Supplementation of Omega-3 Fatty Acids

MODULATES THE ENDOCANNABINOID SYSTEM IN PERIPARTUM DAIRY COWS

Dr. Maya Zachut
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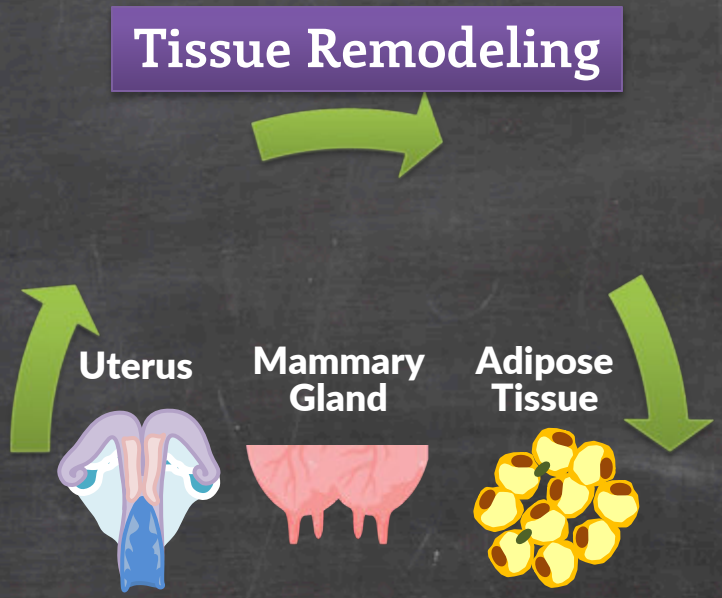
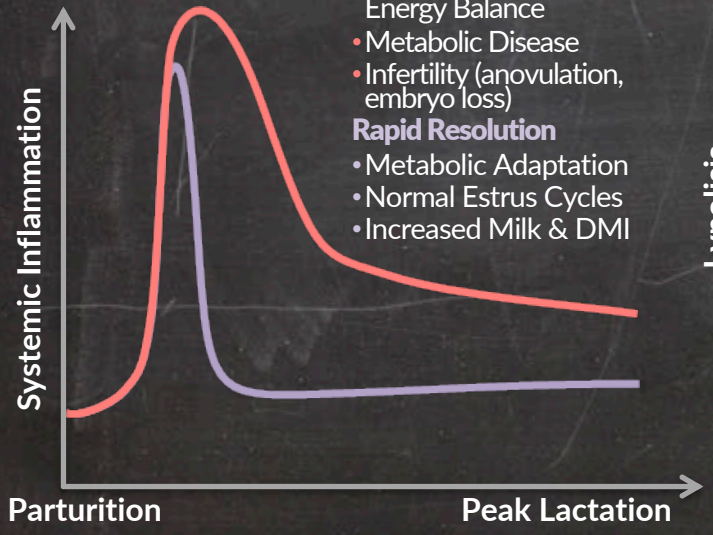
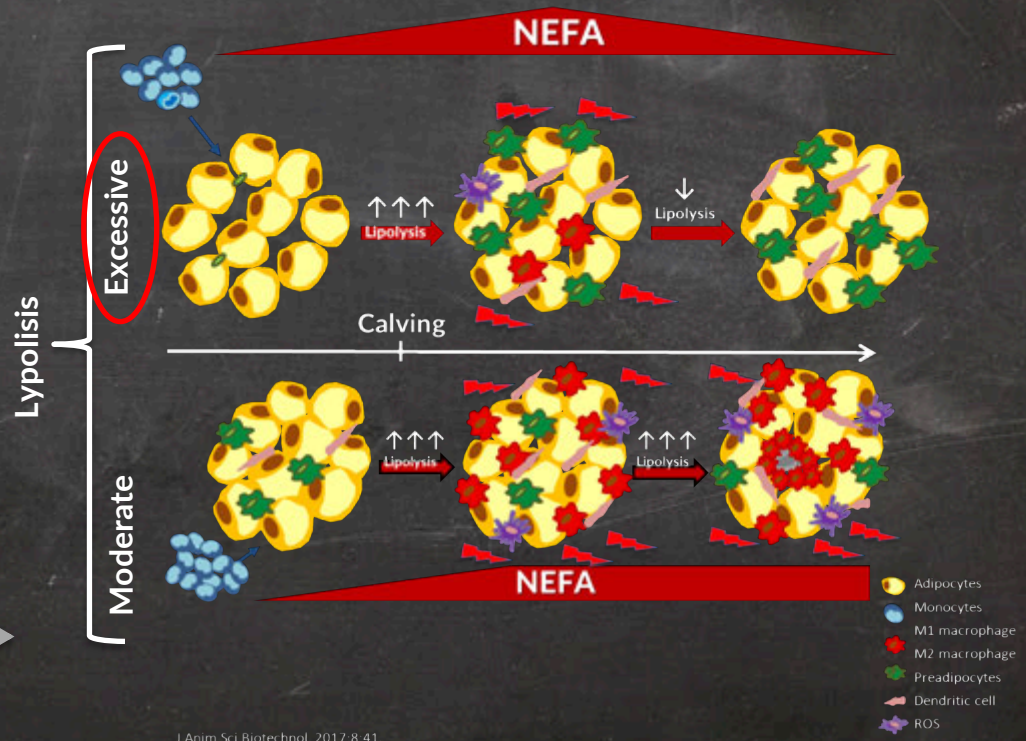
Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows
Subacute Inflammation in Transition Cows



Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows
Excessive Lipolysis and Uncontrolled Inflammation

- Excessive lipolysis is related to adipose inflammation and adverse health outcome (Contreras et al., 2018)
- Sustained inflammation can suppress appetite, cause collateral tissue damage, and directly suppress milk production (Krogstad and Bradford, Hoards Dairyman, 2022)





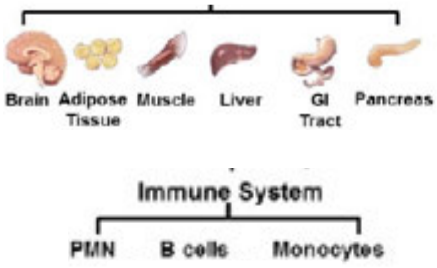
J Anim Sci Biotechnol. 2017;8:41.

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows
Degree of Inflammation and Lipolysis

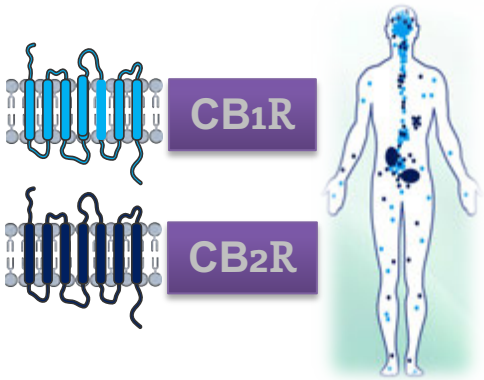
Can we affect the degree of inflammation and lipolysis postpartum?

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

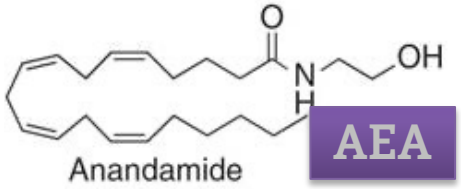
The Endo-cannabinoid System (ECS)



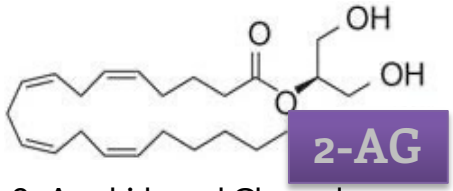
Cannabinoid Receptors



Endocannabinoids (eCBs)



Anandamide



2- Arachidonoyl Glycerol

Enzymes

- NAPEPLD
- FAAH
- MGLL
- DAGL

- A central regulator of metabolism and energy homeostasis in mammals (Silvestri and Di Marzo, 2013)
- ECS is modulated by exposure to stress and has an effect on inflammatory responses (Morena et al., 2016)

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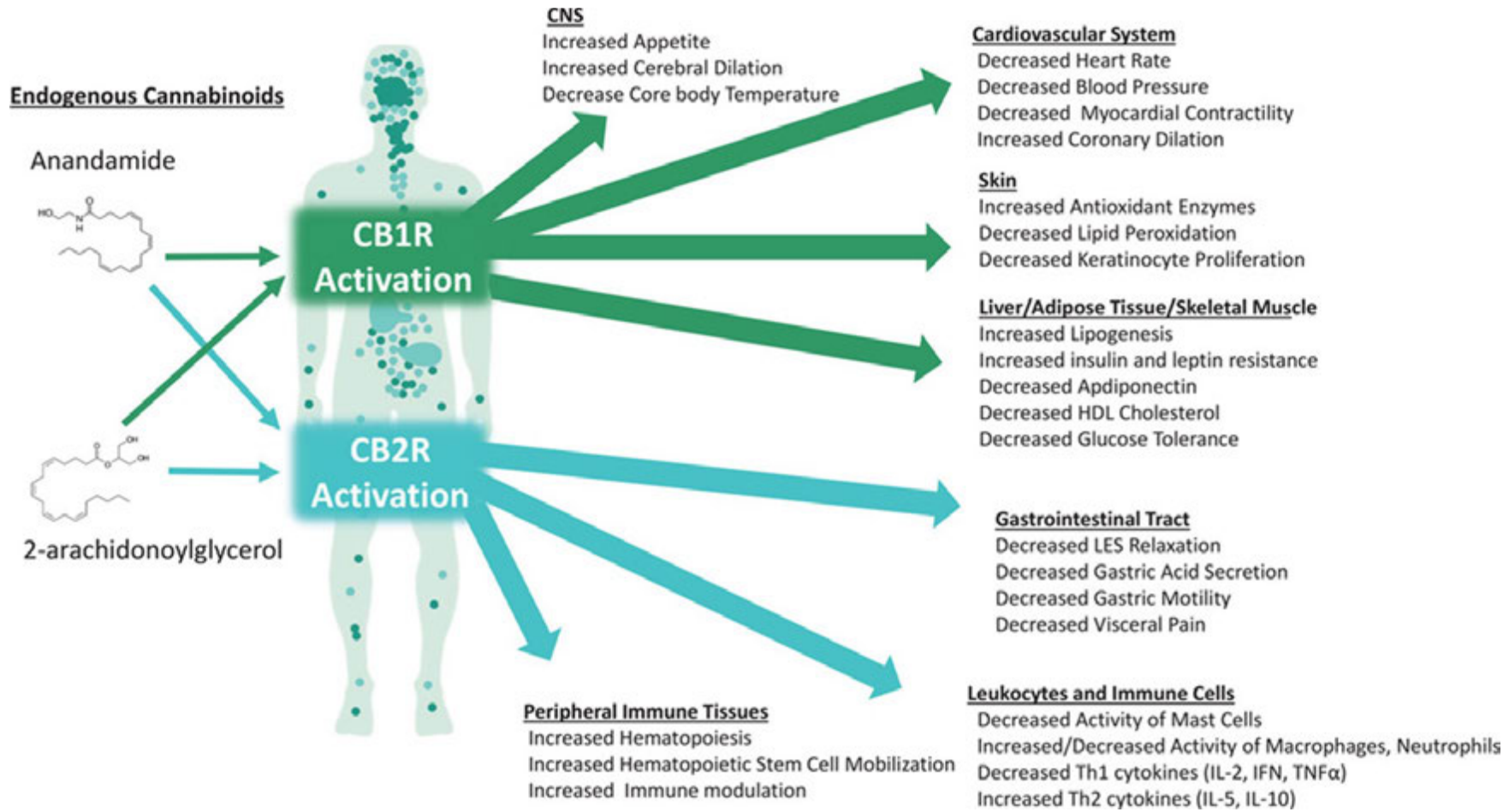
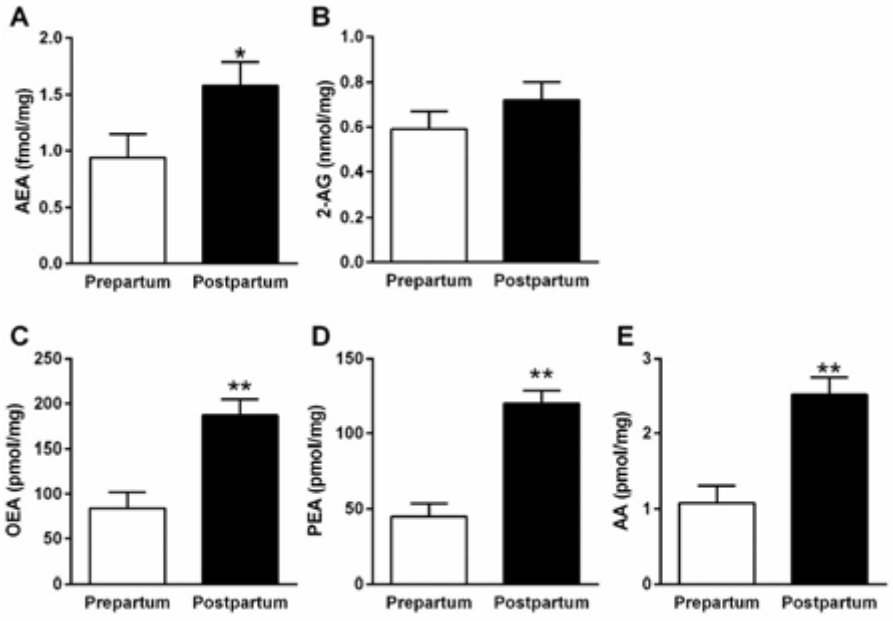
Metabolic and Inflammatory Effects of ECS



Page et al., Circulation, 2020

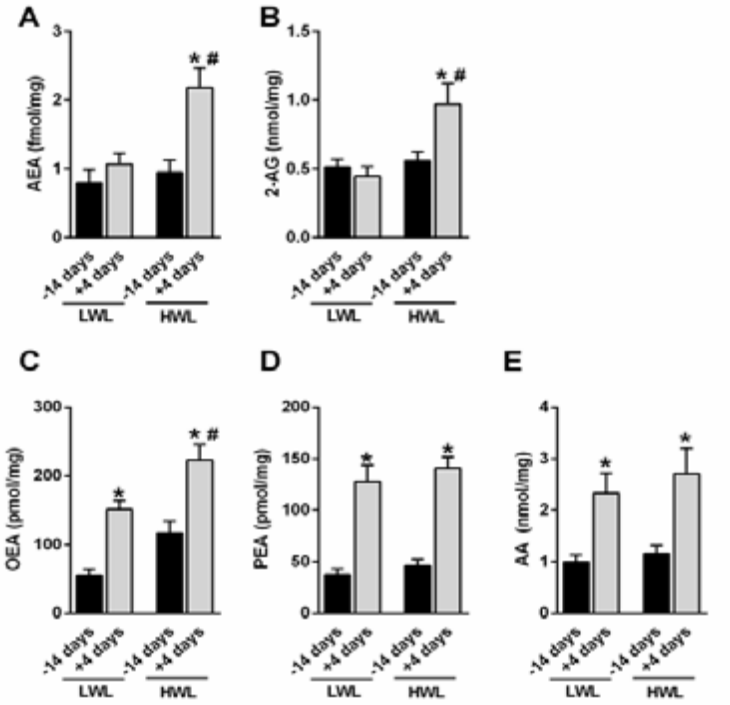
Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows
Characterizing the ECS in Transition Dairy Cows



N-arachidonoylethanolamine (AEA) & 2-arachidonoylglycerol (2-AG)

Oleoylethanolamide (OEA), palmitoylethanolamide (PEA), & arachidonic acid (AA)

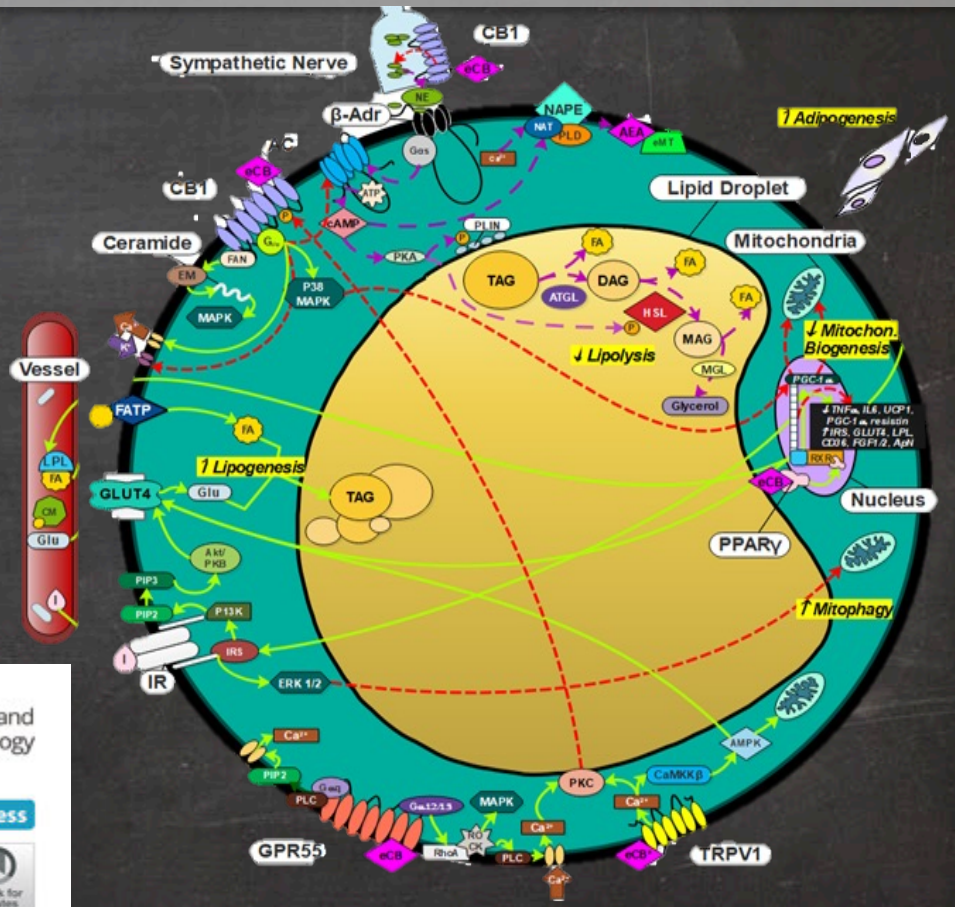
Tendency for increased gene expression of CNR1 and CNR2 in adipose of high-lipolysis cows



Zachut et al., 2018

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows ECS

The ECS promotes energy conservation and reduces lipolysis in adipocytes



Myers et al. Journal of Animal Science and Biotechnology (2021) 12:21
https://doi.org/10.1186/s40104-021-00549-3

Journal of Animal Science and Biotechnology

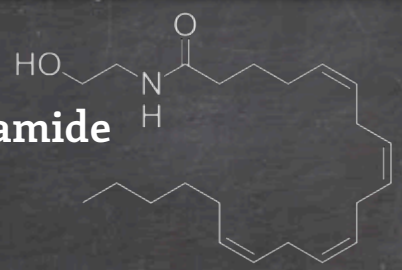
REVIEW Open Access

A proposed modulatory role of the endocannabinoid system on adipose tissue metabolism and appetite in periparturient dairy cows

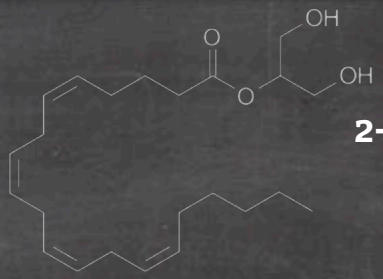
Madison N. Myers[1], Maya Zachut[2*], Joseph Tam[3] and G. Andres Contreras[1*]

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

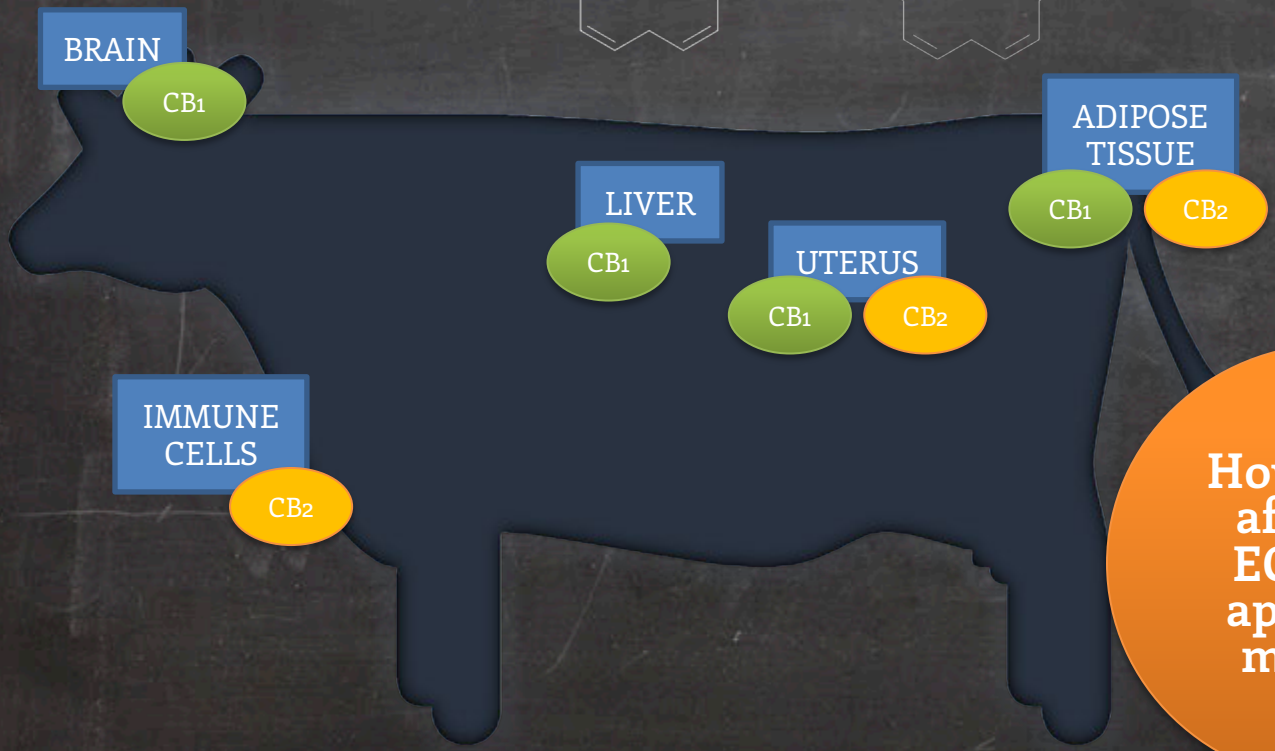
The ECS in Dairy Cows



eCSs: Anandamide



2-Arachidonoylglycerol



How can we affect the ECS in an applicable manner?

Zachut et al., Animal Frontiers ,2022, in press

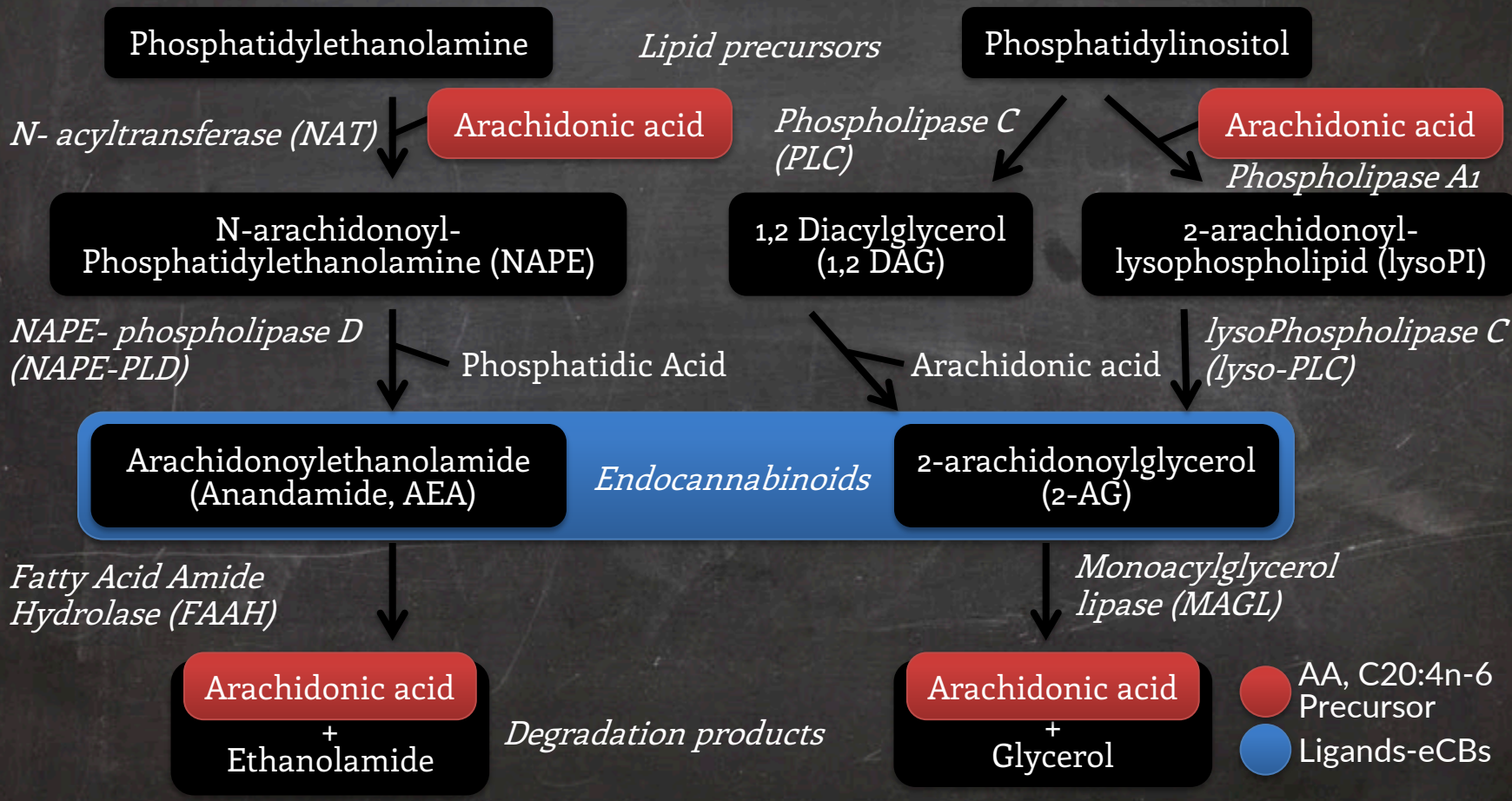
Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

How Can Dietary Omega-3 Effect the ECS?

- C20:4n-6 (AA) is a main precursor of endocannabinoids.
- Supplementing n-3 can lower the n-6/n-3 ratio and reduce the availability of AA in membranes.
- Lower AA is expected to lower ECS activation.

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

ECS Biosynthesis



Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows Research Hypothesis

J. Dairy Sci. 103:1049–1049
https://doi.org/10.3168/jds.2019-17328

Letter to the editor: Are the physiological effects of dietary n-3 fatty acids partly mediated by changes in activity of the endocannabinoid system in dairy cows?

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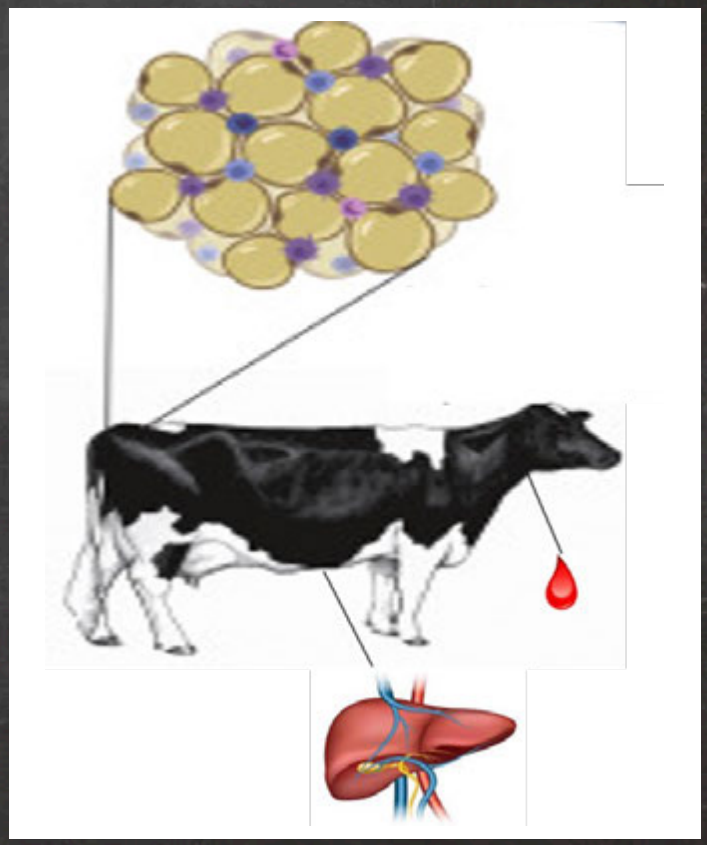
n-3 > lower ECS “tone” > affect metabolism and inflammation

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

Effects of n-3 Supplementation on ECS in Transition Dairy Cows



Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows
Excessive Lipolysis and Uncontrolled Inflammation

- 28 multiparous Holstein late pregnant dairy cows at individual feeding barn.
- Treatments started at 257 d of pregnancy until 21 d in lactation:
  - CTL (n = 14) – basal diet, supplemented with encapsulated saturated fat at 240 and 560 g/d per cow prepartum and PP, respectively.
  - FLX (n = 14) – the same basal diet, supplemented prepartum at 300 g/d per cow with encapsulated fat providing α-linolenic acid (ALA) at 56.1 g/d, and PP at 700 g/d per cow providing 131.0 g/d ALA from FLX.
- **Blood, liver and adipose tissue** were sampled postpartum for metabolic, inflammatory and ECS components.

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

Results

- FLX increased plasma % ALA (3.9% vs. 1.8, SEM = 0.15, P < 0.0001).
- n-6/n-3 tended to decrease in FLX (24.2 vs. 9.8, SEM = 5.32, P = 0.07).
- Milk yields and fat corrected milk 4% were similar.
- DMI was 8.1% lower in the FLX than in CTL (P = 0.006).
- Calculated energy balance was not different between groups.
- No differences in plasma metabolites or cytokines.

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

n-3 Modulates eCBs in Plasma, Adipose & Liver

Plasma	CTL	FLX	SEM	P-value
2-AG[2],(fmol/mL)	10.5	9.1	2.13	0.65
AA[3], (pmol/mL)	581.2[a]	324.3[b]	61.18	0.02
AEA[4], (fmol/mL)	232.2[a]	116.8[b]	31.82	0.03
PEA[5], (fmol/mL)	0.4	0.0	0.31	0.33
OEA[6], (fmol/mL)	34.1	34.3	9.66	0.99

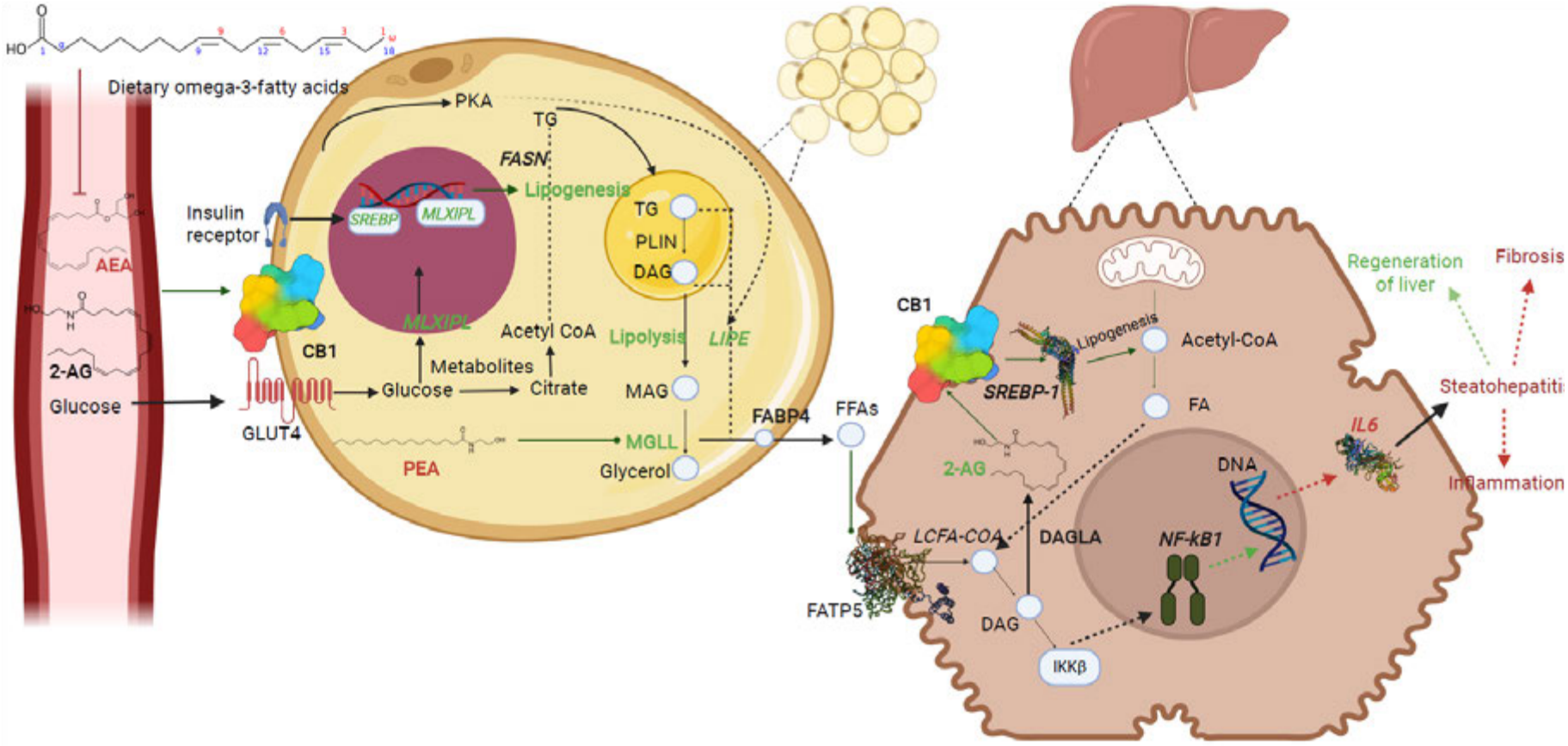
Adipose Tissue	CTL	FLX	SEM	P-value
2-AG[2], (fmol/mL)	97.0	69.6	25.90	0.48
AA[3], (pmol/mL)	1.3	1.0	0.16	0.24
AEA[4], (fmol/mL)	0.7	0.7	0.17	0.97
PEA[5], (fmol/mL)	16.1[a]	6.2[b]	2.53	0.02
OEA[6], (fmol/mL)	125.2	100.2	15.90	0.30

Liver	CTL	FLX	SEM	P-value
2-AG[2],(fmol/mL)	287.6	497.8	72.03	0.07
AA[3], (pmol/mL)	6.9	8.2	1.65	0.59
AEA[4], (fmol/mL)	0.7	0.9	0.40	0.73
PEA[5], (fmol/mL)	13.9	10.6	8.17	0.78
OEA[6], (fmol/mL)	44.2	15.9	15.16	0.22

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows Components in Blood, Adipose, and Liver

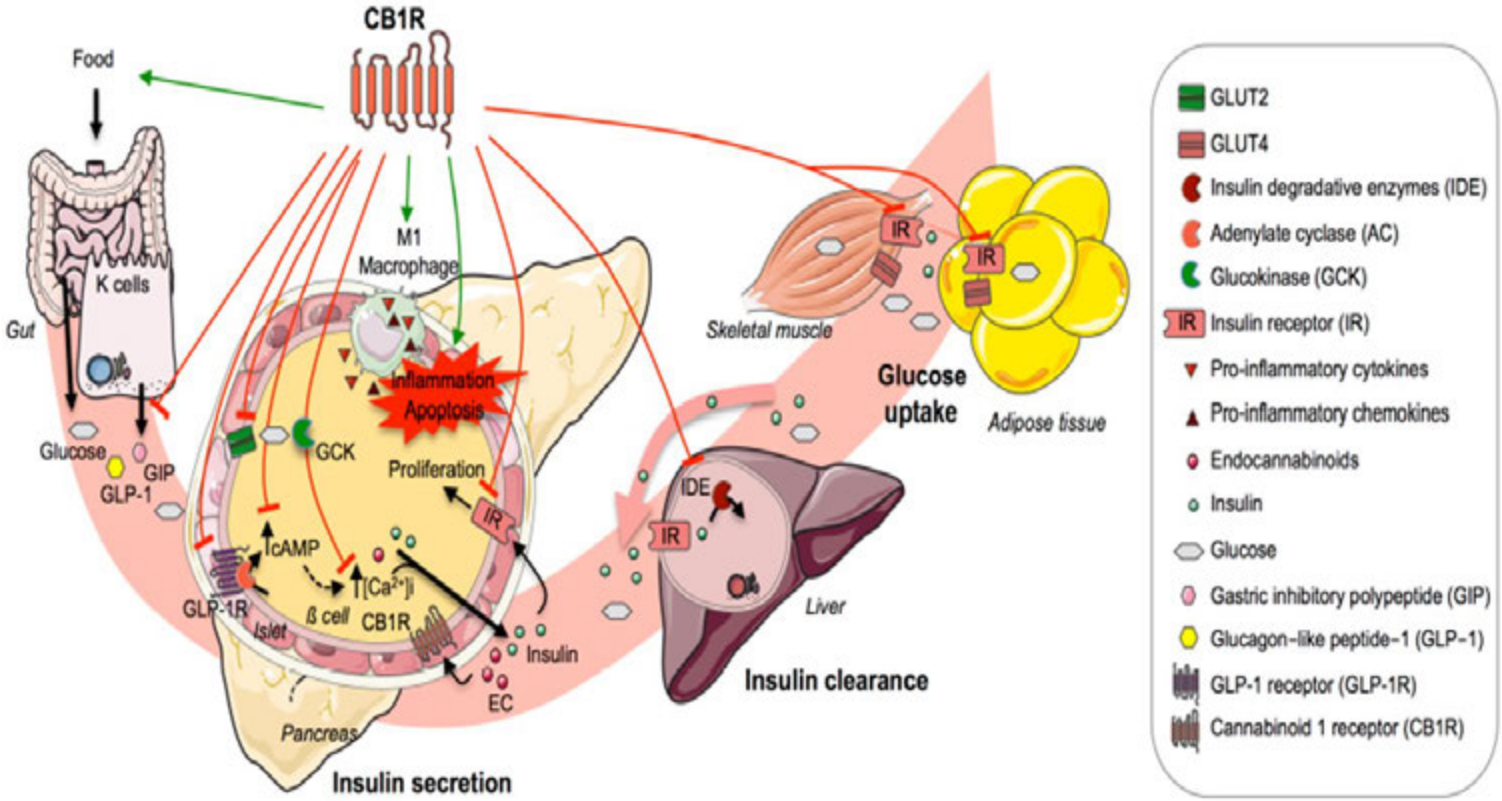
- **White blood cells:** mRNA of CB1 (CNR1) tended to be lower in FLX
- **PBMC:** protein abundance of ECS enzyme MGLL was higher in FLX
- **Adipose:** mRNA of lipid metabolism genes were higher, and protein abundances of CB2 and MGLL tended to be higher in FLX
- **Liver:** interlukin-6 mRNA was lower in FLX than in CTL

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows
n-3 Supplementation Modulates ECS in Blood, Adipose & Liver of Postpartum Cows



Kra et al, JASB, 2022 (in press)

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows
The Next Frontier: Assessing Insulin Sensitivity & ECS



Abstracts #1424, #1425 ADSA 2022
Jourdan et al., 2020, Lipid Signaling and Metabolism. http://dx.doi.org/10.1016/B978-0-12-819404-1.00015-4

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

Summary

- Omega-3 supplementation was related to moderate alterations in ECS components, increased lipid metabolism in adipose and lower inflammation in liver
- Lower feed intake could be related to lower ECS tone; however, we did not observe increased lipolysis in FLX cows
- Supplementation of n-3 was related to tissue-dependent responses in ECS components in peripartum dairy cows

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows Excessive Lipolysis and Uncontrolled Inflammation

Livestock Science 242 (2020) 104302

Contents lists available at ScienceDirect

Livestock Science

journal homepage: www.elsevier.com/locate/livsci

The effects of omega-3 α-linolenic acid from flaxse
high-yielding dairy cows on production, health, an

U. Moallem*, H. Lehrer, L. Livshits, M. Zachut

Department of Ruminant Science, Institute of Animal Sciences, the Volcani Center, 68 HaMaccabim Road, Rishon

Incidence of health events by treatment groups in cows supplemented with extruded flaxseed.

	Treatment[1]			
Event	Control	EFLX	SEM	*P*-value
Without metritis,%	64.6 (155/240)	67.8 (187/276)		NS
Mild metritis,%	10.4 (25/240)	8.3 (23/276)		NS
Moderate metritis,%	12.1 (29/240)	14.9 (41/276)		NS
Severe metritis,%	12.9 (31/240)	9.1 (25/276)		0.15
Without ketosis,%	68.9 (166/240)	76.5 (211/276)		0.05
Mild ketosis,%	11.7 (28/240)	8.7 (24/276)		NS
Moderate ketosis,%	8.3 (20/240)	7.6 (21/276)		NS
Severe ketosis,%	10.8 (26/240)	7.2 (20/276)		0.03
Udder edema,%	5.8 (14/240)	2.2 (6/276)		0.03
Mastitis[2],%	5.0 (11/240)	5.1 (14/276)		NS
Milk fever,%	0.8 (2/240)	1.1 (3/276)		NS
Mortality,%	4.6 (11/240)	0.7 (2/276)		0.005
BCS post-calving	3.45	3.65	0.03	<0.0006
BCS peak lactation	2.84	3.03	0.03	<0.0003
BW (kg)	648.7	660.8	0.5	<0.0001

EFLX (*n* = 276) - pre- and postpartum diet extruded flaxseed supplement.
CTL; (*n* = 240) - a diet with a different composition but a similar nutrient content.

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows
Take Home Message

- Omega-3 supplementation to transition cows modulates ECS in blood, liver and adipose tissue
- Further research will examine how manipulating ECS activity can affect physiology and immunometabolism in dairy cows

Supplementation of Omega-3 Fatty Acids Modulates the Endocannabinoid system in Peripartum Dairy Cows

Special Thanks

Zachut lab: Gitit Kra, Jayasimha Rayalu Daddam Uzi Moallem, Volcani Institute, Israel

BARD collaborators: Yossi Tam, HUJI and Andres G. Contreras, MSU

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