# The Relationship Between Mild Endocrine Failure and Oxidative stress.

Dr. Brendan McCarthy NMD

"Aging is the progressive accumulation of changes with time that are associated with, or responsible for, the ever-increasing susceptibility to disease and death which accompanies advancing age" and "the sum of the deleterious free radical reactions going on continuously throughout the cells and tissues constitutes the aging process or is a major contributor to it"

Harman, Denham. "The aging process." Proceedings of the National Academy of Sciences 78.11 (1981): 7124-7128.

"The common denominator that underlies all modern theories of biological aging is change in molecular structure and, hence, function"

Hayflick, Leonard. "Entropy explains aging, genetic determinism explains longevity, and undefined terminology explains misunderstanding both." *PLoS genetics* 3.12 (2007): e220.

## Aging is an ambiguous state to the average patient.

- They feel tired, less energetic, less strength, skin becomes thin, wrinkles, seeing and hearing decrease, memory declines, easier to become sick and recovery is diminished. Grey hair, more susceptible to infections like a common cold, grumpy, muscle and joint pain
- The average person accepts aging as a "natural side effect" of living.
- The average person, and most health care provider do not have a nuanced understanding of what causes aging. They may say its diet, or its activity related, but there is no real thought to the synergistic relationship between numerous factors that lead to the state we call aging.



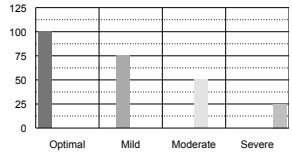
## What are the major causes of aging ?

- Mild to moderate endocrine failure
- Oxidative damage
  - Inflammation
  - Increases in advanced glycosylation end products
  - Malnutrition
  - Infection



## Mild endocrine failure

- The lab reference range is 100%-25%
- Pathology begins somewhere below 100%
- We are trained to treat at 25%



# Oxidative damage and aging

- NAD+ is decreased In aging
- Exogenous NAD+improves healthspan and lifespan.
  - Braidy, Nady, et al. "Role of nicotinamide adenine dinucleotide and related precursors as therapeutic targets for age-related degenerative diseases: rationale, biochemistry, pharmacokinetics, and outcomes." *Antioxidants & Redox Signaling* 30.2 (2019): 251-294.
  - Chu, Xiaogang, and Raghavan Pillai Raju. "Regulation of NAD+ metabolism in aging and disease." *Metabolism* 126 (2022): 154923.

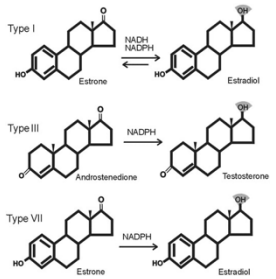


# What Is The Link Between Oxidative Damage And Mild Endocrine Failure?

# Steroidogenesis Relies On Redox Reactions

- Hydroxysteroid dehydrogenases interconvert relatively active and inactive steroid hormones with the help of nicotinamide cofactors NADPH/NADP+ and NADH/NAD+
- Specific to the lecture we will discuss the reproductive steroid pathways that are powered by 17 beta hydroxysteroid dehydrogenase.
  - Agarwal, Anil K., and Richard J. Auchus. "Minireview: cellular redox state regulates hydroxysteroid dehydrogenase activity and intracellular hormone potency." *Endocrinology* 146.6 (2005): 2531-2538.






# 17 beta hydroxysteroid dehydrogenase 1 & 7

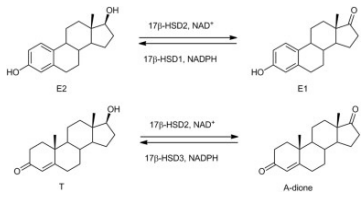
- 17BHSD1 catalyzes the follicular phase biosynthesis of estradiol from estrone with NADPH as the cofactor 17BHSD7 continues the conversion of E1 to E2 during luteal phase.
  - Payne, Anita H., and Dale B. Hales. "Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones." Endocrine reviews 25.6 (2004): 947-970.



# 17 beta hydroxysteroid dehydrogenase 3

- 17HSD3 converts androstenedione to testosterone, using NADPH as a cofactor
  - Payne, Anita H., and Dale B. Hales. "Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones." Endocrine reviews 25.6 (2004): 947-970.

# Type 2




# 17 beta hydroxysteroid dehydrogenase type 2

- 17BHSD2 catalyzes oxidation of Androstenediol to DHEA with NAD+ as the cofactor
- 17BHSD2 also oxidizes Testosterone to Androstenedione with NAD+ as the cofactor.
- Finally 17BHSD2 converts Estradiol into Estrone using NAD+
  - Payne, Anita H., and Dale B. Hales. "Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones." Endocrine reviews 25.6 (2004): 947-970.



# Can txt of oxidative damage help MEF?

# The Role of NAD+ and 17β-hydroxysteroid dehydrogenase

- Will building NAD+ change balance?
- Can we use exogenous NAD+ to effect 17β-hydroxysteroid dehydrogenase?



# NADPH and NAD+ for Steroidogenesis.

- Deficiencies in NAD+ and NADPH do cause down regulation in HSD
- The amount of active steroids in cells containing HSDs are modulated by NADPH/NADP+ and NADH/NAD+ cofactor abundance. This shows that steroidogenesis is driven in part by the intracellular redox state of the adrenals.
  - Agarwal, Anil K., and Richard J. Auchus. "Minireview: cellular redox state regulates hydroxysteroid dehydrogenase activity and intracellular hormone potency." *Endocrinology* 146.6 (2005): 2531-2538.



# Changes in intracellular NAD+ leads to imbalance

- Exogenous NAD+ promotes 17b-HSD2 thereby increasing estrone
  - Zhang, Chen-Yan, et al. "The contribution of 17beta-hydroxysteroid dehydrogenase type 1 to the estradiol-estrone ratio in estrogen-sensitive breast cancer cells." PLoS One 7.1 (2012): e29835.

## NAD+ can have benefit then?

- How does NAD+ benefit MEF?
- Unsure, but we can look to research done worth mitochondrial free radical theory of aging to get an idea.



## Mitochondrial Free Radical Theory of Aging (MFRTA)

- It states that increased levels of mitochondrial reactive oxygen species (ROS) stimulate aging.
- This means that antioxidants protect cells from mitochondrial generated ROS to delay tissue aging.
  - Barja, G. Updating the mitochondrial free radical theory of aging: An integrated view, key aspects, and confounding concepts. Antioxid. Redox Signal. 2013, 19, 1420–1445.



## What happens when it doesn't?

- What about the studies and clinical observations that show supplemented antioxidants or overexpression of SODs or catalase do not generally extend lifespan or healthspan?
  - Gems, D.; Doonan, R. Antioxidant defense and aging in C. elegans: Is the oxidative damage theory of aging wrong? Cell Cycle 2009, 8, 1681–1687.



## When It Doesn't Work

- Several studies show administration of the antioxidants vitamins C, and E (tocopherols) do not extend lifespan in several model organisms
- Antioxidants like C and E rely upon NADPH to be recycled to their active reduced forms and could be expected to provide minimal benefit when a deficiency ofNADPH levels prevent their efficient recycling.
  - Selman, C.; McLaren, J.S.; Meyer, C.; Duncan, J.S.; Redman, P.; Collins, A.R.; Duthie, G.G.; Speakman, J.R. Life-long vitamin C supplementation in combination with cold exposure does not affect oxidative damage or lifespan in mice, but decreases expression of antioxidant protection genes. Mech. Ageing Dev. 2006, 127,897–904.
  - Ernst, I.M.; Pallauf, K.; Bendall, J.K.; Paulsen, L.; Nikolai, S.; Huebbe, P.; Roeder, T.; Rimbach, G. Vitamin E supplementation and lifespan in model organisms. Ageing Res. Rev. 2013, 12, 365–375.



## More Of It Not Working, Now With Antioxidant Enzymes

- Studies show alterations of Manganese Super Oxide Dismutase (MnSOD) levels are correlated with changes in oxidative damage and in the generation of mitochondrial reactive oxygen species. Knocking MnSOD out or slowing it down shortens lifespan. What about ramping MnSOD up?
- Nope. Over expression of antioxidant enzymes, such as MnSOD or catalase doesn't extend life
  - Jang, Y.C.; Perez, V.I.; Song, W.; Lustgarten, M.S.; Salmon, A.B.; Mele, J.; Qi, W.; Liu, Y.; Liang, H.;Chaudhuri, A.; et al. Overexpression of Mn superoxide dismutase does not increase life span in mice. J. Gerontol. A Biol. Sci. Med. Sci. 2009, 64, 1114–1125.
  - Perez, V.I.; Van Remmen, H.; Bokov, A.; Epstein, C.J.; Vijg, J.; Richardson, A. The overexpression of major antioxidant enzymes does not extend the lifespan of mice. Aging Cell 2009, 8, 73–75.



## Why It Didn't Work-

"If free radicals cause a stress that cells can cope with, then damage will not occur because antioxidant defenses will overwhelm such stress. Only if the stress is of such magnitude that it deranges cellular signaling mechanisms, age associated damage will take place."

Sohal RS and Orr WC. The redox stress hypothesis of aging. Free Radic Biol Med 52: 539–555, 2012.

## Redox stress theory

- The Redox Stress Theory of Aging and the Redox Theory of Aging suggest that lifespan is regulated by redox changes. That the loss of balance in the redox equation is the root cause of aging.
  - Go Y.M., Jones D.P. Redox theory of aging: Implications for health and disease. Clin. Sci. (Lond. Engl. 1979) 2017;131:1669–1688. doi: 10.1042/cs20160897.



## Decreased NADPH

- The decrease in NADPH inhibits Glutathione reductase leaving a more oxidized state to the glutatihione redux couple.
- The NADPH deficiency induced oxidation of the redox systems of the cell also leads to oxidation of Glutaredoxin-1 ascorbate, and tocopherols.



"Antioxidant vitamins such as vitamins C or E that rely upon NADPH to be recycled to their active reduced forms would be expected to provide little longevity benefit in aged organisms where NADPH levels have declined to such an extent to prevent their efficient recycling"

Bradshaw, Patrick C. "Cytoplasmic and mitochondrial NADPH-coupled redox systems in the regulation of aging." ***Nutrients*** 11.3 (2019): 504.

## NAD+ needs NADPH

- pitcher needs a catcher.
- Huang, Q.; Sun, M.; Li, M.; Zhang, D.; Han, F.; Wu, J.C.; Fukunaga, K.; Chen, Z.; Qin, Z.H. Combination of NAD(+) and NADPH Offers Greater Neuroprotection in Ischemic Stroke Models by Relieving Metabolic Stress. Mol. Neurobiol. 2018, 55, 6063–6075.



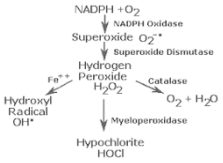
## So NADPH is as important as NAD+

- We know through the studies into MFRTA and Redox stress theory that NAD+ needs NADPH.
- Trying to normalize mild endocrine failure is like trying to restore redox balance it needs a combined approach.

# The Decline Of NADPH

## NADPH Decline

We have established that NAD+ needs NADPH.




- Quick review on NADPH and NADPH Oxidase:
  - NADPH provides reducing power for biosynthetic reactions, maintains the redox state of the cell, and is the electron donor for NADPH oxidase.
  - NADPH oxidase mediated release of ROS (the oxidative burst) in macrophages and neutrophils triggers elimination of invading microorganisms.
  - ROS has also been associated with cellular malfunction and diseases, such as cardiovascular pathology, immunodeficiency and pulmonary diseases.
  - Goldilocks

## What causes the decline of NADPH?

- Decline in NADPH has several causes:
  - Damage to the ETC
  - Inhibition of the Kyurenic pathway
  - Dietary excess
  - Loss of circadian rhythm
  - Loss of endocrine balance



# Damage to ETC

## Damage to ETC

- Age related decline in cellular NADPH and an increase in oxidative stress results from a decrease in the levels of cellular NAD+
  - Zhu, Xiao-Hong, et al. "In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences." Proceedings of the National Academy of Sciences 112.9 (2015): 2876-2881.



## Damage to ETC

- Decreases in cellular NAD+ causes alterations in mitochondrial ETC resulting in elevated ROS production that is sirtuin independent.
- This increase in ROS goes on to triggers nuclear DNA damage and activates poly-ADP-ribose polymerase (PARP)
  - Braidy, Nady, et al. "Age related changes in NAD+ metabolism oxidative stress and Sirt1 activity in wistar rats." PloS one 6.4 (2011): e19194.

## Damage to ETC

- This PARP activation along with an age related up regulation of CD38 production leads to increased hydrolysis of NAD+ and NADP+
- PARP also inhibits hexokinase, a necessary enzyme in the NADPH-generating pentose phosphate pathway (PPP)
  - Camacho-Pereira, Juliana, et al. "CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism." Cell metabolism 23.6 (2016): 1127-1139.



## Alterations To The Kyurenic Pathway

## Kyurenic

- Estradiol and especially its ester estradiol disulfate influences the breakdown of tryptophan. Tryptophan is the precursor for the serotonin pathway and the kynurenine pathway.
  - Hargreaves, K. M., and W. M. Pardridge. "Neutral amino acid transport at the human blood-brain barrier." Journal of Biological Chemistry 263.36 (1988): 19392-19397.
- Dietary tryptophan is metabolized via the kynurenine pathway. The pathway includes pyridoxal 5'-phosphate (PLP)-dependent enzymes such as: kynurenine aminotransferase (KAT), kynureninase and kynurenine monooxygenase.



## Kyurenic

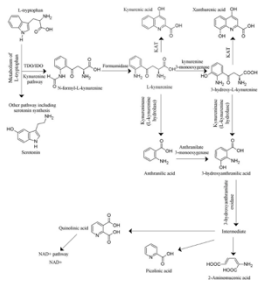
- Estradiol and estradiol disulfate (OBCP) exert activity on various PLP-dependent enzymes
- Estrogen has long been known to inhibit the conversion of tryptophan to nicotinamide
  - Katsumi Shibata & Takako Kondo (1993) Effects of Progesterone and Estrone on the Conversion of Tryptophan to Nicotinamide in Rats, Bioscience, Biotechnology, and Biochemistry, 57:11, 1890-1893, DOI: 10.1271/bbb.57.1890
  - Mason, M., Ford, J. & Wu, H. L. Effects of steroid and nonsteroid metabolites on enzyme conformation and pyridoxal phosphate binding. Ann. N. Y. Acad. Sci. 166, 170–183 (1969).
  - Scardi, V., Iaccarino, M. & Scarano, E. The action of sulphate and phosphate esters of oestrogens on the reconstitution of two pyridoxal 5-phosphate-dependent enzymes. Biochem. J. 83, 413–416 (1962



## Kyurenic

- Estradiol and especially estradiol disulfate are potent inhibitors of PLP-dependent enzyme activity, such as: kynureninase, and kynurenine monooxygenase.
  - Jayawickrama, Gayan S., et al. "Inhibition of human kynurenine aminotransferase isozymes by estrogen and its derivatives." Scientific reports 7.1 (2017): 1-11.
  - Mason, M., Ford, J. & Wu, H. L. Effects of steroid and nonsteroid metabolites on enzyme conformation and pyridoxal phosphate binding. *Ann. N. Y. Acad. Sci.* 166, 170–183 (1969).
  - Scardi, V., Iaccarino, M. & Scarano, E. The action of sulphate and phosphate esters of oestrogens on the reconstitution of two pyridoxal 5-phosphate-dependent enzymes. *Biochem. J.* 83, 413–416 (1962)
  - Rose, D. P. & Brown, R. R. The influence of sex and estrogens on liver kynureninase and kynurenine aminotransferase in the rat. *Biochim. Biophys. Acta* 184, 412–419 (1969).





# CRON

## CRON

- CRON diet promotes longevity through decreasing mitochondrial ROS production
- CRON diet also has been shown to increase NADPH and GSH.
  - Rodgers, Joseph T., et al. "Nutrient control of glucose homeostasis through a complex of PGC-1α and SIRT1." Nature 434.7029 (2005): 113-118.
- Hyperglycemia increases NADPH oxidase
  - Jansen, Felix, et al. "High glucose condition increases NADPH oxidase activity in endothelial microparticles that promote vascular inflammation." Cardiovascular research 98.1 (2013): 94-106.



## CRON

- Patients with Diabetes have decreased levels of NAD+. This comes from the oxidation of excessive substrates i.e. glucose through the polyol pathway, free fatty acids and lactate.
  - Fan, Lan, Jose M. Cacicedo, and Yasuo Ido. "Impaired nicotinamide adenine dinucleotide (NAD+) metabolism in diabetes and diabetic tissues: Implications for nicotinamide–related compound treatment." Journal of diabetes investigation 11.6 (2020): 1403-1419.



## EMP CRON

- Increased Glycosilation up regulates NADPH oxidase, further depleting NADPH.
  - Endothelial micro particles (EMP) trigger inflammation, thrombosis, and coagulation leading to atherogenesis.
  - EMP also promotes cell survival, with anti-inflammatory effects, modulating coagulation processes, and inducing endothelial regeneration.
  - Goldilocks
  - EMP from diabetic endothelial cells increase vascular inflammation.
  - "EMP derived under pathological high glucose conditions induce adhesion protein expression in endothelial cells and subsequent monocyte adhesion in a NADPH oxidase-ROS-p38-dependent way."
    - Felix Jansen, Xiaoyan Yang, Bernardo S. Franklin, Marion Hoelscher, Theresa Schmitz, Jörg Bedorf, Georg Nickenig, Nikos Werner, High glucose condition increases NADPH oxidase activity in endothelial microparticles that promote vascular inflammation, Cardiovascular Research, Volume 98, Issue 1, 1 April 2013, Pages 94–106



# Sleep

## Sleep Fragmentation

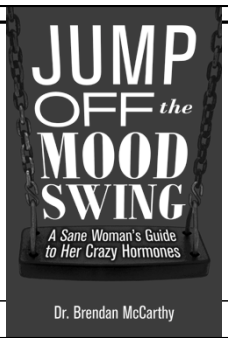
- Sleep fragmentation can lead to impaired cognitive function.
- Uninterrupted sleep for a minimum length of time is required for optimal daytime vigilance and neurocognitive function.
  - Franken P. Long-term vs. short-term processes regulating REM sleep. J Sleep Res 2002;11:17–28
  - Stepanski EJ. The effect of sleep fragmentation on daytime function. Sleep 2002;25:268–276.

## Sleep Fragmentation

- Sleep deprivation causes oxidative stress leading to formation of ROS, which in neural tissue, leads to neuronal and cellular damage.
  - Gopalakrishnan A, Ji LL, Cirelli C. Sleep deprivation and cellular responses to oxidative stress. Sleep 2004;27:27–35.
- Animal studies show that sleep fragmentation increases NADPH oxidase levels.
  - Nair, Deepti, et al. "Sleep fragmentation induces cognitive deficits via nicotinamide adenine dinucleotide phosphate oxidase–dependent pathways in mouse." *American journal of respiratory and critical care medicine* 184.11 (2011): 1305-1312.



## Hormone Balance




## Shameless Plug
## I wrote a book

- The heart of my practice is restoring endocrine balance in patients with hormone influenced neurotransmitter imbalances.

## Hormonal Influence On Neural Redox

- Redox homeostasis and mitochondrial function show sex differences in the brain
  - T.G. Demarest, M.M. McCarthy, Sex differences in mitochondrial (dys)function: implications for neuroprotection, J. Bioenerg. Biomembr. 47 (2015) 173–188
- Female sexual hormones, estradiol (E2) and progesterone, possess neuroprotective effects in vivo and in vitro at physiological concentrations.
  - E.B. Engler-Chiurazzi, C.M. Brown, J.M. Povroznik, J.W. Simpkins, Estrogens as neuroprotectants: estrogenic actions in the context of cognitive aging and brain injury, Prog. Neurobiol. 157 (2017) 188–211
  - A.N. Siddiqui, N. Siddiqui, R.A. Khan, A. Kalam, N.R. Jabir, M.A. Kamal, C.K. Firoz, S. Tabrez, Neuroprotective role of steroidal sex hormones: an overview, CNS Neurosci. Ther. 22 (2016) 342–350



## Hormonal Influence On Neural Redox

- Testosterone is associated with neurotoxicity
  - Liu, Mingyue, et al. "Neuroprotection of sex steroids." *Minerva endocrinologica* 35.2 (2010): 127.
- Estradiol binding to ERα or ERβ upregulating anti-inflammatory and anti-apoptotic genes.
- Estrogen receptor activation also activates several protein kinases that reduce oxidative stress, apoptosis, and inflammation modulation.
  - Torrens-Mas, Margalida, et al. "Sexual hormones regulate the redox status and mitochondrial function in the brain. Pathological implications." *Redox biology* 31 (2020): 101505.
  - R.Ventura-Clapier,M.Moulin,J.Piquereau,C.Lemaire,M.Mericskay,V.Veksler, A. Garnier, Mitochondria: a central target for sex differences in pathologies, Clin. Sci. (2017)



## Hormonal Influence On Neural Redox

- Synthetic progesterone decreases MnSOD and ecSOD transcription rates
- Synthetic progesterone increased ROS release in VSMCs that was prevented by concomitant treatment with 17β-estradiol
  - Wassmann, Kerstin, Sven Wassmann, and Georg Nickenig. "Progesterone antagonizes the vasoprotective effect of estrogen on antioxidant enzyme expression and function." *Circulation research* 97.10 (2005): 1046-1054.

# How We Treat

## CRON

- Calorie Restrictive Optimal Nutrition diet.
- Diet is a tricky tool to use. Compliance is an issue.
- Labs- HBA1C, fasting Insulin, IGF-BP1.
- Medications- Semaglutide, Contrave, naltrexone pellet.
- Diets- fasting (all kinds) HFLC, CRON
- Trauma



## Sleep

- Sleep study, stress history
- Labs- pregnenalone, progesterone, cortisol, HS-CRP, CBC ALT,AST.
- CPAP, normalize pregnenalone, progesterone. Address adrenal balance. Consider trauma.



## ECT

- Magnesium acts as an antioxidant in the mitochondria.
- It has been shown to ncreases mitochondrial NADPH and ATP synthesis.
  - "Villa-Bellosta, Ricardo. "Dietary magnesium supplementation improves lifespan in a mouse model of progeria." *EMBO molecular medicine* 12.10 (2020): e12423.

## Inhibit NADPH oxidase.

- Berberine reduces superoxide levels in LPS- stimulated macrophages. Through selective inhibition of gp91phox expression and increased SOD activity
  - Sarna LK, Wu N, Hwang SY, Siow YL, O K. Berberine inhibits NADPH oxidase mediated superoxide anion production in macrophages. Can J Physiol Pharmacol. 2010 Mar;88(3): 369-78. doi: 10.1139/Y09-136. PMID: 20393601.



## Inhibit NADPH oxidase.

- Blueberry polyphenols, specifically wild Alaska bog blueberries, inhibit NADPH oxidation.
  - S. J. Gustafson, K. L. Dunlap, C. M. McGill, and T. B. Kuhn, "A nonpolar blueberry fraction blunts NADPH oxidase activation in neuronal cells exposed to tumor necrosis factor-$\alpha$," Oxidative Medicine and Cellular Longevity, vol. 2012, Article ID 768101, 12 pages, 2012.

## Inhibit NADPH oxidase.

- EGCG inhibits ANG II induced NADPH oxidase activity.
  - H. Y. Ahn, C. H. Kim, and T. S. Ha, "Epigallocatechin-3-gallate regulates NADPH oxidase expression in human umbilical vein endothelial cells," Korean Journal of Physiology and Pharmacol- ogy, vol. 14, no. 5, pp. 325–329, 2010.



## Inhibit NADPH oxidase.

- Ginkgo inhibits LPS-induced NADPH oxidase activation
  - ] F. Y. Lin, Y. H. Chen, Y. L. Chen et al., "Ginkgo biloba extract inhibits endotoxin-induced human aortic smooth muscle cell proliferation via suppression of toll-like receptor 4 expression and NADPH oxidase activation," Journal of Agricultural and Food Chemistry, vol. 55, no. 5, pp. 1977–1984, 2007.



## Inhibit NADPH oxidase.

- A compound found in delicious kimchi, 3-(4'-hydroxyl-3',5'-dimethoxyphenyl)propionic acid (HDMPPA) significantly lowers aortic NADPH oxidase activity.
  - J.S. Noh, H.J.Kim, M.J.Kwon, and Y.O. Song, "Active principle of kimchi, 3-(4'-hydroxyl-3',5'-dimethoxyphenyl)propionic acid, retards fatty streak formation at aortic sinus of apolipoprotein E knockout mice" Journal of Medicinal Food, vol. 12, no. 6, pp. 1206–1212, 2009.



## Inhibit NADPH oxidase.

- Magnolia inhibits interferon-Y and LPS induced indictable nitric oxide synthase expression thereby reducing NADPH activation.
  - D. Y. Chuang, M. H. Chan, Y. Zong et al., "Magnolia polyphenols attenuate oxidative and inflammatory responses in neurons and microglial cells," Journal of Neuroinflammation, vol. 10, article 15, 2013.



## Inhibit NADPH oxidase.

- Reservatrol inhibits NF-κB/NADPH oxidase/ROS pathway
  - F. Chen, L. H. Qian, B. Deng, Z. M. Liu, Y. Zhao, and Y. Y. Le, "Resveratrol protects vascular endothelial cells from high glucose-induced apoptosis through inhibition of nadph oxidase activation-driven oxidative stress," CNS Neuroscience & Therapeutics, vol. 19, no. 9, pp. 675–681, 2013.
  - [89] Y. Tang, J. Xu, W. Qu et al., "Resveratrol reduces vascular cell senescence through attenuation of oxidative stress by SIRT1/NADPH oxidase-dependent mechanisms," Journal of Nutritional Biochemistry, vol. 23, no. 11, pp. 1410–1416, 2012.



## Hormone Balance

- Estradiol progesterone synthetic progesterone and testosterone balance.
  - Itagaki, Tatuzo, et al. "Opposing effects of oestradiol and progesterone on intracellular pathways and activation processes in the oxidative stress induced activation of cultured rat hepatic stellate cells." *Gut* 54.12 (2005): 1782-1789.
  - Wassmann, Kerstin, Sven Wassmann, and Georg Nickenig. "Progesterone antagonizes the vasoprotective effect of estrogen on antioxidant enzyme expression and function." *Circulation research* 97.10 (2005): 1046-1054.

# In Conclusion

- 17B HSD is dependent on the nicotinamide cofactors NAD and NADPH.
- Advancing NAD+ without NADPH will cause imbalance.
- This is similar to what we see in the Mitochondrial Free Radical Theory of Aging vs The Redox Stress Theory of Aging.
- Through the support of NADPH we can expect better results when treating redox based pathology.