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Intensieve Geneeskunde

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AUTOPHAGY, FGF21 AND GLUCAGON DURING CRITICAL ILLNESS:
INTERACTIONS AND THERAPEUTIC PERSPECTIVES

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Brussels, 23/06/2017

Overview

1. Introduction
2. Objectives
3. Results
    1. The role of ***autophagy*** during critical illness
    2. The role of ***FGF21*** during critical illness
    3. The role of ***glucagon*** during critical illness
4. General conclusions and therapeutic perspectives

Introduction

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1. Multiple organ failure (MOF)

Table 2 ICU and hospital mortality rates according to the number, type, and combinations of failed organs

	On admission to the ICU			At any time during ICU stay		
	Incidence (%)	Mortality (%)		Incidence (%)	Mortality (%)	
		ICU	Hospital		ICU	Hospital
Number of failed organs						
1	927 (32)	17	23	942 (32)	5	11
2	524 (18)	28	37	677 (23)	24	33
3	181 (6)	45	50	334 (11)	44	51
>3	43 (1)	58	70	157 (5)	73	79

The pathogenesis of MOF is incompletely understood

More insight is necessary to identify new *therapeutic perspectives*

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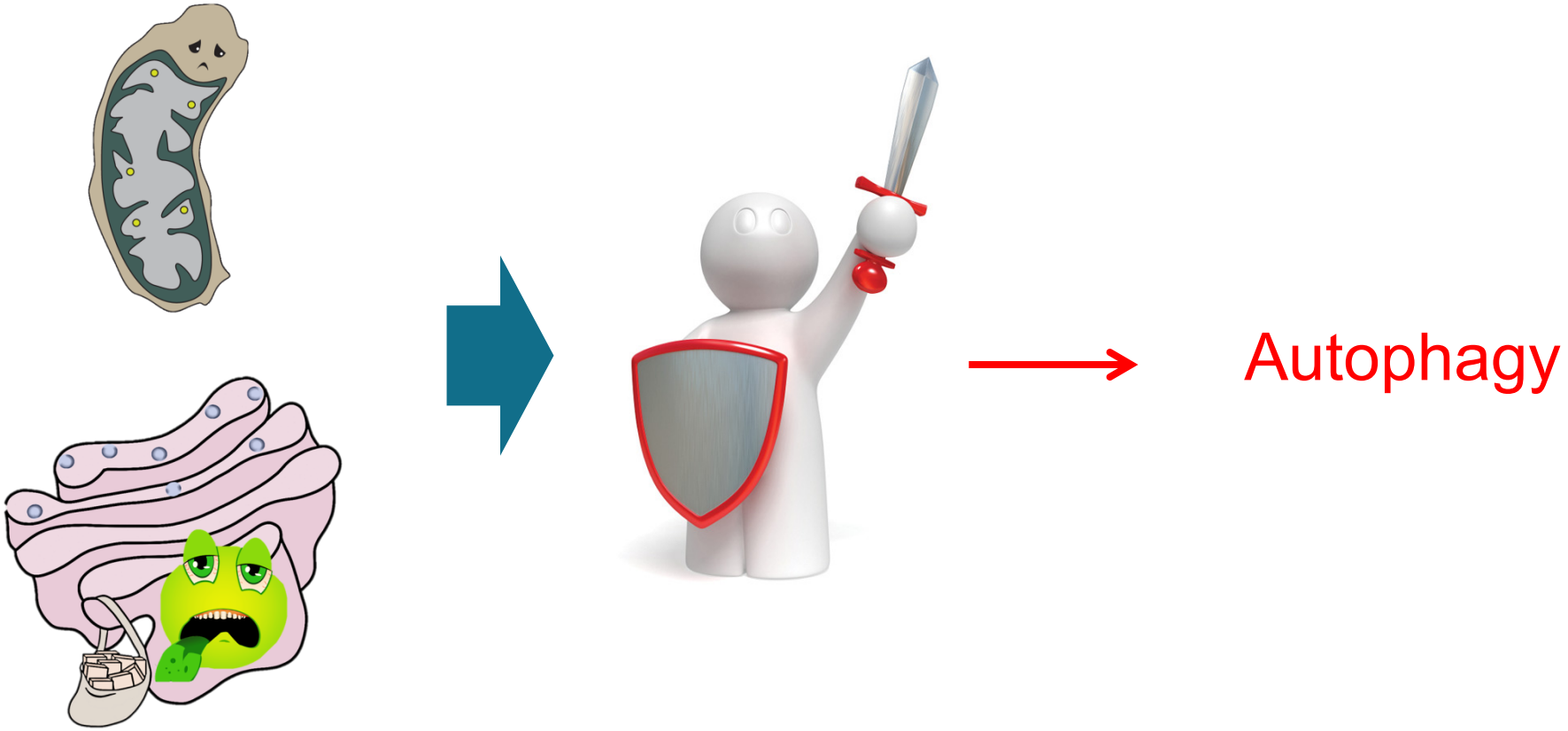
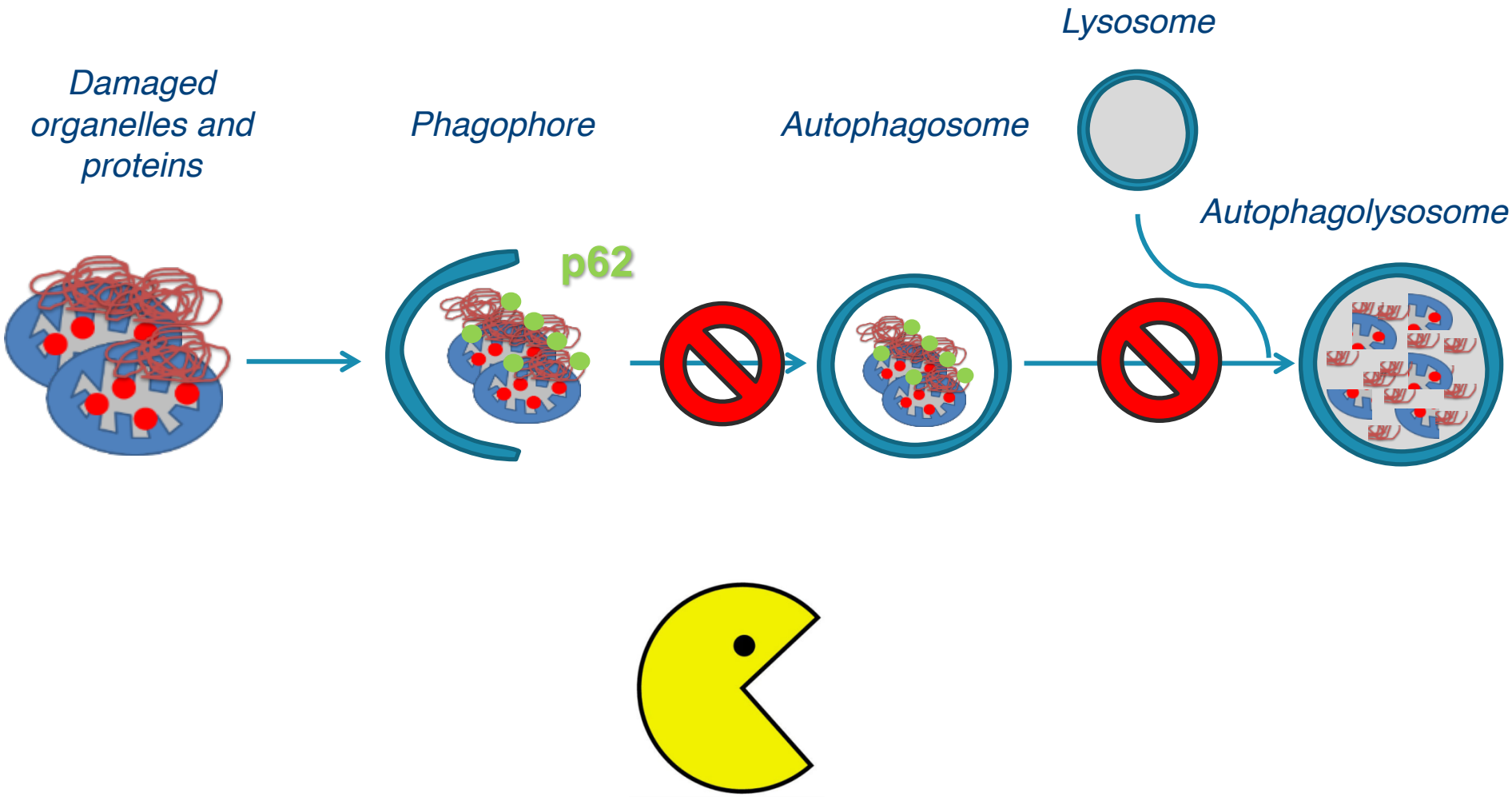
Sakr et al. 2012 Crit Care, Thiessen et al. 2017 BBA-Mol Basis Dis

1. Cellular dysfunction in MOF



1. Autophagy



1. Deranged metabolism during critical illness

Critical illness

Endocrine and metabolic disturbances

Biphasic neuroendocrine response

Hyperglycemia
Muscle wasting
Hypoaminoacidemia
Increased lipolysis

Cellular stress

Photo courtesy of Prof. Dr. G. Meyfroidt

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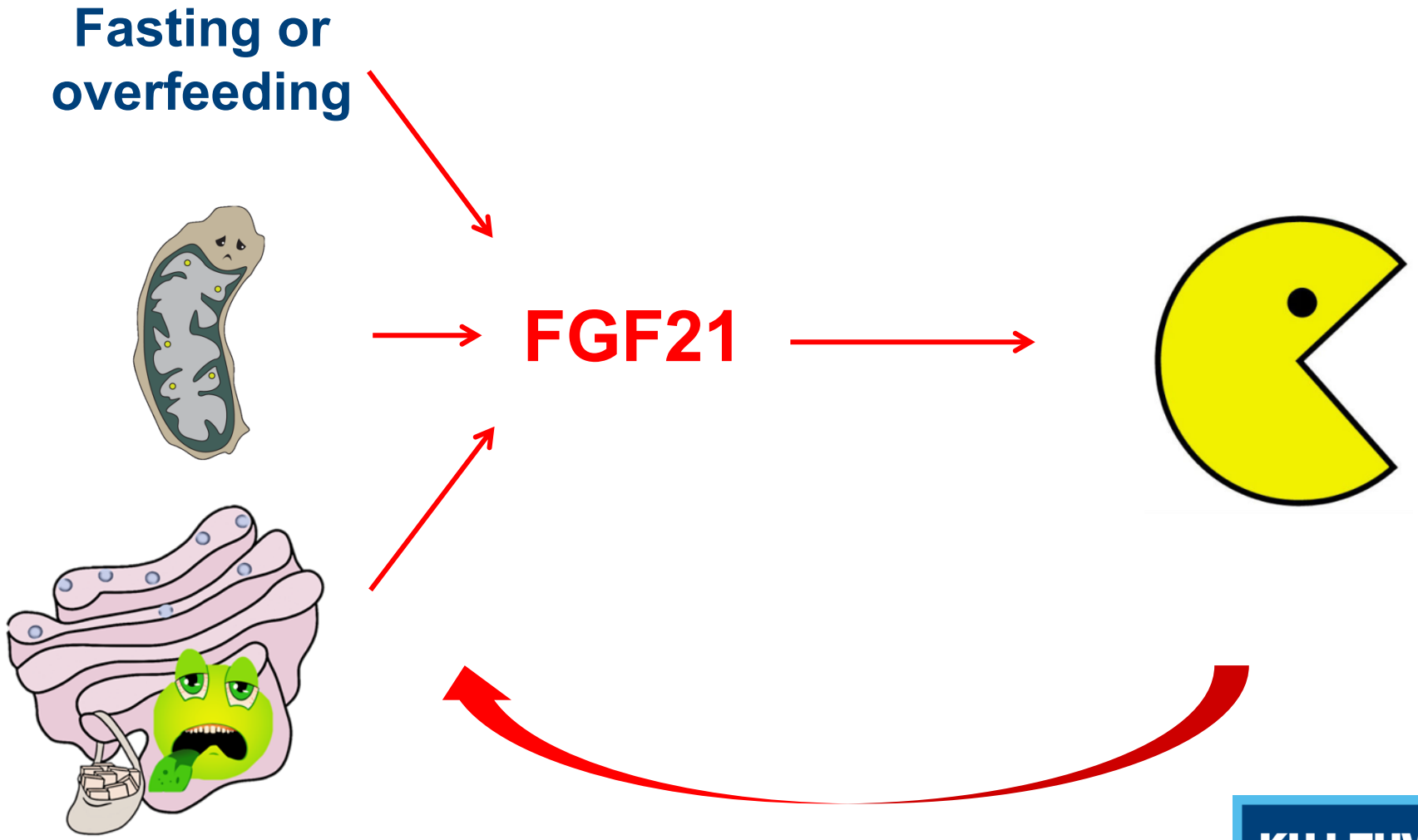
1. Fibroblast growth factor 21 (FGF21)



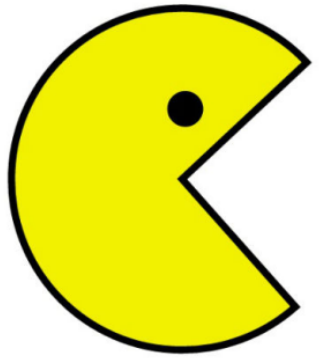
1. Glucagon

Critical Illness

Fasting

?

Glucagon



Objectives

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2. Objectives

To gain more insight in the
metabolic mechanisms of organ failure during critical illness,
in order to identify therapeutic perspectives

Focused on

1. *The role of **autophagy** in safeguarding organ function*
2. *The role of **FGF21** during critical illness*
3. *The role of **glucagon** during critical illness*

Results

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Part 1:
The role of autophagy in safeguarding vital organ function during critical illness

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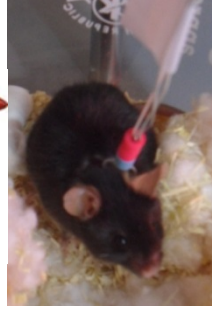
Methods: Autophagy KO mice



Day 1: Sacrifice **Day 3: Sacrifice**

Critically ill mice

Crit Ill-KO

Crit Ill-WT

Healthy pair-fed mice

Healthy-WT

Healthy-KO

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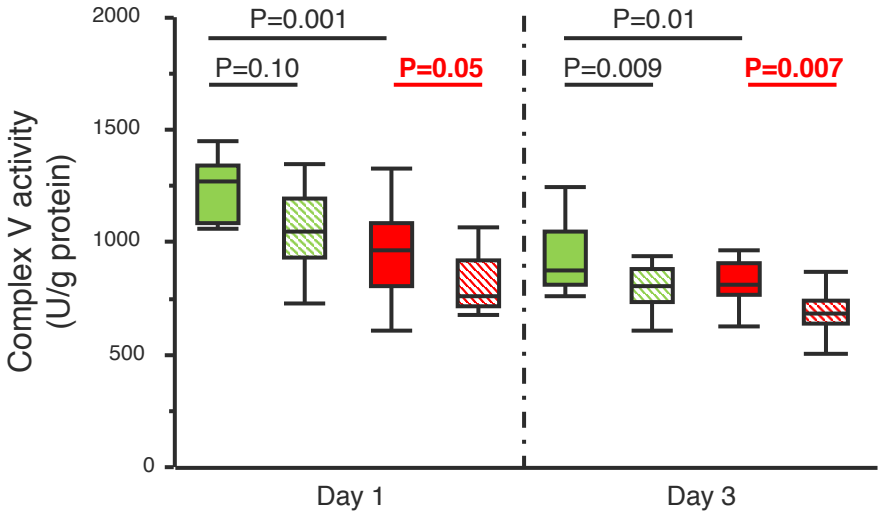
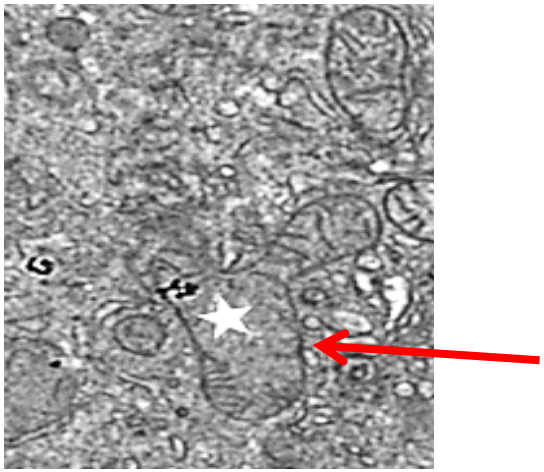
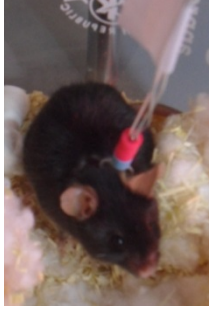
Results







Healthy-WT Healthy-KO Crit Ill-WT Crit Ill-KO

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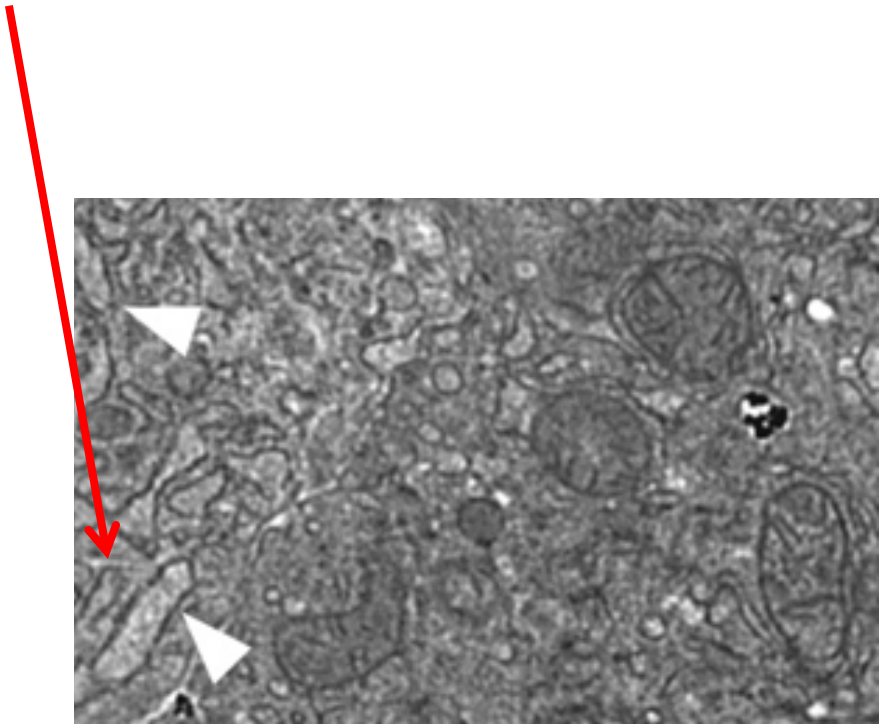
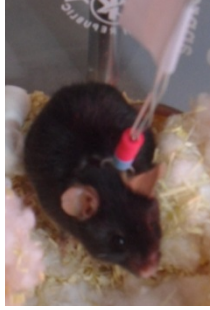
Results





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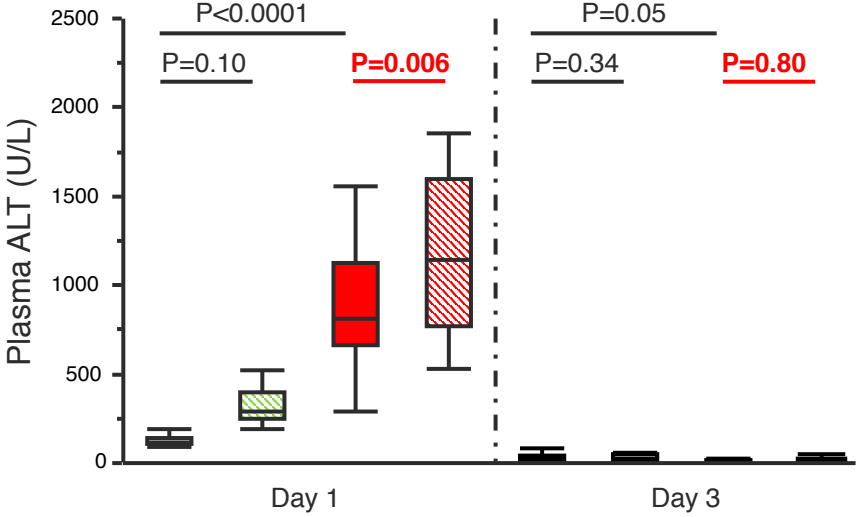
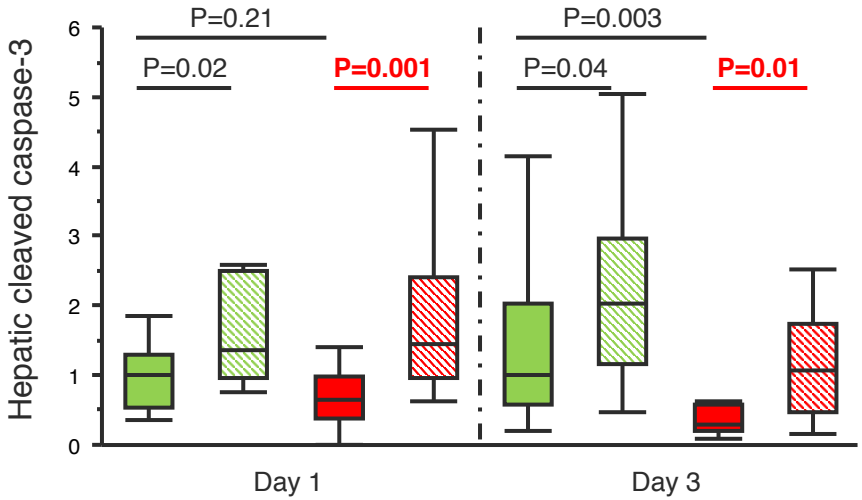
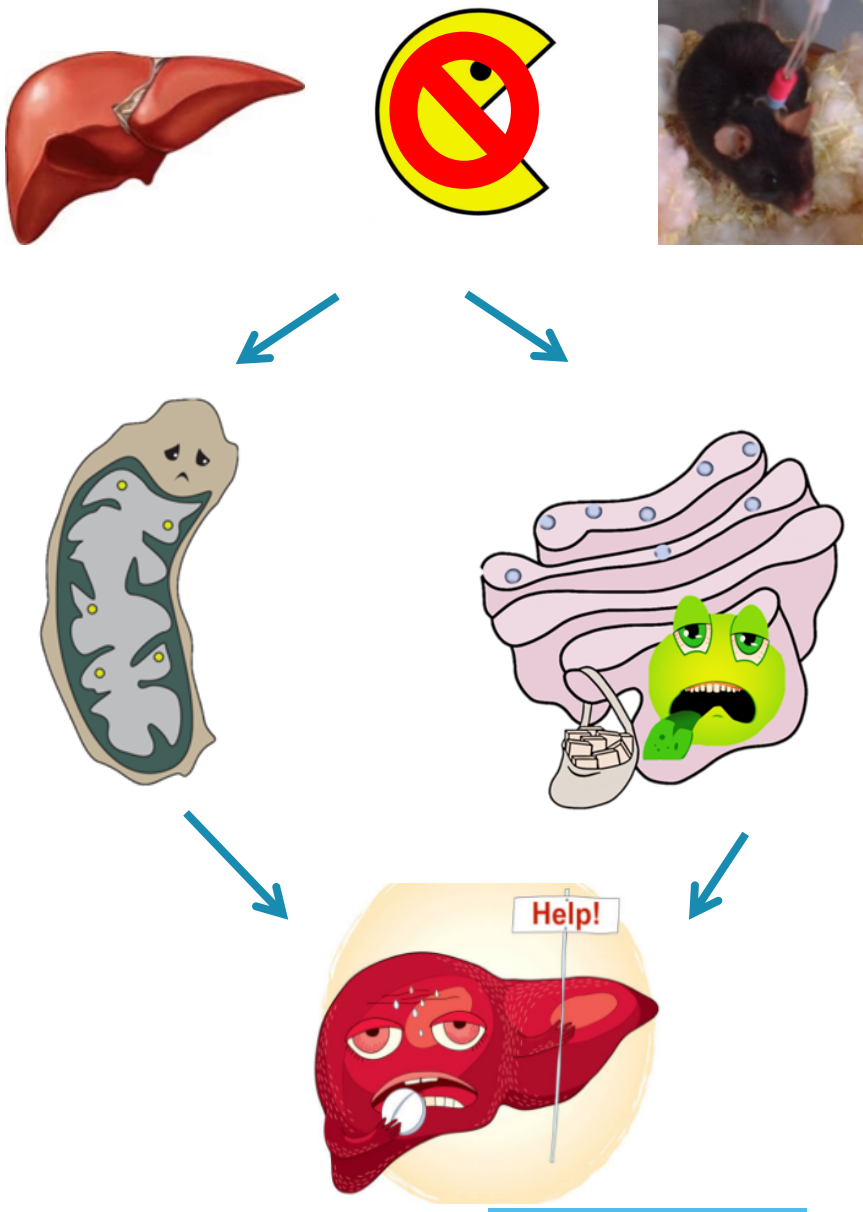
Results







Healthy-WT Healthy-KO Crit Ill-WT Crit Ill-KO

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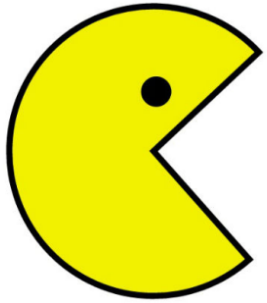
Conclusion



Part 2:
The role of FGF21 during critical illness

JCEM 2015;100:E1319-E1327

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Is FGF21 elevated during critical illness and does it relate to cellular stress?

Critically ill patients

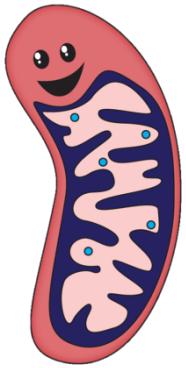
FGF21

Healthy matched controls

Hyperglycemia

FGF21

Normoglycemia



FGF21

Van den Berghe et al. 2001. NEJM; Vanhorebeek et al. 2005 Lancet.

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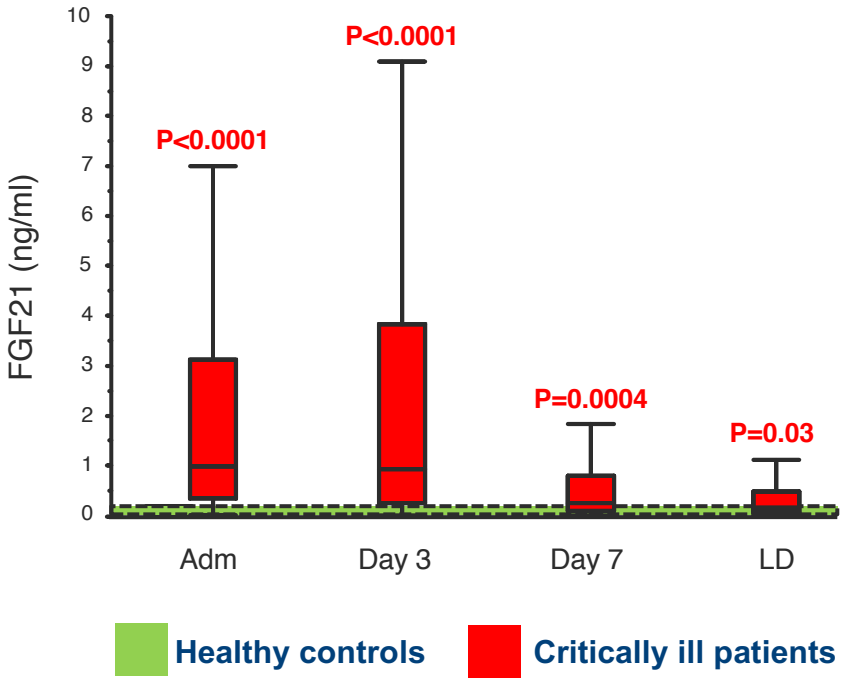
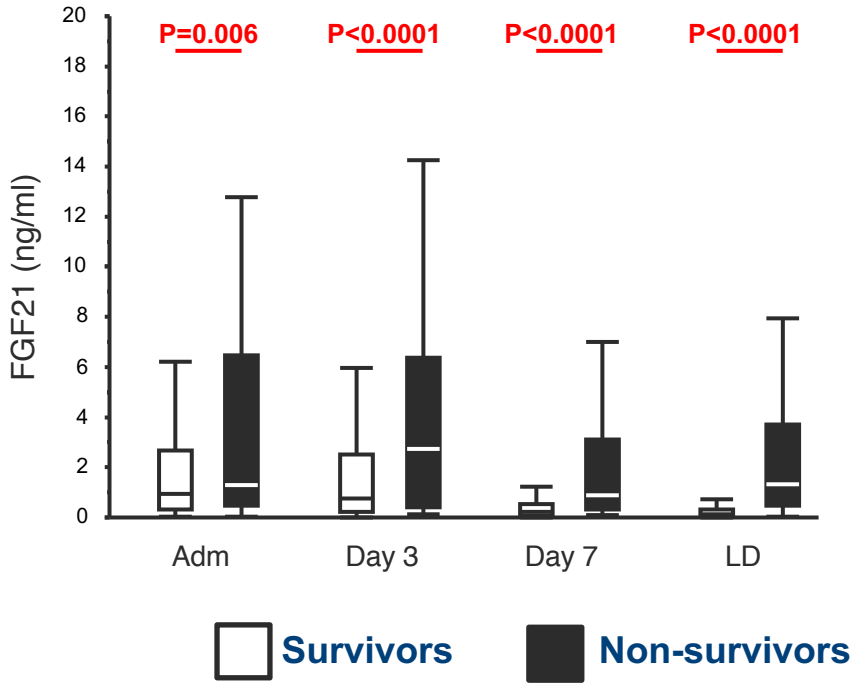
Results

Critical illness



Survivors vs. non-survivors



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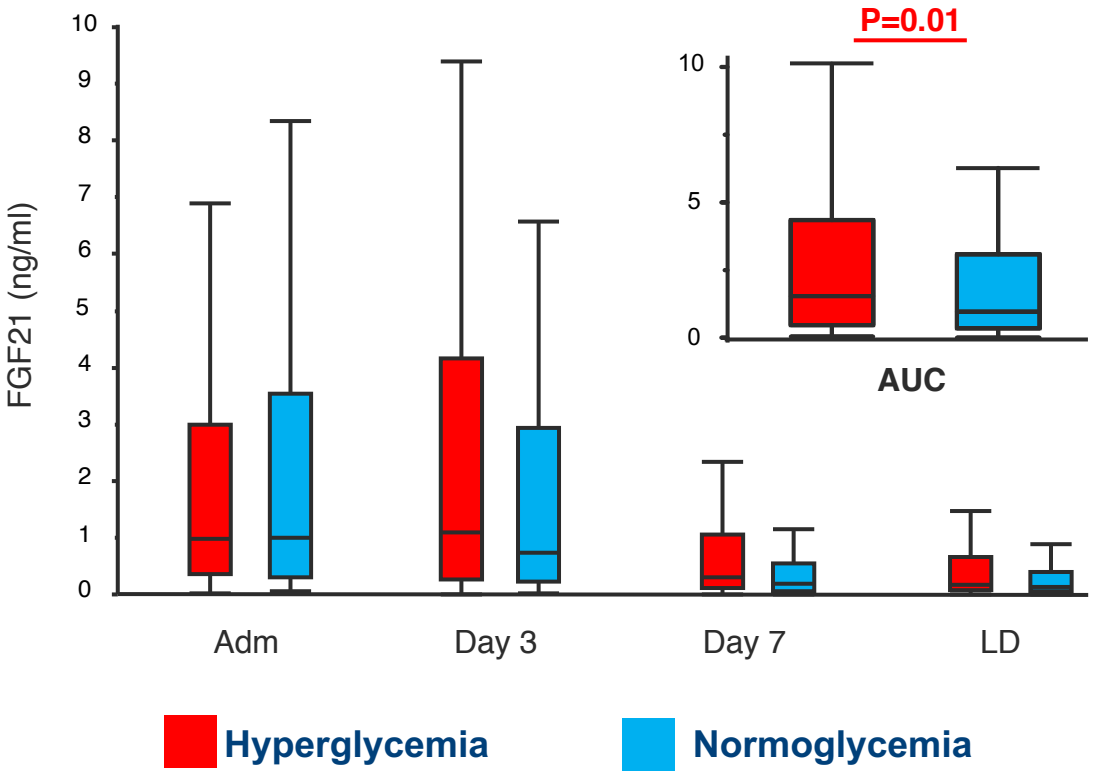
Results

Effect of targeting normoglycemia



?

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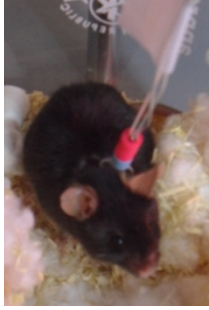
Methods: FGF21 KO mice



Day 1: Sacrifice

Critically ill mice

fgf21$^{+/+}$

fgf21$^{-/-}$

Healthy pair-fed mice

fgf21$^{+/+}$

fgf21$^{-/-}$

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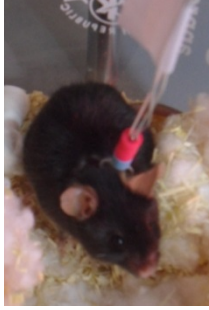
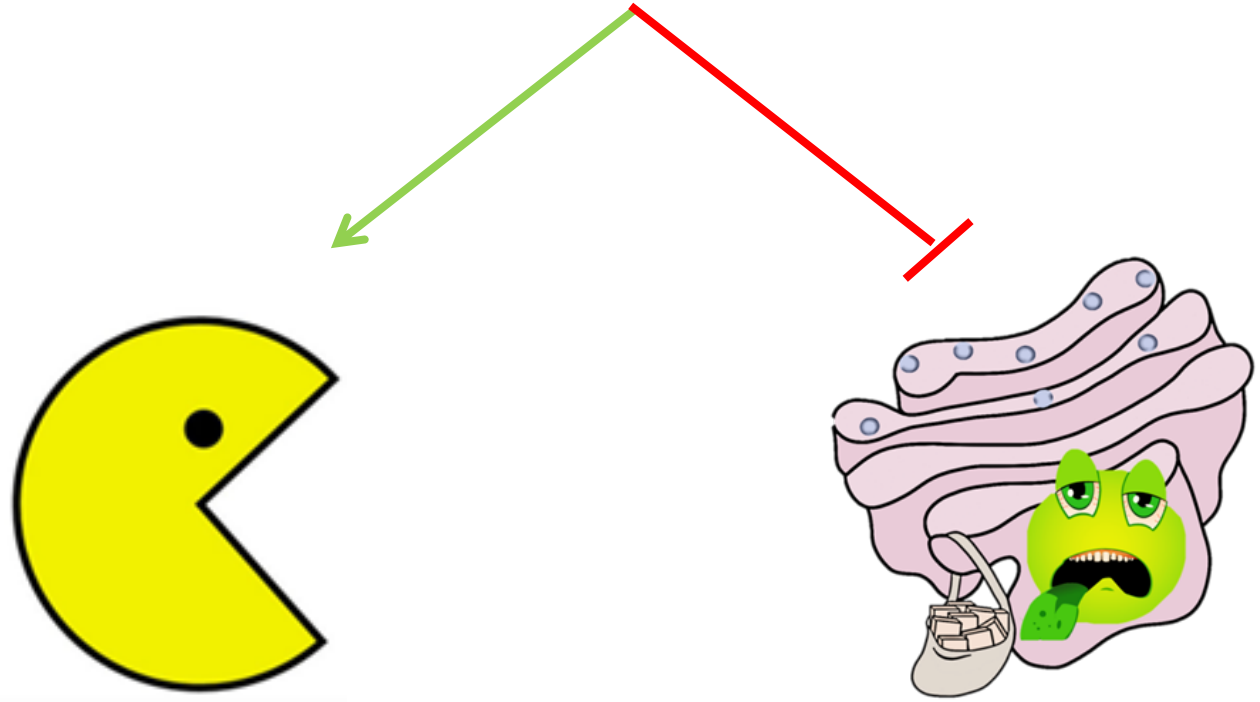
Results

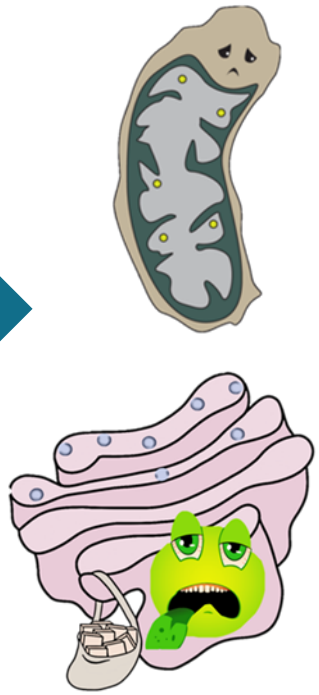


FGF21



Conclusion

Critical illness



FGF21

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Part 3: The role of glucagon during critical illness

Am J Respir Crit Care Med *2017, in press*

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Objectives

1. Is glucagon elevated during critical illness and affected by providing nutrition?

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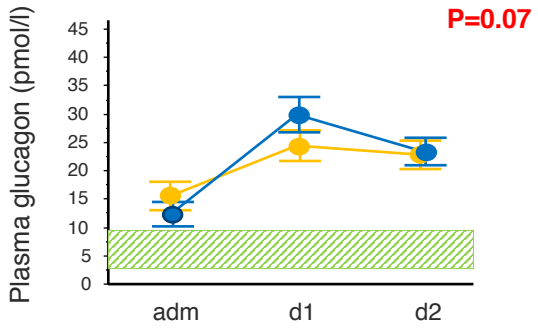
Results

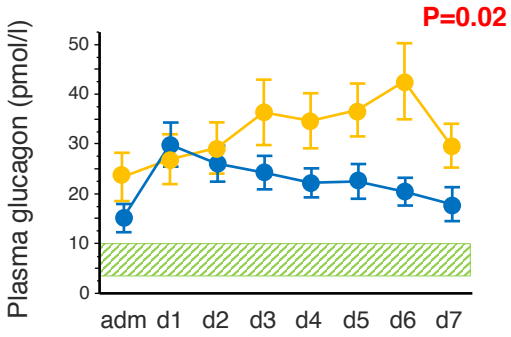
Human patients

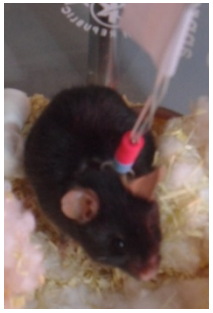
Early PN Late PN

Glucose administration



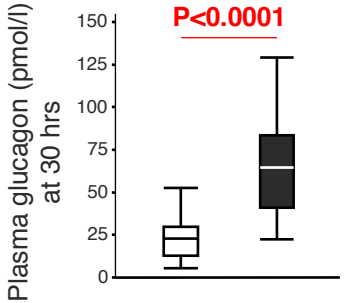
+AA and lipids

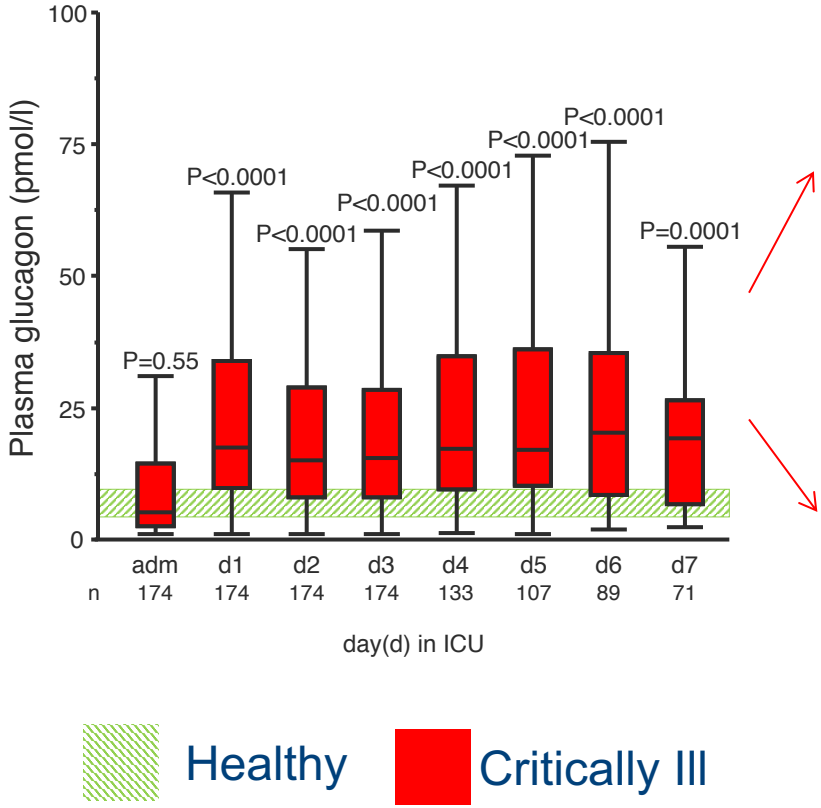




Mice

AA administration





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Objectives

1. Is glucagon elevated during critical illness and affected by providing nutrition?

2. What is the metabolic role of glucagon during critical illness?

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Methods

10 hrs: Sacrifice | **Day 1: Sacrifice** | **Day 3: Sacrifice**

Critically ill mice

Glucagon Antibody

Inert Antibody

Healthy pair-fed mice

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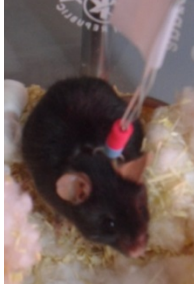
Brand et al. Diabetologia.1994; Sörensen et al. Diabetes. 2006.

Results



Glucagon

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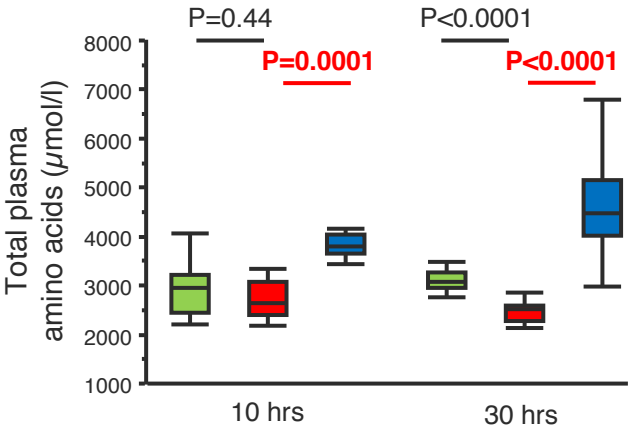
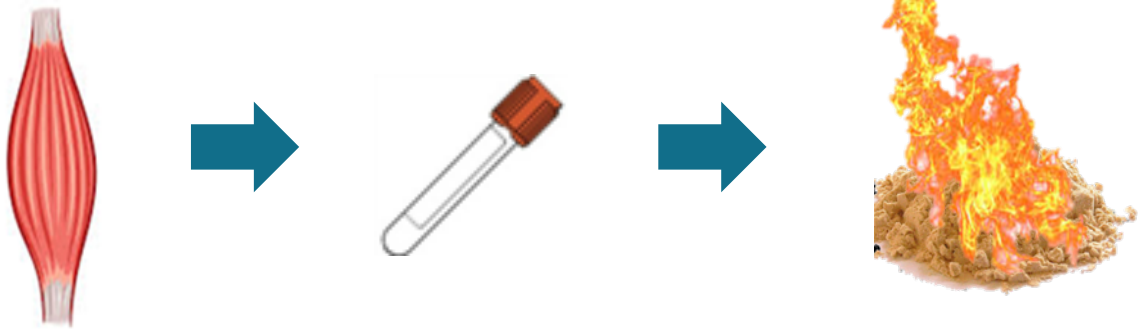
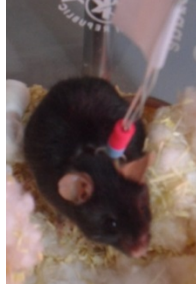
Results







Healthy Crit Ill Crit Ill-glucagon neutralized

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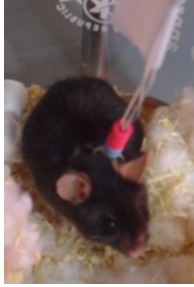
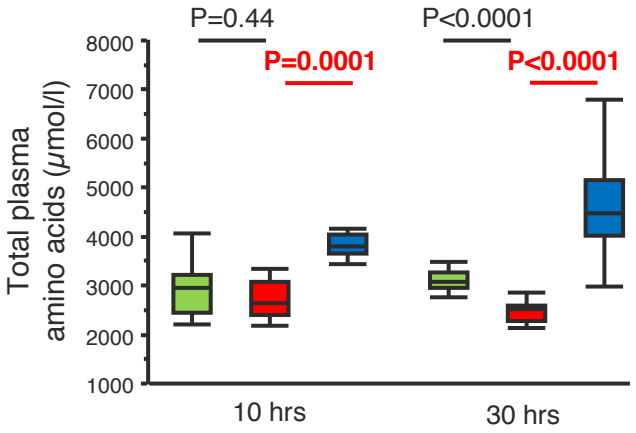
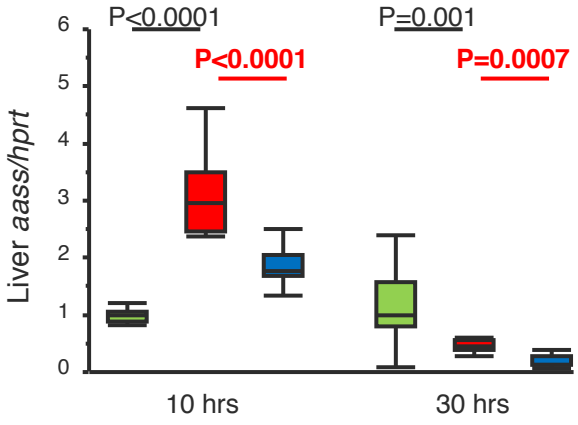
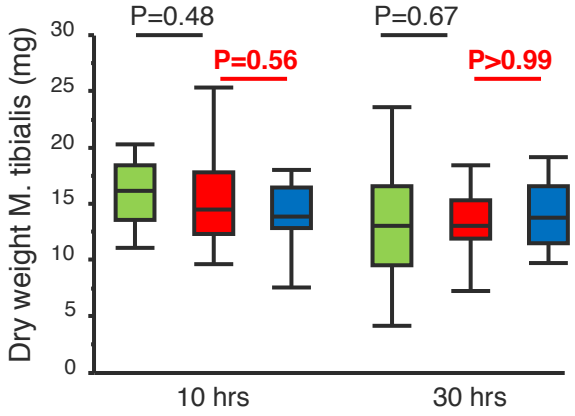
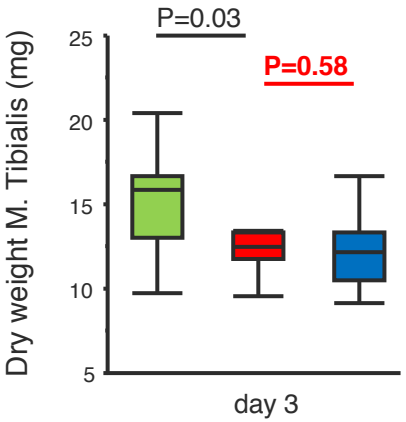
Results











Healthy Crit Ill Crit Ill-glucagon neutralized

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Objectives

1. Is glucagon elevated during critical illness and affected by providing nutrition?

2. What is the metabolic role of glucagon during critical illness?

3. Does glucagon stimulate hepatic autophagy during critical illness?

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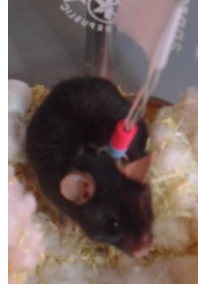
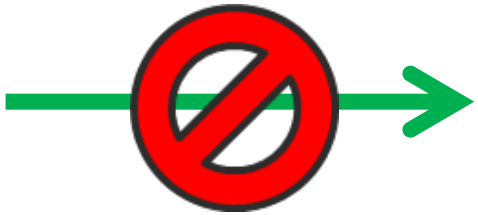
Results

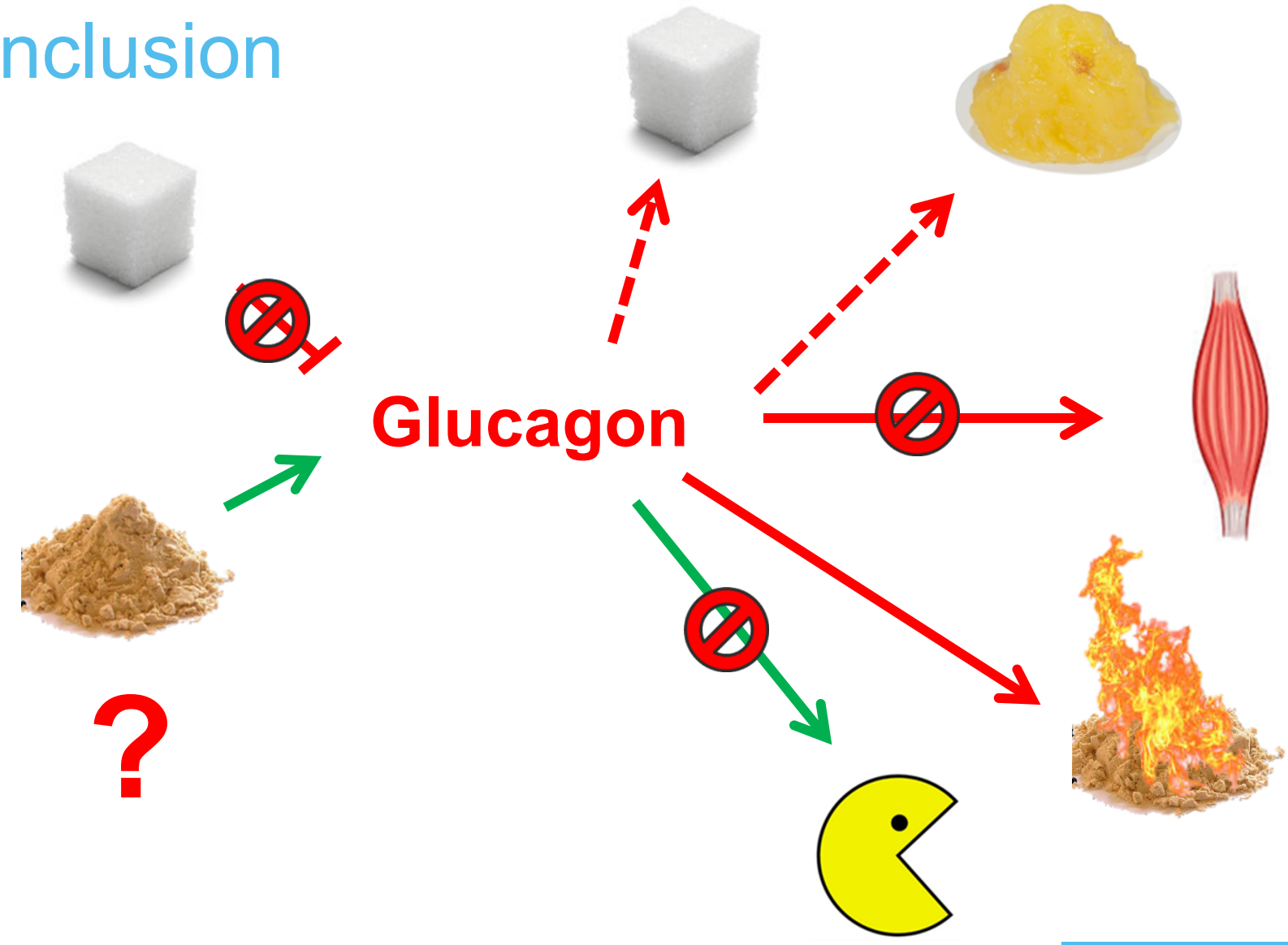


Critical illness

Glucagon



Conclusion



General conclusions and therapeutic perspectives

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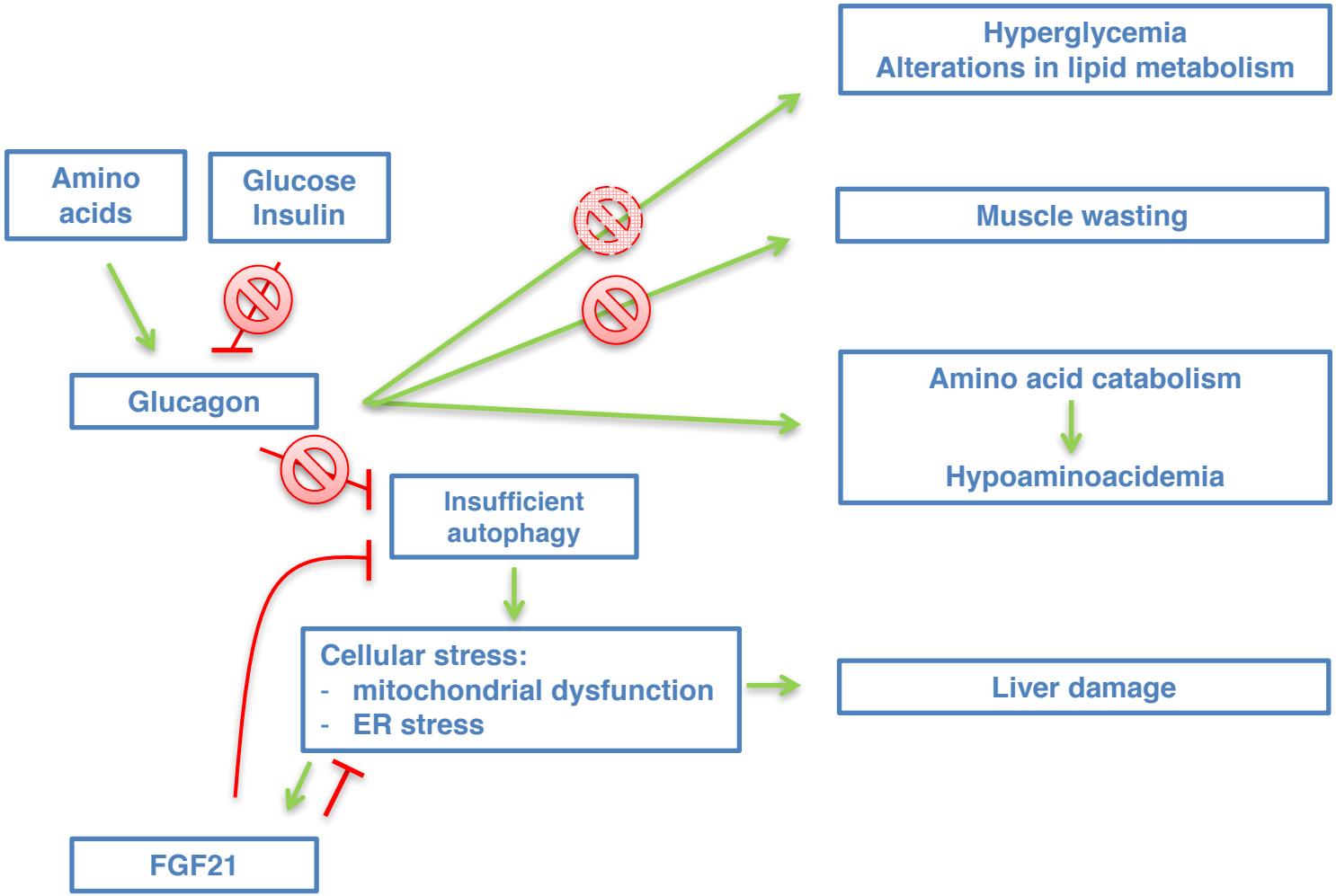
Hyperglycemia
Alterations in lipid metabolism
Amino acids
Glucose
Insulin
Muscle wasting
Glucagon
Amino acid catabolism
Hypoaminoacidemia
Insufficient autophagy
Cellular stress:
- mitochondrial dysfunction
- ER stress
Liver damage
FGF21

Therapeutic perspectives

- **Autophagy activators** as a potentially useful therapy for critically ill patients.
- **FGF21** as a promising **autophagy activator** and cellular stress-reducing agent during critical illness.
- **Glucagon modulation** as a potential therapy for attenuating amino acid catabolism during critical illness.

Acknowledgements

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External collaborators

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Jens J. Holst (Univ. Copenhagen)
David Mangelsdorf (Univ.Texas)

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Thank you for this award and for your attention!

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