Casual Friday Series

Working Through Menopause, Part 2

A Biogenetix Clinical Presentation

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Disclaimer

- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

Menopause: What your patients are reading…

In the months or years leading up to menopause (perimenopause):

- Irregular periods
- Vaginal dryness
- Hot flashes
- Chills
- Night sweats
- Sleep problems
- Mood changes
- Weight gain and slowed metabolism
- Thinning hair and dry skin
- Loss of breast fullness

https://www.mayoclinic.org/diseases-conditions/menopause/symptoms-causes/syc-20353397

Menopause: What your patients are reading…

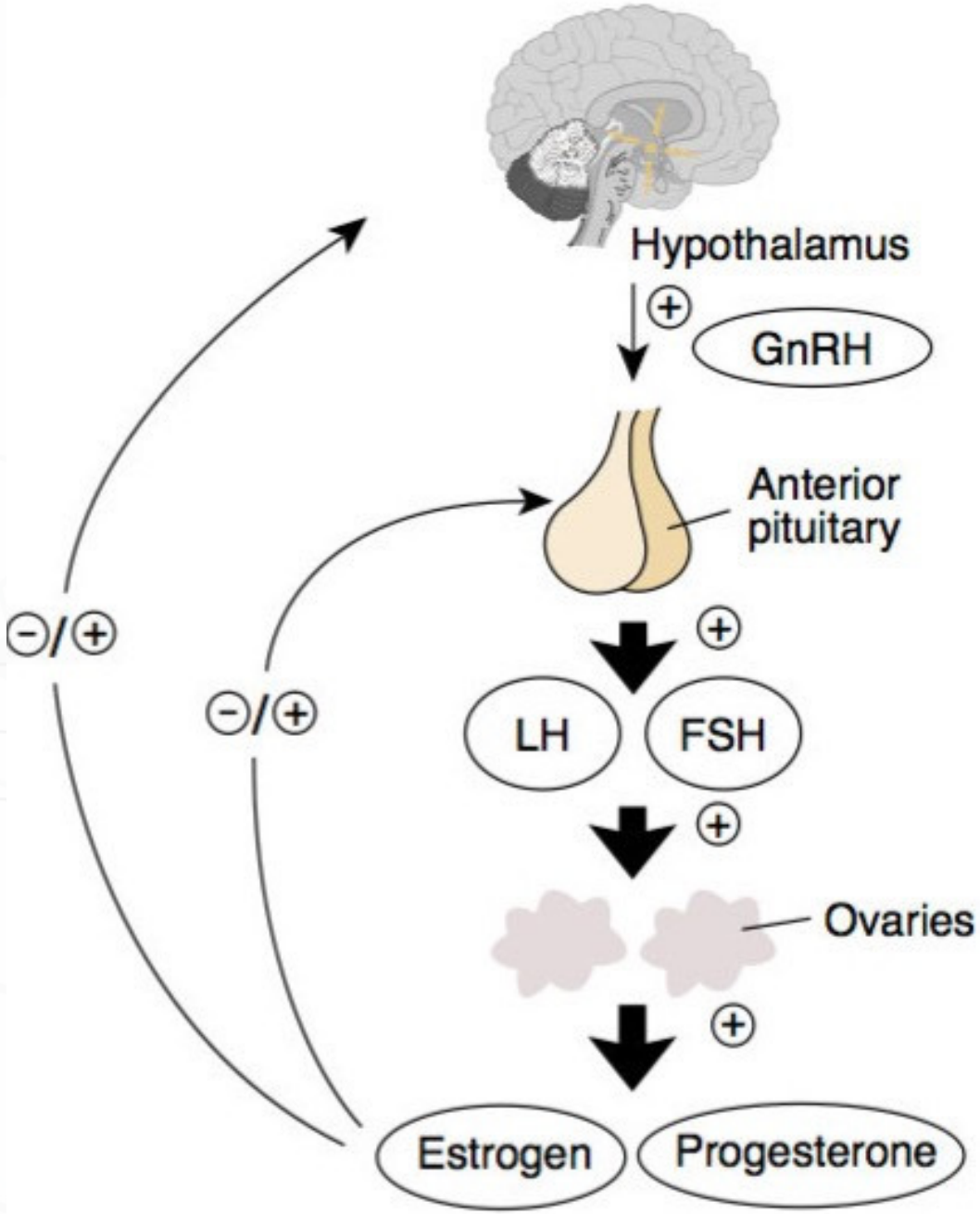
Causes:

1. Naturally declining reproductive hormones
2. Surgery that removes ovaries (oophorectomy)
3. Chemo and radiation therapy
4. Primary ovarian insufficiency

Results:

1. Increased risk for CVD
2. Osteoporosis
3. Bladder function
4. Sexual function
5. Weight gain

https://www.mayoclinic.org/diseases-conditions/menopause/symptoms-causes/syc-20353397



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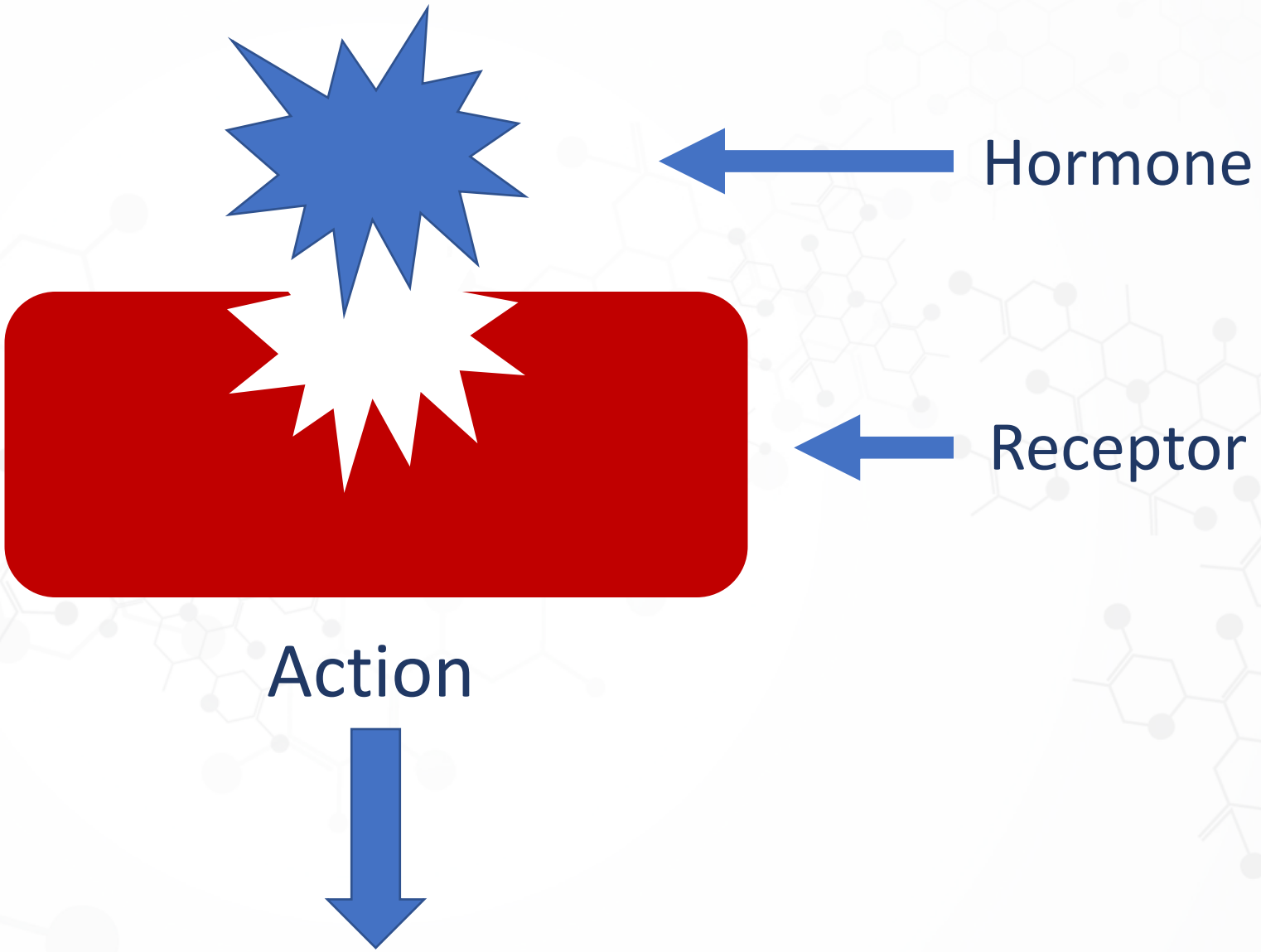
Hormone
Receptor
Action

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doi: 10.1097/gme.0b013e31823df577

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NIHMSID: NIHMS339770
PMID: 22415563

Androstenediol Complements Estrogenic Bioactivity during the Menopausal Transition

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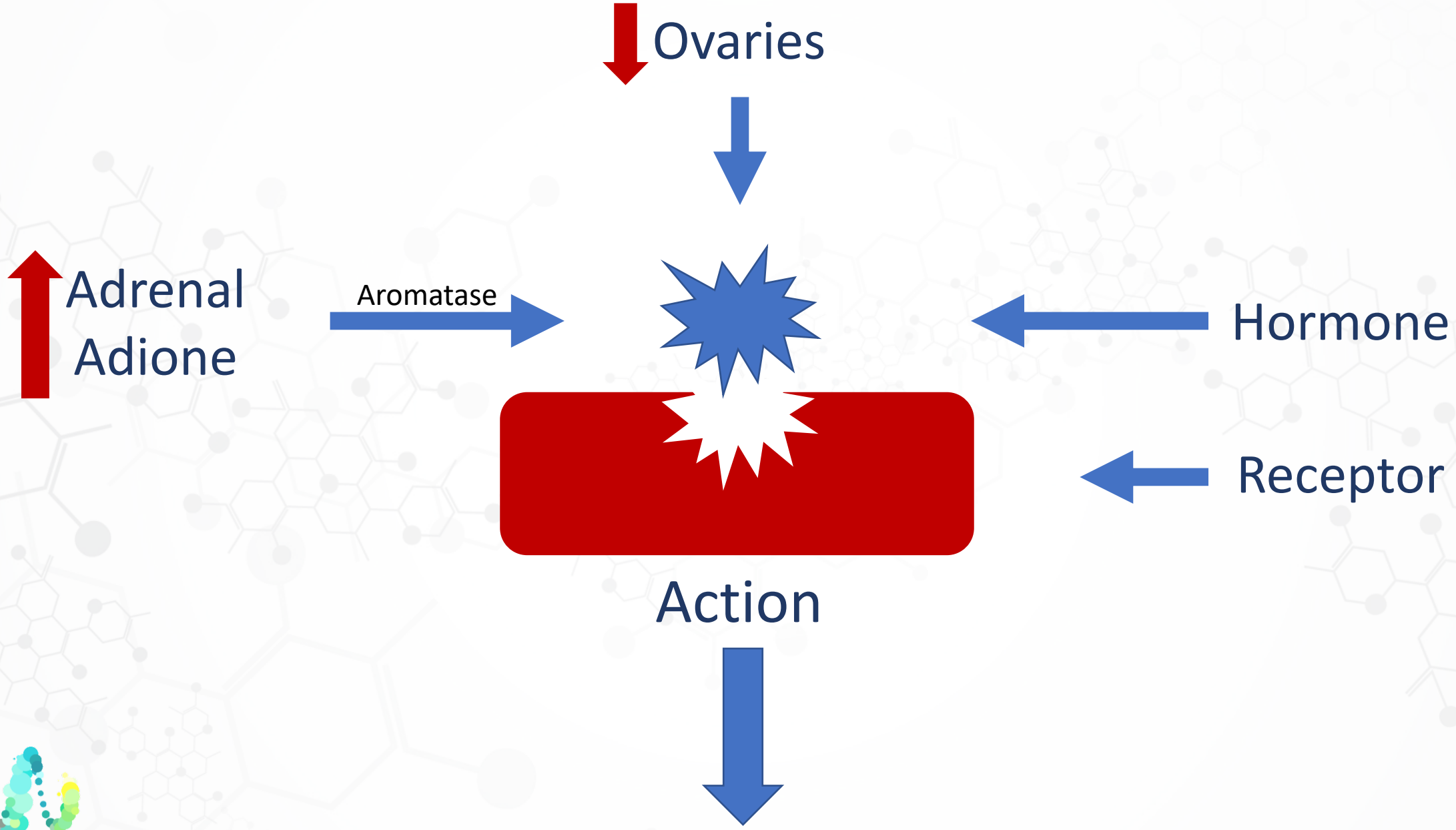
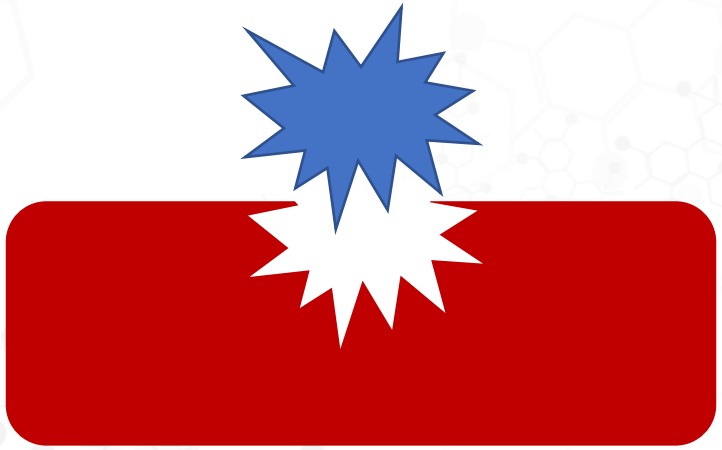
A two-fold increase in circulating Adione and T was found to rise in parallel with the rise in circulating DHEAS, while DHEA and Adiol concentrations rose seven to eightfold. Circulating Adiol, which has both androgenic and estrogenic biological activity, was significantly associated ($p<0.02$) with circulating estrogen bioactivity only when E2 concentrations were low and Adiol levels were high.

The wide range of circulating levels of Adiol and its contribution to total circulating estrogenicity during the MT is consistent with the observed inter-woman difference in symptoms at this time. Therefore, we conclude that Adiol contributes to circulating estrogenicity when E2 production falls at menopause and may contribute significantly to the endocrine changes experienced by midlife women.

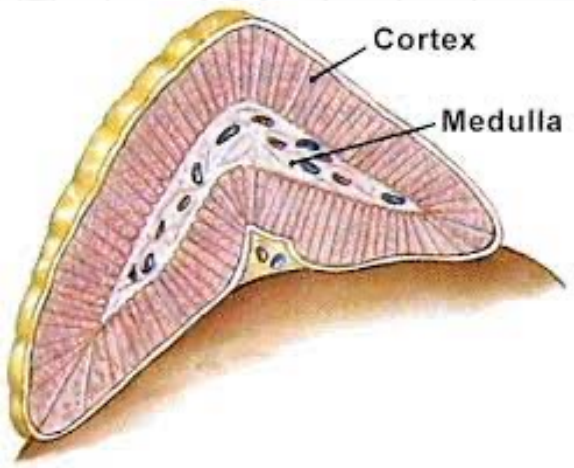

Ovaries
Adrenal
Adione
Aromatase
Hormone
Receptor
Action

3 Options for intervention:

replace

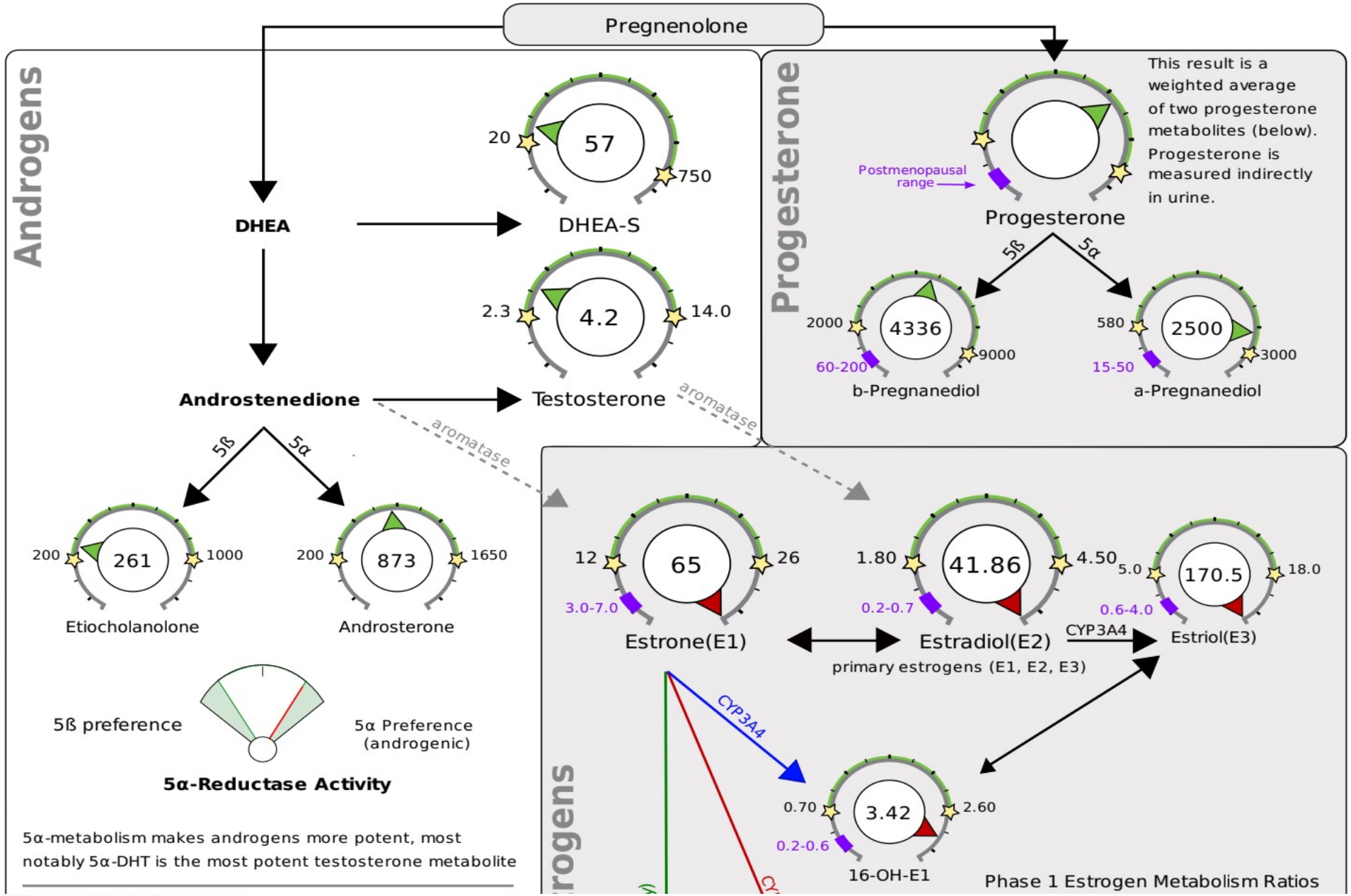


sensitize



support

1


Pregnenolone
Androgens
DHEA
20
57
750
DHEA-S
2.3
4.2
14.0
Androstenedione
Testosterone
aromatase
aromatase
5ß
5α
200
261
1000
Etiocholanolone
200
873
1650
Androsterone
5ß preference
5α Preference (androgenic)
5α-Reductase Activity
5α-metabolism makes androgens more potent, most notably 5α-DHT is the most potent testosterone metabolite
Progesterone
This result is a weighted average of two progesterone metabolites (below). Progesterone is measured indirectly in urine.
Postmenopausal range
Progesterone
5ß
5α
2000
4336
9000
60-200
b-Pregnanediol
580
2500
3000
15-50
a-Pregnanediol
12
65
26
3.0-7.0
Estrone(E1)
1.80
41.86
4.50
0.2-0.7
Estradiol(E2)
CYP3A4
5.0
170.5
18.0
0.6-4.0
Estriol(E3)
primary estrogens (E1, E2, E3)
CYP3A4
0.70
3.42
2.60
0.2-0.6
16-OH-E1
Phase 1 Estrogen Metabolism Ratios

Endocrinology. 2009 Jun; 150(6): 2537–2542.
Published online 2009 Apr 16. doi: 10.1210/en.2009-0070
PMCID: PMC2689796
PMID: 19372199

Obesity and Breast Cancer: The Estrogen Connection

Margot P. Cleary and Michael E. Grossmann

There is now substantial evidence that overweight and/or obesity and/or weight gain are risk factors for the development of postmenopausal breast cancer. In addition, obesity and/or elevated body mass index at breast cancer diagnosis has a negative impact on prognosis for both premenopausal and postmenopausal women. Therefore, understanding the mechanism of how obesity affects the mammary tumorigenesis process is an important health issue. Elevated serum estrogen levels as well as enhanced local production of estrogen have been considered primary mediators of how increased body weight promotes breast cancer development in postmenopausal women. Here, we provide an overview of estrogen's relationship with both obesity and breast cancer as separate entities. Human and relevant preclinical studies are cited. In addition, other growth factors that may be involved in this relationship are considered.

For postmenopausal women significant increases in estrone, estradiol, and free estradiol are associated with increasing BMI (45,46,47,48,49,50,51). This relationship may be modified by physical activity resulting in lower serum levels of estrogens from higher levels of activity (47). If not considered during data analysis, this could impact interpretation of results about estrogen's relationship to body weight. Data

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The biosynthesis of estrogens differs between premenopausal and postmenopausal women (53). Premenopausal women mainly synthesize estrogens in the ovary. However, in postmenopausal women ovarian biosynthesis is replaced by peripheral site synthesis, and in obese postmenopausal women, adipose tissue is the main source of estrogen biosynthesis. The primary mediator of postmenopausal estrogen biosynthesis is aromatase, which is actually a complex of enzymes (54) that is found in adipose tissue in the breast as well as tumor tissue itself (55). Androgens produced by the adrenal cortex and the postmenopausal ovary are converted into estrogens by aromatase (56,57). This mechanism of estrogen production can lead to local estrogen levels in breast tumors that are as much as 10-fold higher compared with the circulation (58), although this is something that cannot routinely be measured. In addition, TNFα and IL-6 are both secreted by adipocytes and can act in either autocrine or paracrine manners to increase production of aromatase, which is directly related to increased synthesis of estrogen (59). A number of different aromatase inhibitors are currently used to control the peripheral production of estrogens in women who have had breast cancer, and additional applications for the aromatase inhibitors are being evaluated (55).

1. Decreasing ovarian function
   → decreasing estrogen, progesterone
2. Increasing adrenal function
   → increased cortisol
   → increased DHEA
   → increased androstenedione

"increased estrogenicity." How? Aromatization and the awakening of body fat.

3. Cortisol-stimulated centralization of body fat
4. Shift from global to localized estrogenic activity

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Weight loss through either caloric restriction or gastric bypass surgery has been shown to lead to a reduction in circulating estrogens, although the relationship of the amount of weight lost to reductions in serum estrogens was not always proportional. For example, calorie restriction resulting in intakes of 1200 kcal/d using the American Heart Association step 2 diet for an average of 13.9 months resulted in an average weight loss of 14.5 kg (−15.6% of initial body weight) for postmenopausal women, whereas serum estradiol was reduced from an initial average of 25.5 to 17.9 pg/ml (82). In another study, weight reduction of 4% was associated with an 18% decrease of estradiol. This was not significant in women 50–65 yr of age, but there was a significant increase in SHBG (83).

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A study of women with a mean age of 43.9 yr who had undergone Roux-en-Y gastric bypass surgery found that an average weight loss of 38.5 kg was accompanied by a decrease in estradiol from 53.9–35.7 pg/ml as well as a decrease in estrone from 69.6–48.1 pg/ml (84). Younger women with a mean age of 34.7 yr who underwent vertical banded gastroplasty lost 59 kg (percentage of body weight was not reported) 12 months after the procedure, whereas their serum levels of estradiol decreased from 94.85–73.62 pg/ml over the same period (85). Because many breast tumors in postmenopausal women are dependent on estrogen for growth, it seems likely that weight loss and the concomitant reduction in estrogen levels should lead to a reduction in breast tumor growth. In fact, a recently published paper supports this indicating that the incidence of breast cancer was reduced by 85% after gastric bypass surgery (86).

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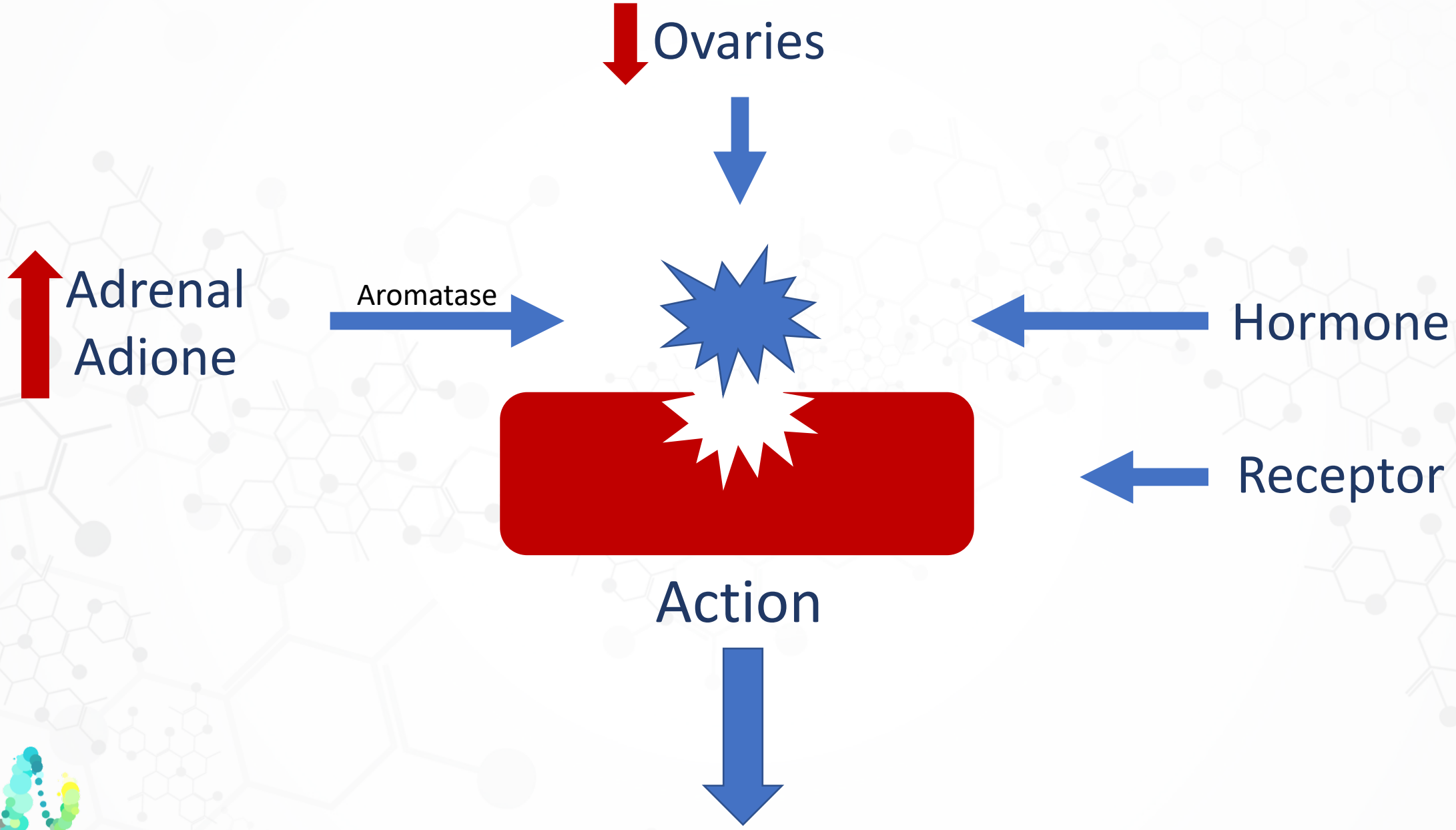
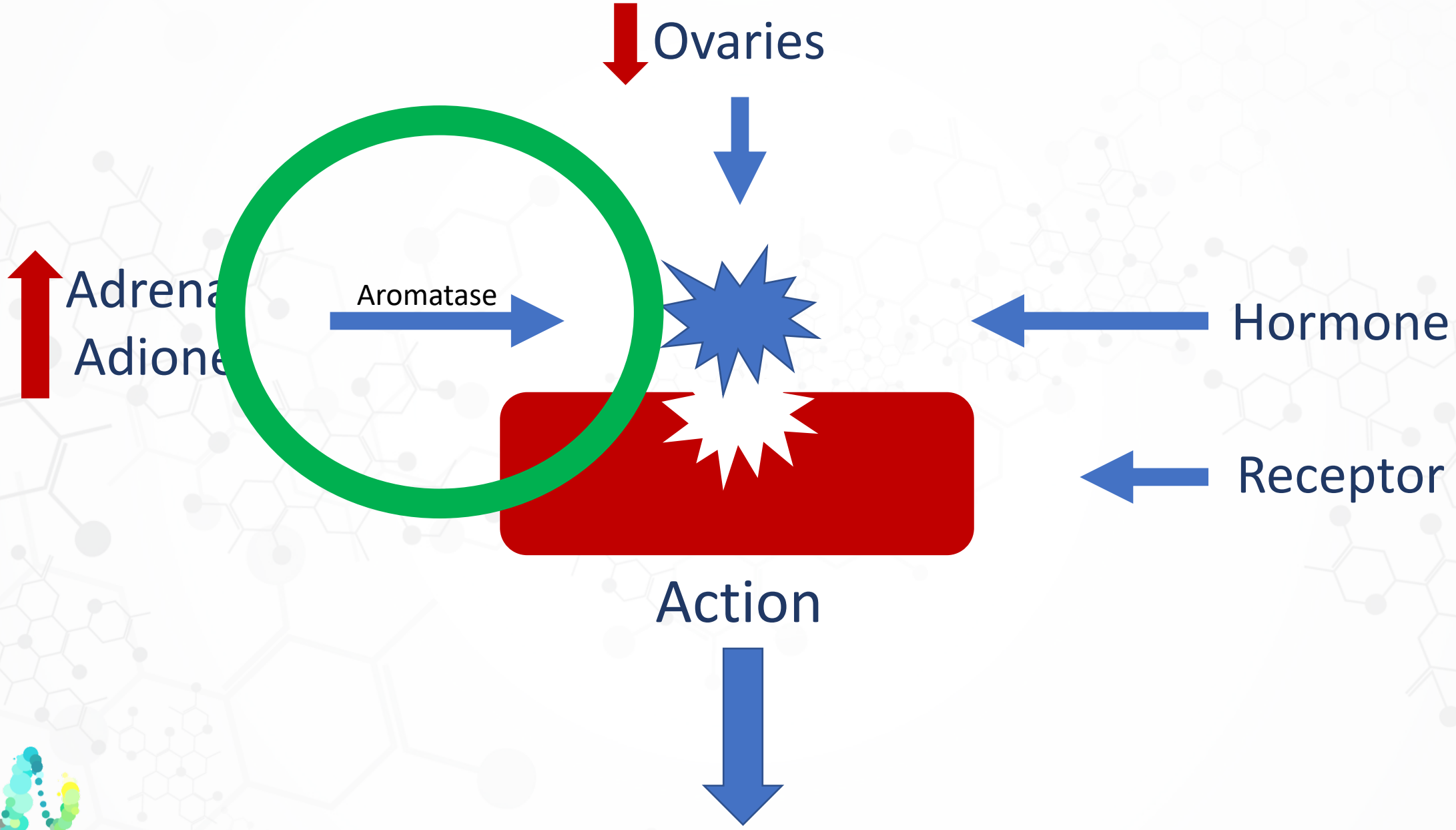
Obesity is associated with a number of additional circulating factors that may work independently as well as in concert with estrogen to impact breast cancer development. Most of the supporting evidence for these interactions results from *in vitro* studies in relationship to the ER status of human breast cancer cell lines. For example, insulin and IGF-I have had various effects on estrogen signaling in breast cancer cell lines, as reviewed in Ref. 53. There is increasing evidence that leptin, an adipose tissue-derived protein, which is positively associated with BMI and body fat, has different effects on ER+ and ER− human breast cancer cell lines. ER+ MCF-7 and T47-D cells express high levels of the leptin receptor signaling isoform, ObRl/Rb, whereas the shorter forms are present in ER− MDA-MB-231 and MDA-MB-435 cell lines (102). In addition, leptin receptor and ERα are coexpressed in breast cancer cell lines. In ER+ T47-D breast cancer cells, leptin induced cellular transformation (anchorage-independent growth) that was not observed in normal breast epithelial cells (103). In this and other ER+ breast cancer cell lines, the addition of leptin increases cell proliferation (103,104,105,106,107). Of particular interest to the focus of this review, it has been found that leptin modulates estrogen synthesis and ERα activity by up-regulation of aromatase gene expression and aromatase activity in MCF-7 cells, leading to increased estrogen synthesis (108).


Ovaries
Adrenal
Adione
Aromatase
Hormone
Receptor
Action


Ovaries
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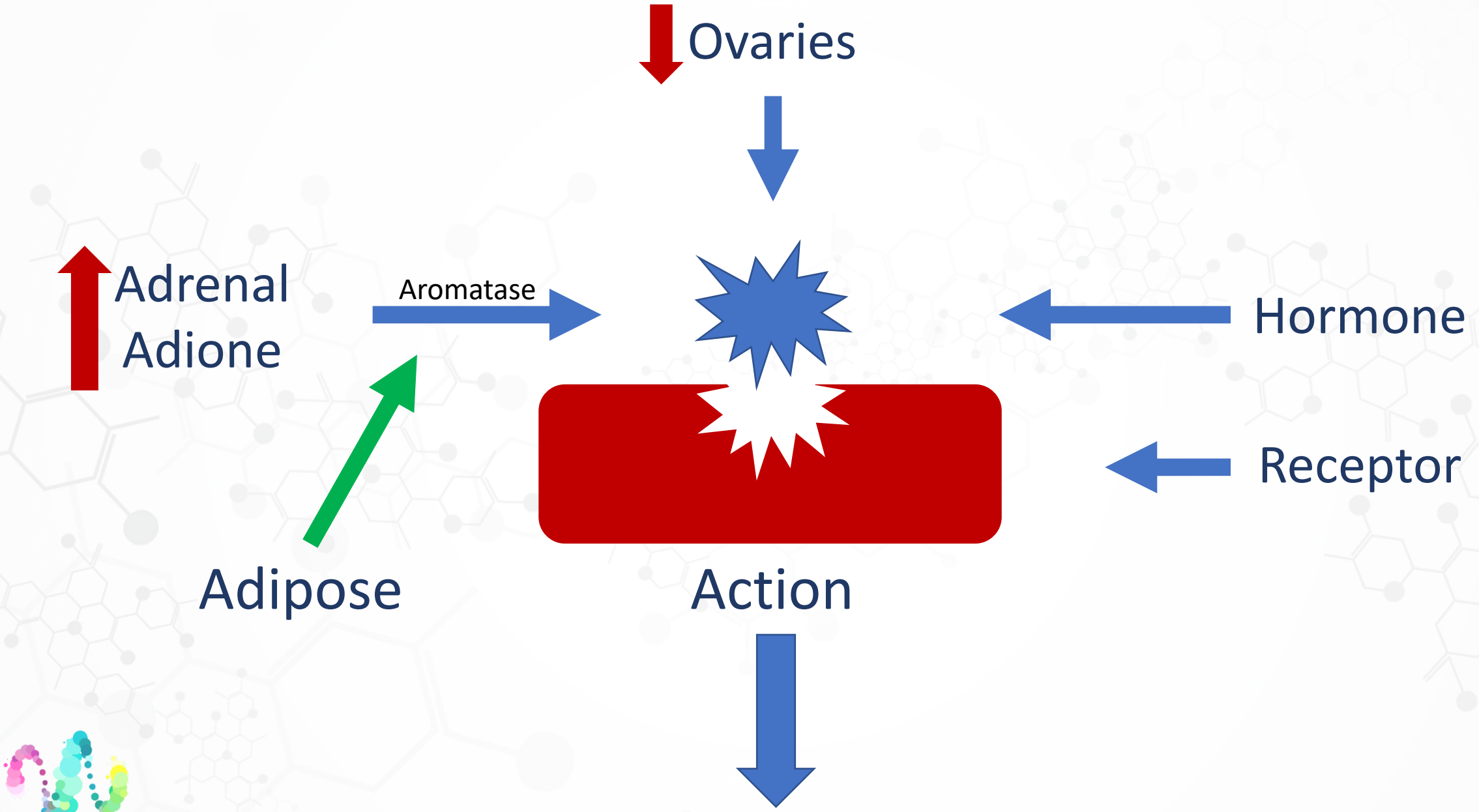
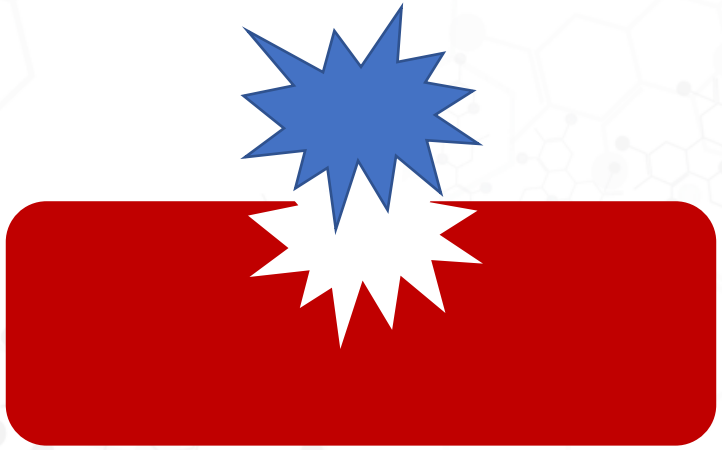
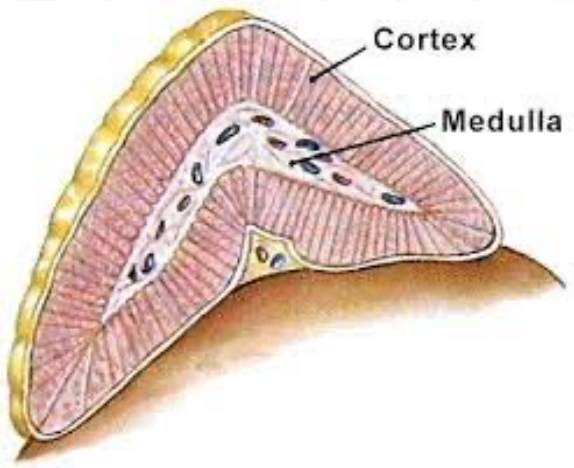

Ovaries
Adrenal
Adione
Aromatase
Hormone
Receptor
Adipose
Action

3 Options for intervention:

replace



sensitize



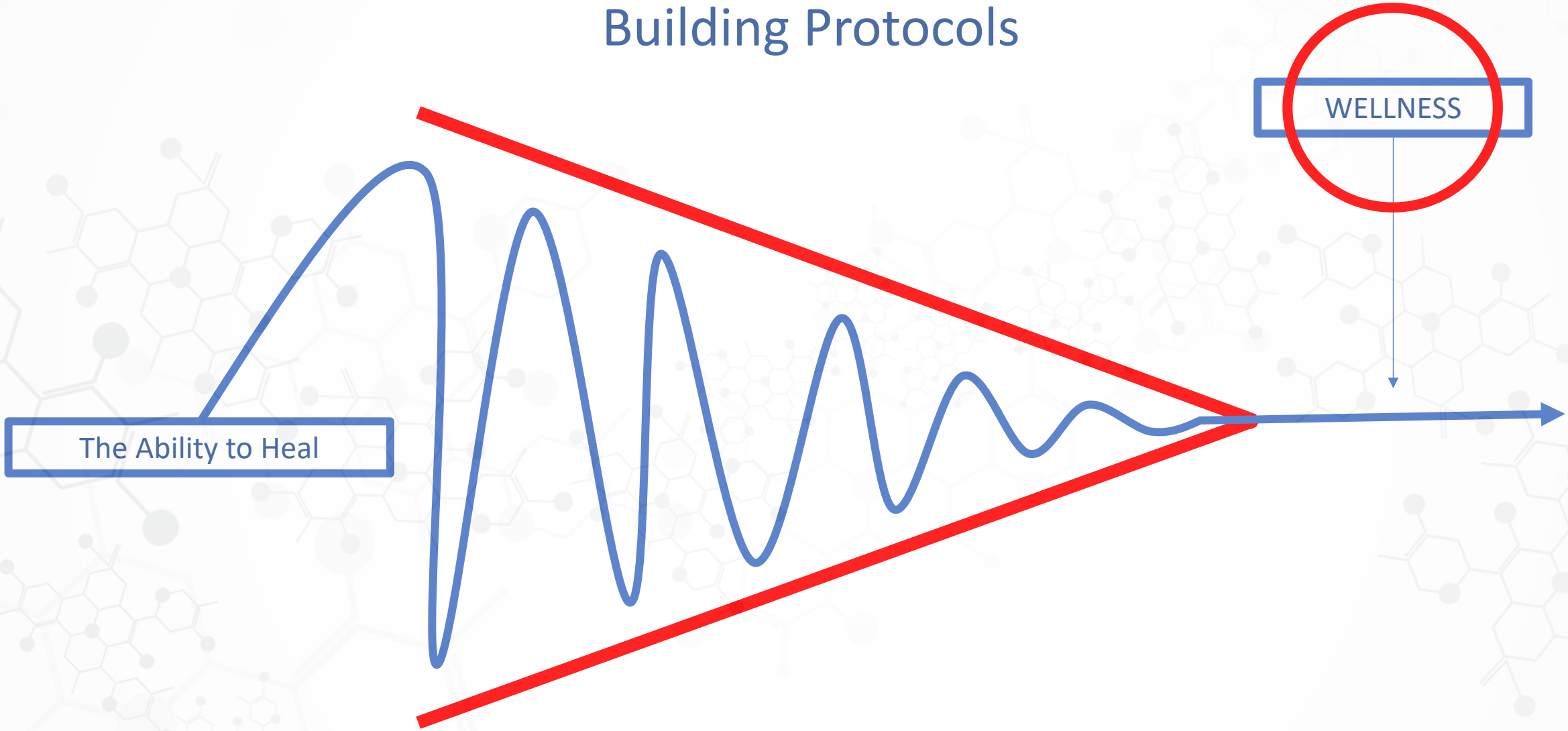
support

To be continued…

Further Reading on obesity/estrogen/toxicity connections:

Link -----> https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3964739/

Building Protocols



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