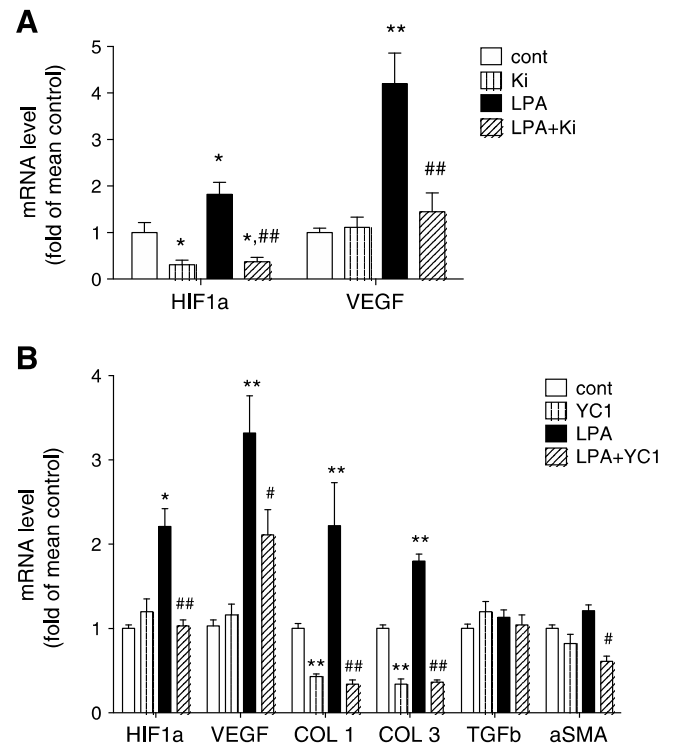
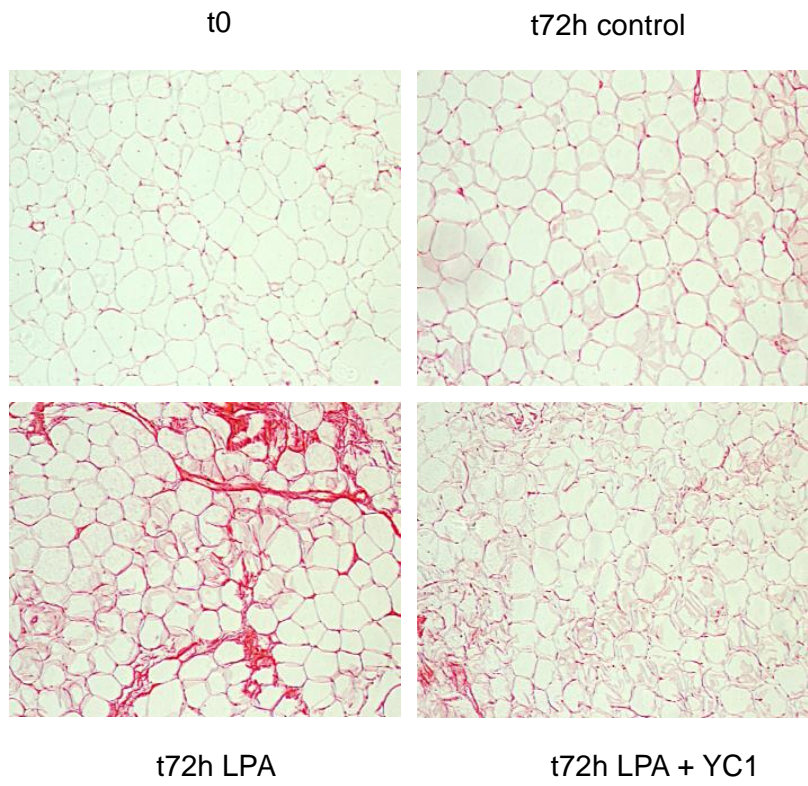
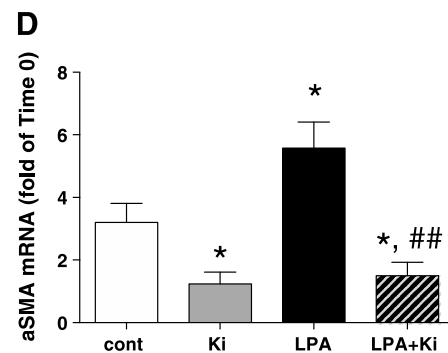
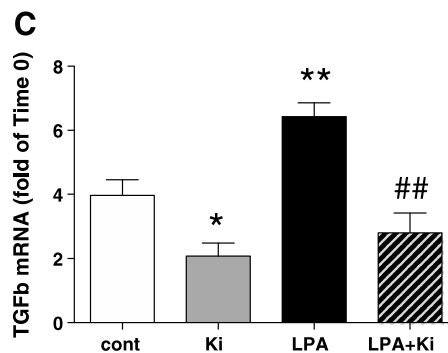
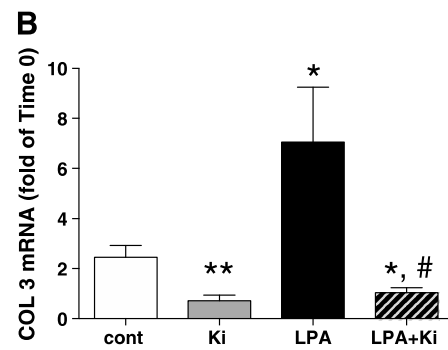
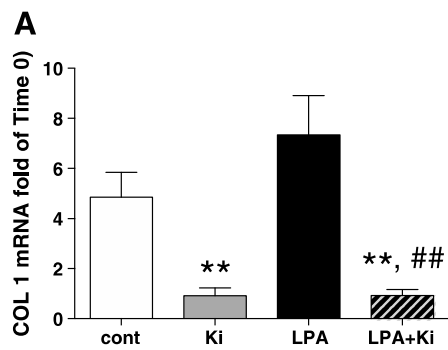
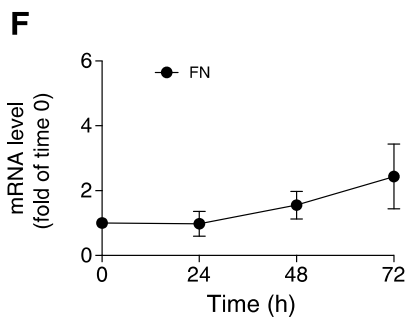
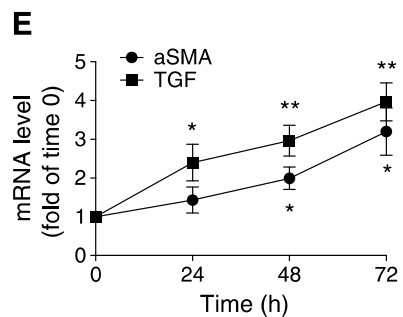
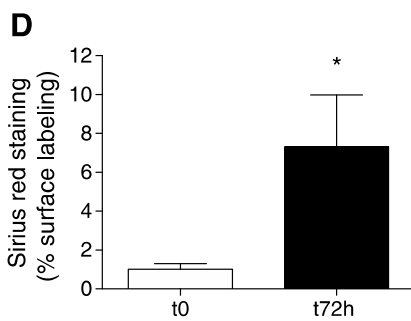
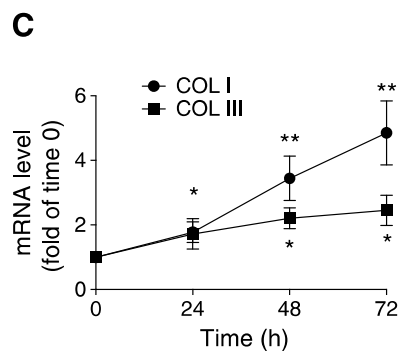
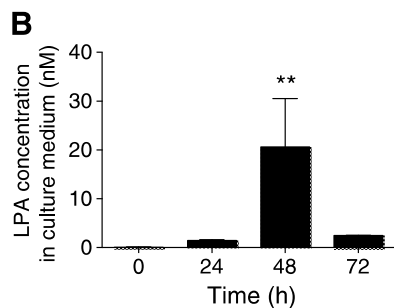
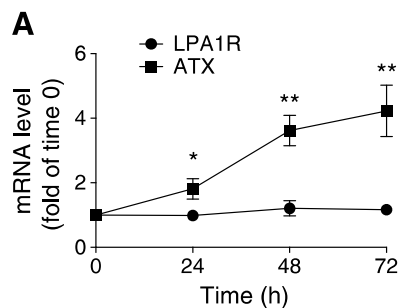


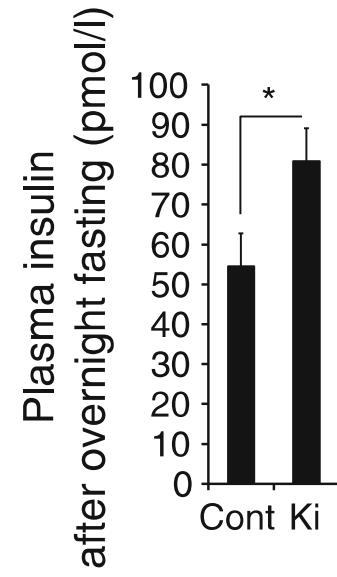
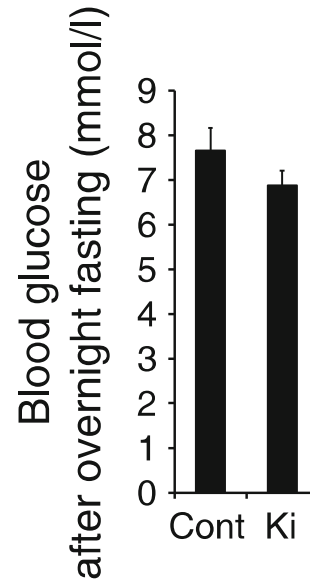
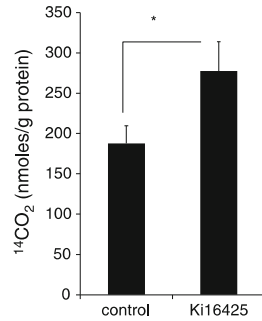
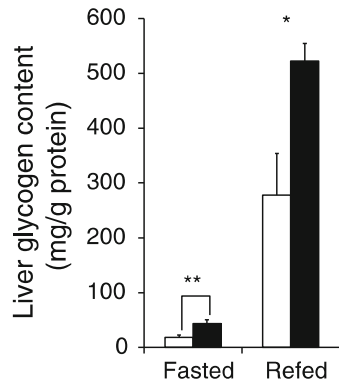
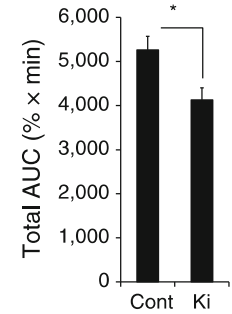
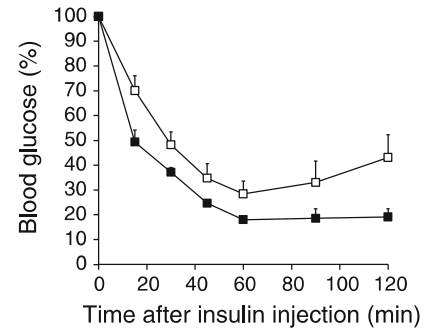
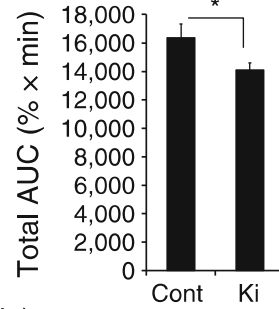
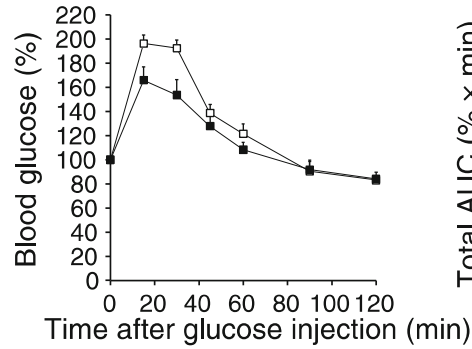
Figure S1. Chronic treatment with Ki16425 reduces collagen content in adipose tissue of db/db mice. Db/db mice were treated for 6 weeks with Ki16425 (5 mg/kg/day ip) and inguinal (IAT) and perigonadal (PGAT) adipose tissues were stained with Sirius-red as described in Methods (quantification is shown in Figure 1).





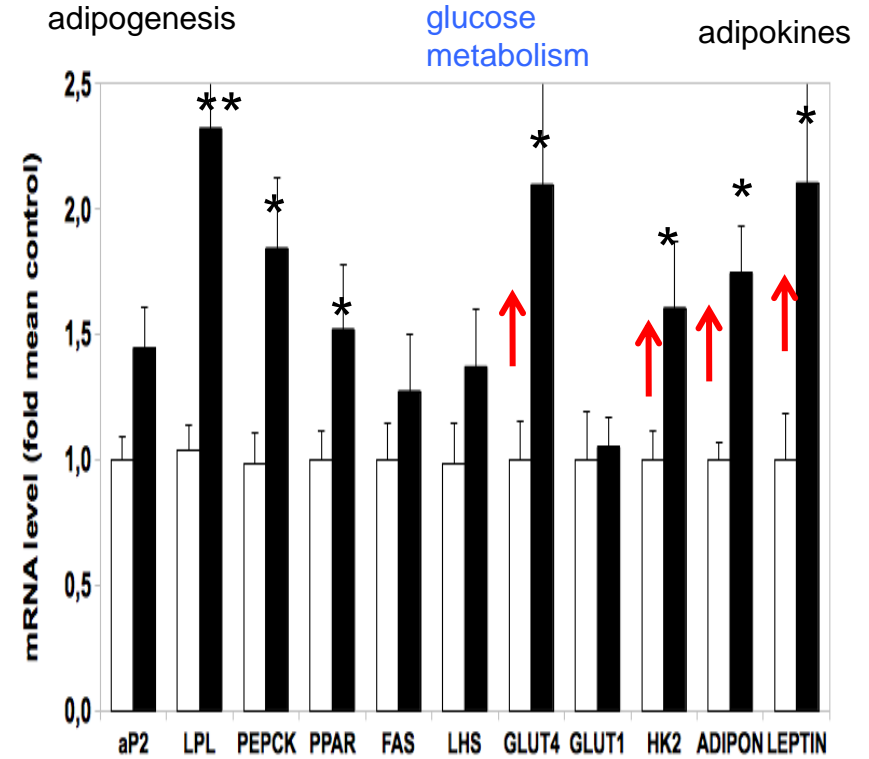
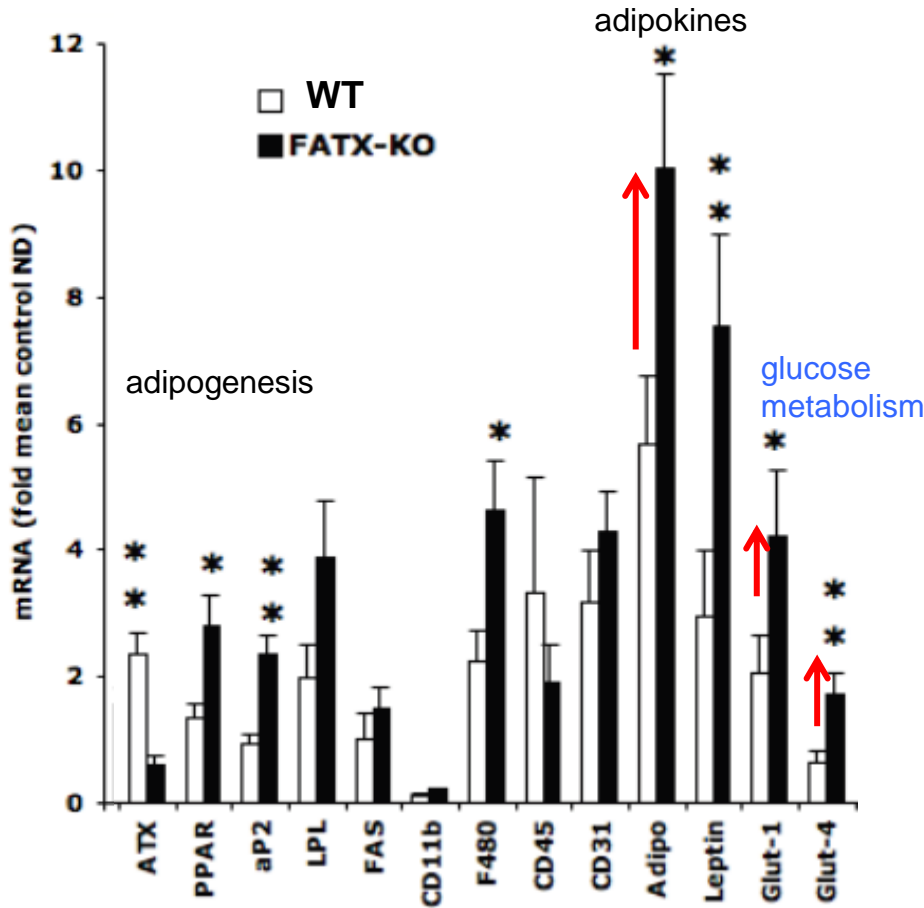
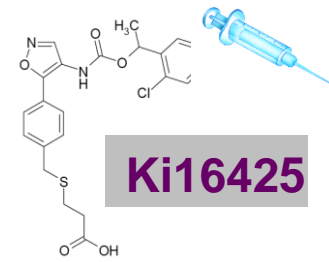


Ki16425-treatment (9 weeks)

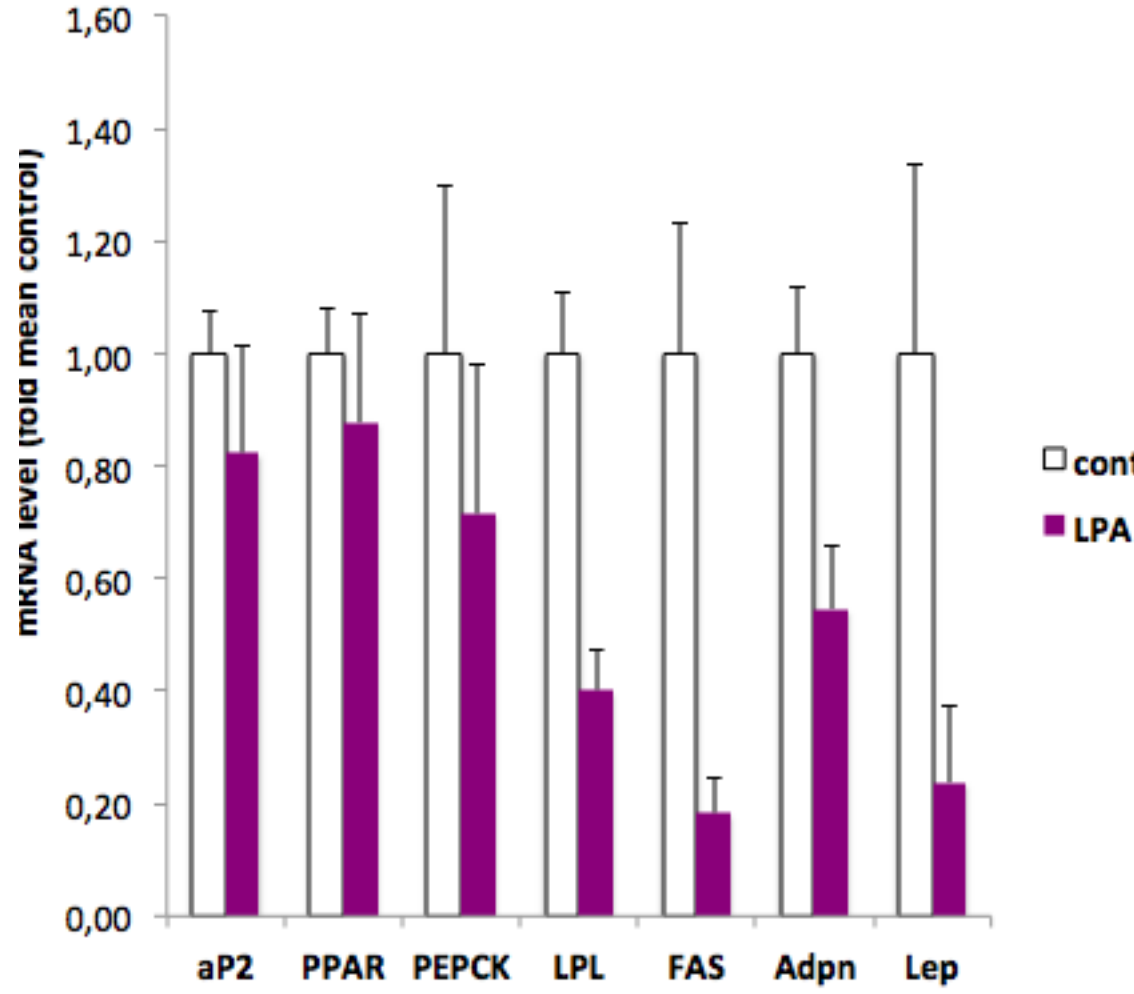
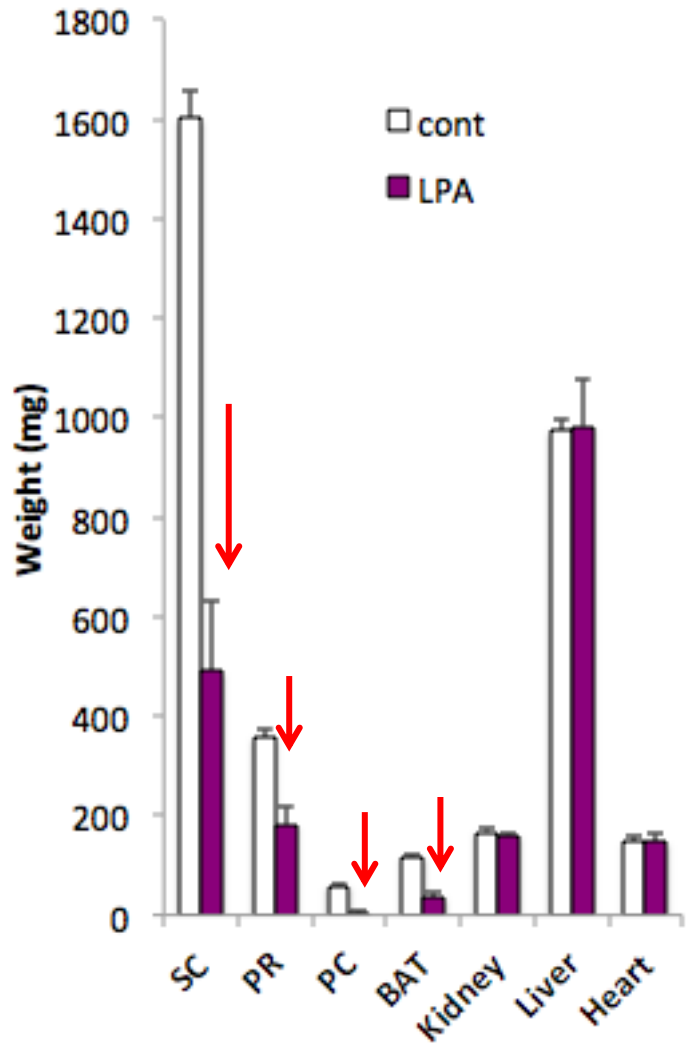
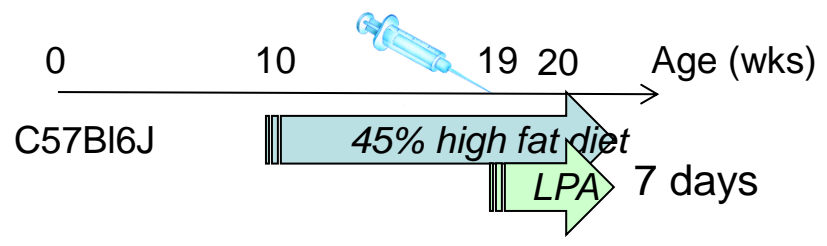
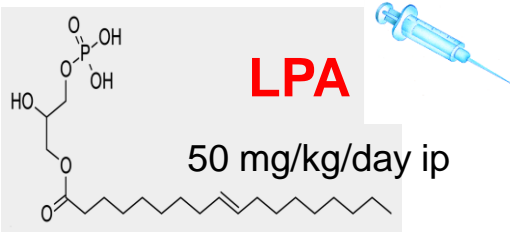




FATX-KO



Up-regulation of genes involved in glucose metabolism

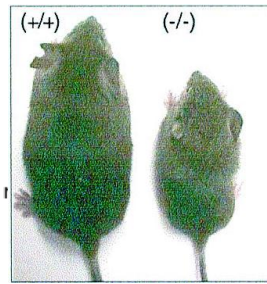


Requirement for the lp_{A1} lysophosphatidic acid receptor gene in normal suckling behavior

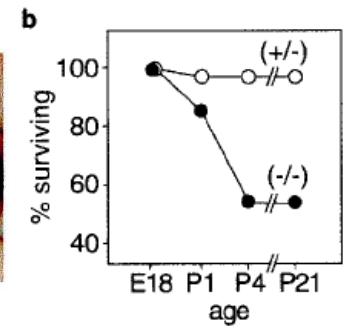
James J. A. Contos*, Nobuyuki Fukushima¹, Joshua A. Weiner^{2,4}, Dhruv Kaushal⁵, and Jerold Chun^{6,5†}

¹Department of Pharmacology, ²Neuroscience Graduate Program, ³Biomedical Sciences Program, School of Medicine, University of California, San Diego, La Jolla, CA 92093-0636

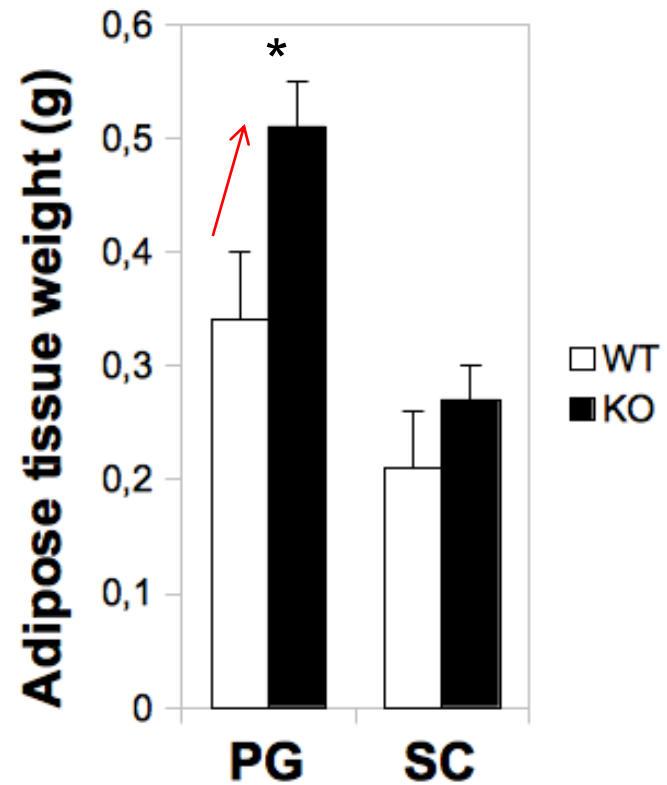
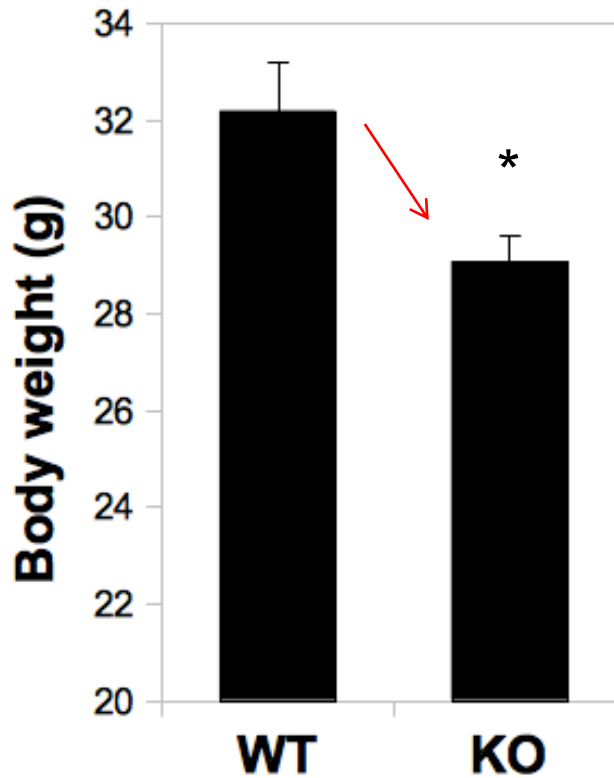
13384–13389 | PNAS | November 21, 2000 | vol. 97 |



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Simon et al. J. Biol. Chem. 2005



LPA1R-KO are obesity-insensitive because of impaired food-intake

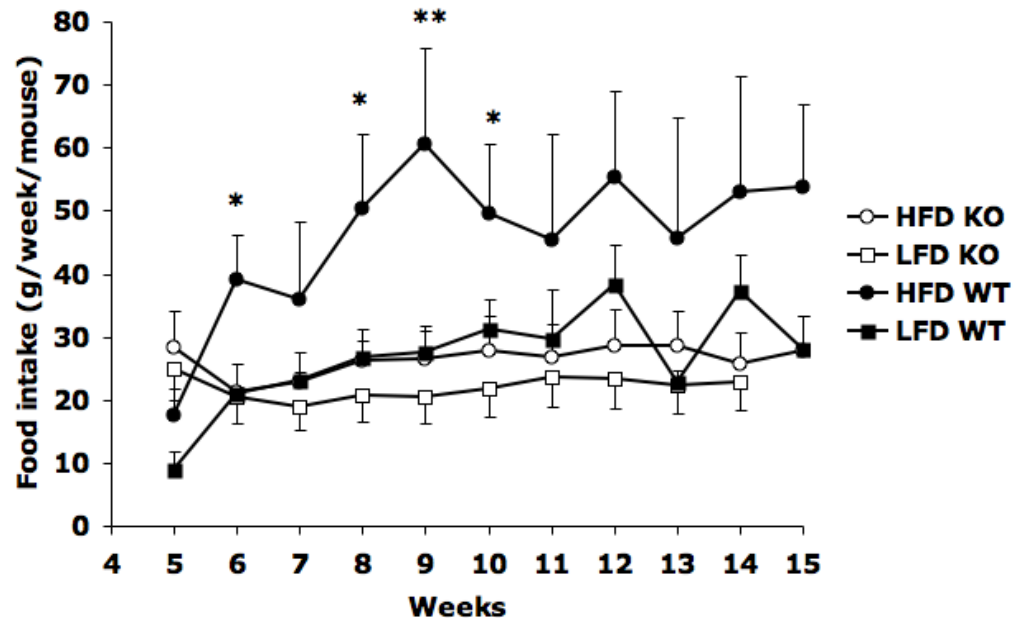
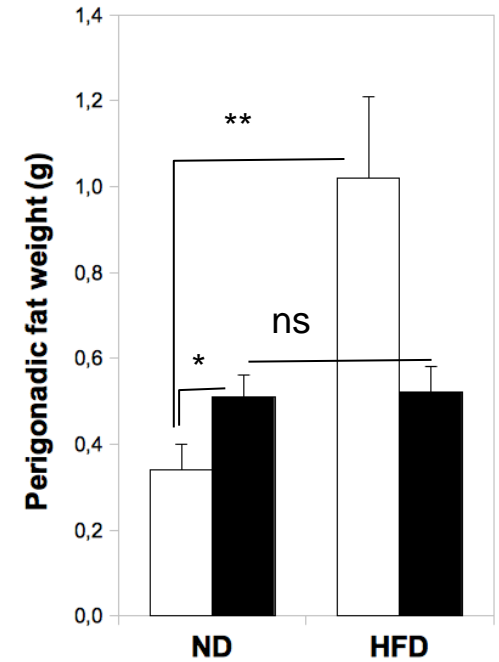
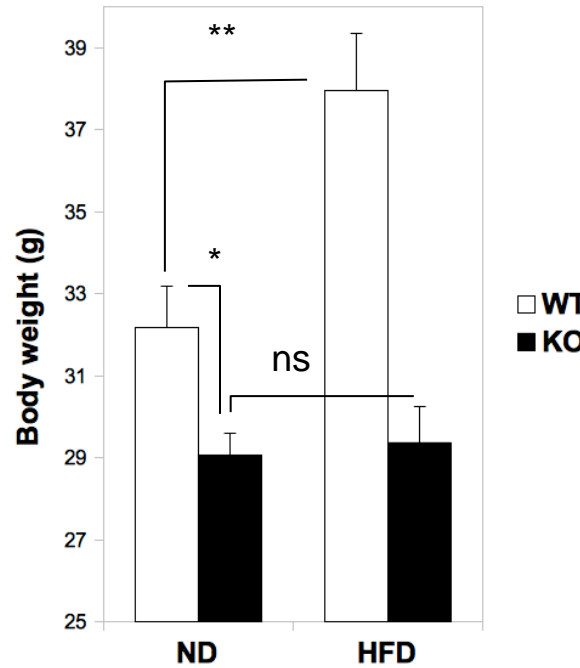
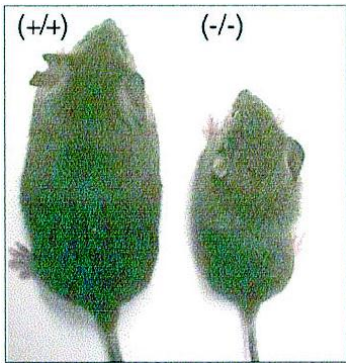


Table I. Weight and plasma parameters in wild type (WT) and LPA1R-KO (KO) mice fed low and high fat diet.

	WT		KO	
	LFD (n=8)	HFD (n=12)	LFD (n=5)	HFD (n=12)
Body weight (g)	32.2 ± 0.09	37.9 ± 1.4 **	29.1 ± 0.5	29.4 ± 0.9
PG weight (g)	0.34 ± 0.06	1.02 ± 0.19 **	0.51 ± 0.05 \$	0.52 ± 0.06
SC weight (g)	0.21 ± 0.04	0.52 ± 0.09 **	0.27 ± 0.03	0.27 ± 0.02
BAT weight (g)	0.07 ± 0.01	0.13 ± 0.02 *	0.09 ± 0.01	0.08 ± 0.01
TG (g/l)	0.36 ± 0.03	0.44 ± 0.05	0.31 ± 0.03	0.34 ± 0.03
FFA (nM)	0.65 ± 0.06	0.72 ± 0.04	0.77 ± 0.06	0.65 ± 0.06
Glucose (g/l)	1.73 ± 0.13	2.25 ± 0.19 *	2.02 ± 0.15 \$	1.81 ± 0.51
Leptin (ng/ml)	2.2 ± 0.2	14.2 ± 3.8 **	4.6 ± 0.8 \$\$	3.6 ± 0.5

Student's *t*-test was used to compare : LFD vs. HFD (P<0.05 * ; P<0.01 **) and WT LFD vs. KO LFD (P<0.05 \$; P<0.01 \$\$).

