BOTANICAL INFLUENCES ON DYSGLYCEMIA

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Botanical Influences on Dysglycemia

This session will review influences that affect blood sugar regulation and botanical interventions.

INFLUENCES INCLUDING

- Hormonal cycles
- Stress and adrenal function
- Liver function
- Diet

WE WILL FOCUS ON THE FOLLOWING:

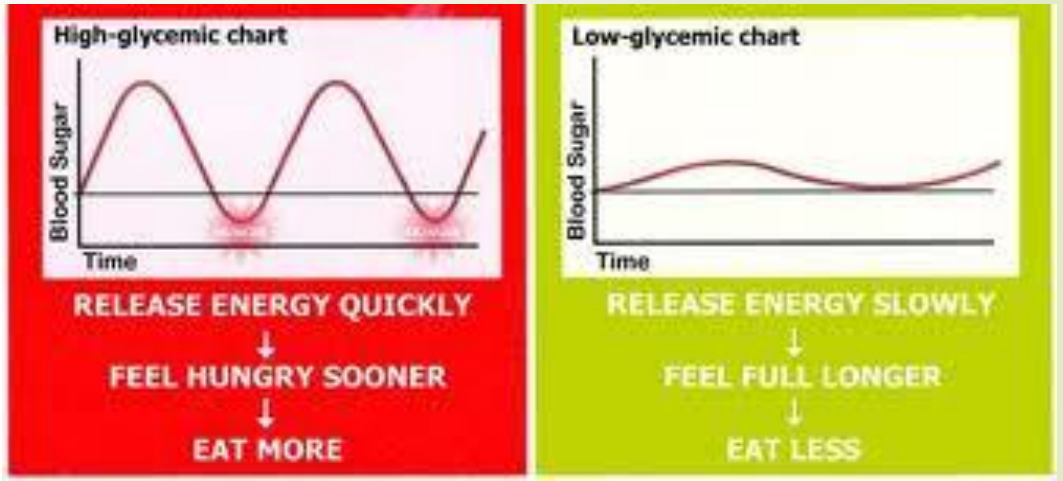
- How Diet contributes the Dysglycemia
- How adrenal and thyroid function, influence blood sugar control.
- How reproductive hormone cycles influence blood sugar control
- Various mechanisms by which herbs improve glycemic control
- A brief materia medica summary of herbs to improve glycemic control.

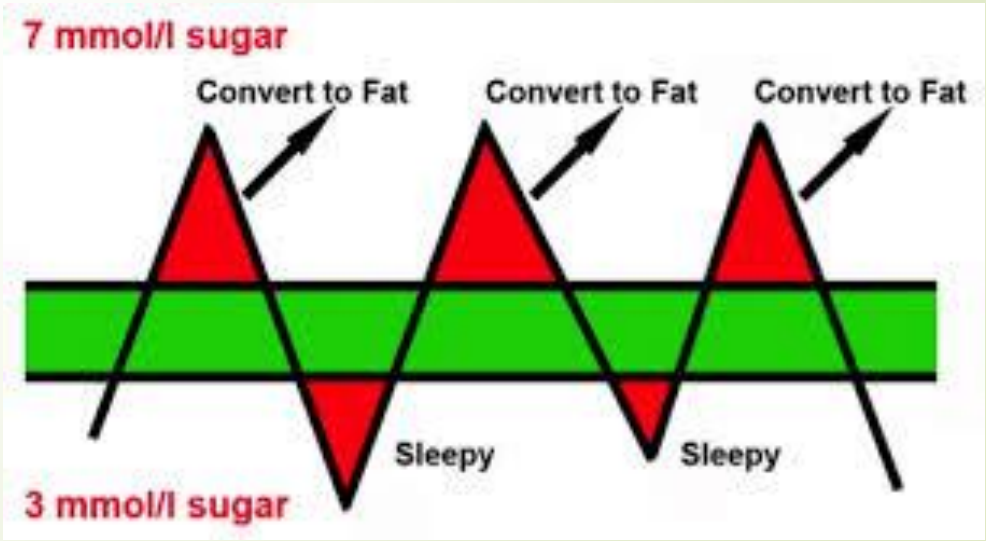
DIET AND GLYCEMIC CONTROL

- The glycemic index measure how quickly ingested carbs are broken down into simple sugars and absorbed into the blood stream.
- The glycemic index is affected by the fat, fiber and other substances in the food as well as the type of carbohydrate found in the food.
- Overall foods with a high glycemic index are undesirable as these foods are quickly broken down and load the blood up with sugar.
- Diets consisting of high glycemic index foods, and without fiber and nutrients may increase the risk of developing dysglycemia.

THE GLYCEMIC INDEX – VIRTUES AND LIMITATIONS

- Low glycemic index foods are desirable as they are digested and assimilated slowly and do not “spike” the blood sugar to a dramatic degree.
- Breads, cereals, sugar, candy, and sweetened drinks have high glycemic indices,
- fruits, vegetables, beans, and nuts have low glycemic indices.
- Dairy products and meats, because of their fat content, also have low glycemic indices.





DON'T BE DUPED BY GLYCEMIC INDEX ALONE

- Some very unhealthy fried and fatty foods have low glycemic indices because fat lowers the glycemic index.
- High fat foods may appear falsely healthy in terms of glycemic index alone,
- And some high glycemic index foods, such as carrots or a slice of watermelon, may not really be so unhealthy after all, because they offer so many antioxidant nutrients having protective and health promoting effects.

MAKING PRACTICAL USE OF THE GLYCEMIC INDEX IN THE DAILY DIET

- The point is to avoid a diet that consists exclusively of the highest glycemic index foods: sugar, bread, rice, potatoes…..
- Especially when excluding fresh fruits and vegetables.
- It is important to consider the diet more broadly then looking at the glycemic index alone.
- Avoid “empty calories”, poor quality fats, and foods lacking redeeming nutritional value.

MAKING PRACTICAL USE OF THE GLYCEMIC INDEX IN THE DAILY DIET

- Because fiber and specific nutrients in fresh fruits and vegetables improve insulin resistance, amongst numerous other health benefits their consumption is encouraged.
- My own diet counseling with patient aims to figure out ways to eat 8-10 fresh whole fruits and veggies, than being a slave to the concept of glycemic index.

MAKING PRACTICAL USE OF THE GLYCEMIC INDEX IN THE DAILY DIET

- Although the long list of the glycemic indices of foods the follows is interesting and useful to providing an awareness, the bottom line of what to do with the information is not to add up all the numbers of various fruit and vegetable combinations of every meal.
- Further more, you do not need to avoid fruits and vegetables that you like because they have a higher glycemic index than other produce.

HIGH GLYCEMIC INDEX FOODS AND INSULIN RESISTANCE

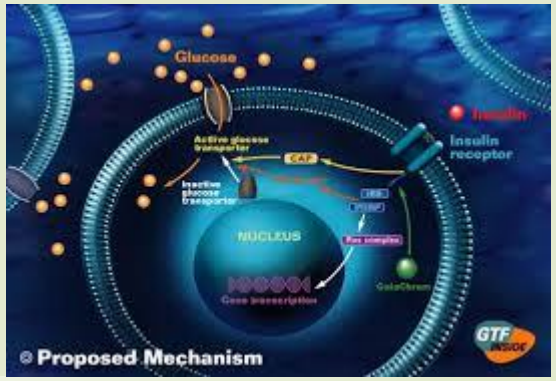
- The glycemic index of most commonly consumed foods has been worked out over the last 30 years by ingesting a precise quantity of a single food, determined to deliver 50 grams of carbohydrates, and then testing the blood sugar several times over the following 2 or 3 hours.

- Foods that cause a large and rapid increase in blood sugar are said to have a high glycemic index.

- Foods that raise the blood sugar to a lesser degree, or that elevate the blood sugar very gradually as the sugars are teased out of the fiber or broken down slowly due to the complexity of the carbohydrate are said to have a low glycemic index.

HIGH GLYCEMIC INDEX FOODS AND DYSGLYCEMIA

- The repeated ingestion of foods with a high glycemic index may contribute to the development of diabetes, obesity and insulin resistance, and certainly worsen the conditions over time.
- When the blood sugar rises, the body responds by releasing insulin from the pancreas to help move the sugar into cells.
- When the insulin receptors on the outer cell membranes are constantly bombarded with insulin, “down regulation” of insulin receptors and impaired signal transduction may ensue.



HIGH GLYCEMIC INDEX FOODS AND DYSGLYCEMIA

- Down regulation involves a decrease in the number of insulin receptors and/or a decrease in the responsiveness of the receptors to insulin.
- Thus, frequent consumption of starchy or sugary refined carbohydrates sets up a domino cascade of physiologic response that over time contribute to diabetes and insulin resistance.
- Unabsorbed glucose in the bloodstream cells causes more insulin to be secreted by the pancreas.
- The cells become inundated with insulin and become less responsive still, creating a vicious cycle of insulin insensitivity.

LEGUMES TO LOWER THE GLYCEMIC INDEX OF WHOLE MEALS

- Even thought Legumes contain a lot of carbohydrate, they have a low glycemic index.
- Legumes are also high in fiber and good quality protein, both of which serve to blunt the glycemic index.
- Legumes also contain saponins, a group of steroid-like molecules credited with an ability to lower elevated blood glucose and cholesterol.

- Legumes also contain *pinnitol*, a relative of *D-Chiro-inositol* noted to improve insulin resistance. Many clinical trials have shown legumes to benefit diabetics, anyone with high cholesterol, and those with hormonal imbalances.

J Med Food. 2004 Spring;7(1):67-78. *Saponins from edible legumes: chemistry, processing, and health benefits.* Shi J, Arunasalam K, Yeung D, Kakuda Y, Mittal G, Jiang Y

LEGUMES TO LOWER THE GLYCEMIC INDEX OF WHOLE MEALS

- **Basing the diet around low glycemic index foods, especially when legumes are included has been shown to improve glucose control in diabetics.**

Diabetes Care 1999;22:10-18. *Improved glycemic control and lipid profile and normalized fibrinolytic activity on a low-glycemic index diet in type 2 diabetic patients.* Jarvi AE, Karlstrom BE, Granfeldt YE, et al.

GLYCEMIC INDEX AND GLYCEMIC LOAD

- In general, an effort should be made to limit foods with high glycemic indices, especially in a large quantity and without high fiber, and high nutrient foods to go along it.
- However, if someone loves a food with a high glycemic index, it doesn't mean that you can never enjoy it, but rather that you must take care to not consume it often and to aim to eat only a small portion of it combined with foods having a high fiber content and lower glycemic indices at the same meal whenever possible.

GLYCEMIC INDEX CALCULATIONS

- High Glycemic Index - 70 and higher
- Moderate Glycemic Index - 50-70
- Low Glycemic Index - below 50

GLYCEMIC INDEX AND GLYCEMIC LOAD

- The glycemic index of a food can be tempered by the quantity in which it is consumed - sometimes mathematically calculated as the *glycemic load*.
- For example, a piece of candy might have a very high glycemic index, but if you just eat the one little piece (not that we are encouraging it), it won't result in a high glycemic load on the body.
- A meal, on the other hand, of two pieces of white toast, jam, hash brown potatoes, and sugar or corn syrup sweetened fruit drink for breakfast, it is both a high glycemic index meal AND puts a high glycemic load.
- Aim to consider the whole big picture of the entire diet.

GLYCEMIC INDICES OF COMMONLY CONSUMED FOODS

Compiled from a number of websites.

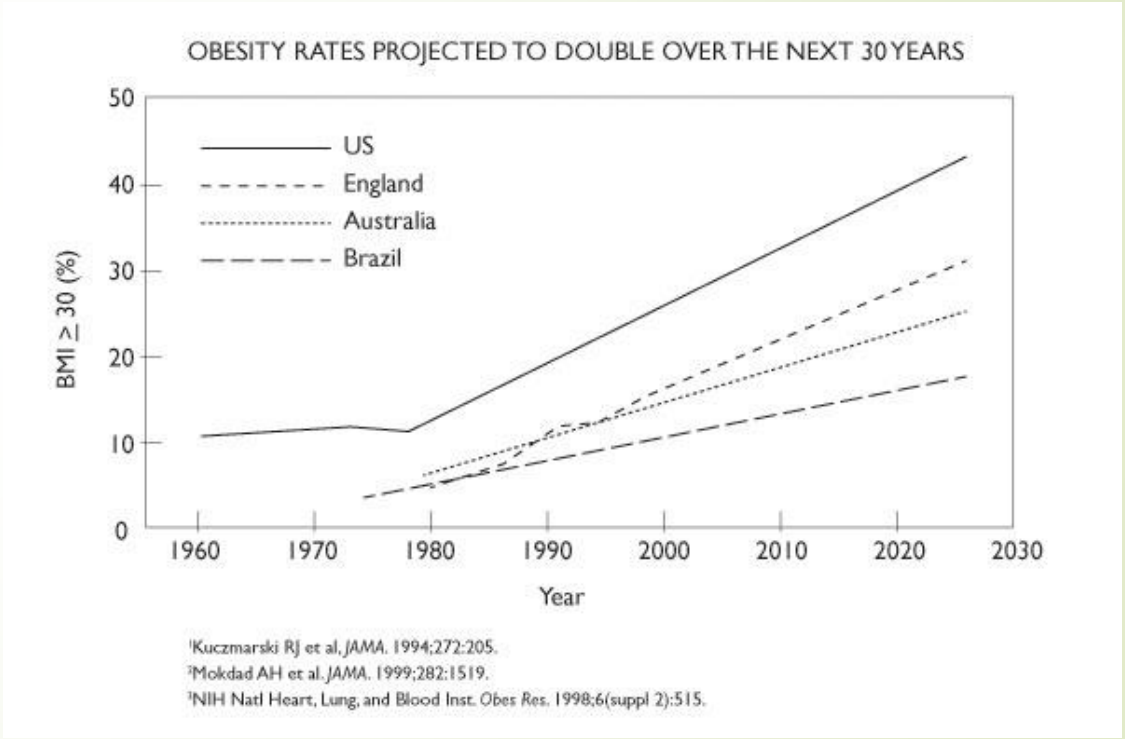
When different sites gave different values for the same food,

the figure was averaged.

www.uwex.edu/ces/flp/conference/handouts/Rakel_GLYCEMIC INDEX, www.mendosa.com.gilists/htm, http://www.montignac.com/en/ig_tableau.php

SWEETENERS

	GLYCEMIC INDEX
Corn Syrup	115
Glucose	100
Rice Syrup	100
Table Sugar (Sucrose)	65
Honey	58
Maple syrup	54
Fructose	19
Agave Nectar	10
Stevia	0



- image from steviafirst.com

BREADS AND GRAIN PRODUCTS

Rice Bread	100
Cooked cornmeal/Polenta	98
Taco shells	97
Baguettes	95
Rice Cakes	81
Corn tortillas	78
Donuts	76
White Bread	70
Croissants	70
Whole Wheat Bread	69
Burger and hot dog buns	67
Pancakes	67
Kamut Flour	54
Rye Bread	50
Quinoa Bread	50
Whole grain Pumpernickel	45
Sprouted grain bread	45
Corn Tortillas	44
Pasta, whole grain	44
Pumpernickel	40
Quinoa flour	40
Sprouted Grain Breads	35
Wheat germ	15

CEREALS

Instant Oats	92
Puffed Rice	85
Corn Flakes	83
Rice Crispies	82
Cheerios	74
Grape nuts	67
Oatmeal	54
Oat bran	15

WHOLE GRAINS (and Pseudo Grains)

- White Rice 90
- Instant Rice 86
- Wild Rice 81
- Whole Corn Kernels 78
- Oatmeal 77
- Millet 71
- Cornmeal 70
- Cooked Bulghar Wheat 67
- Couscous 65
- Brown Rice 55
- Buckwheat 54
- Whole Wheat 48
- Whole Rye 35
- Whole Amaranth 35
- Whole Quinoa 35
- Whole Barley 25
- Sprouted Wheat 25
- Sprouted Barley 15

SNACKS

Rice Cakes	84
Soda Crackers	74
Corn chips	72
Chocolate Bar	68
Rye Crisp Crackers	67
Popcorn	55
Potato Chips	54

NUTS and SEEDS

Chestnuts	60
Peanut butter	40
Tahini	40
Sesame Seeds	35
Sunflower Seeds	35
Cashews	24
Almonds	15
Hazelnuts/Filberts	15
Pistachios	15
Pine nuts	15
Peanuts	14
Walnuts	14
Sprouted Seeds	10

- Although nuts are high fat foods, often averaging around 50% fat, the fat is of a healthy unsaturated type that is beneficial to consume in small quantities.
- One study on walnuts showed their consumption to improve insulin response, adiponectin and sex hormone binding globulin levels, and eating almonds to reduce elevated androgens.

Eur J Clin Nutr. 2011 Mar;65(3):386-93. *Differential effects of walnuts vs almonds on improving metabolic and endocrine parameters in PCOS*. Kalgaonkar S, Almario RU, Gurusinghe D,

BEANS

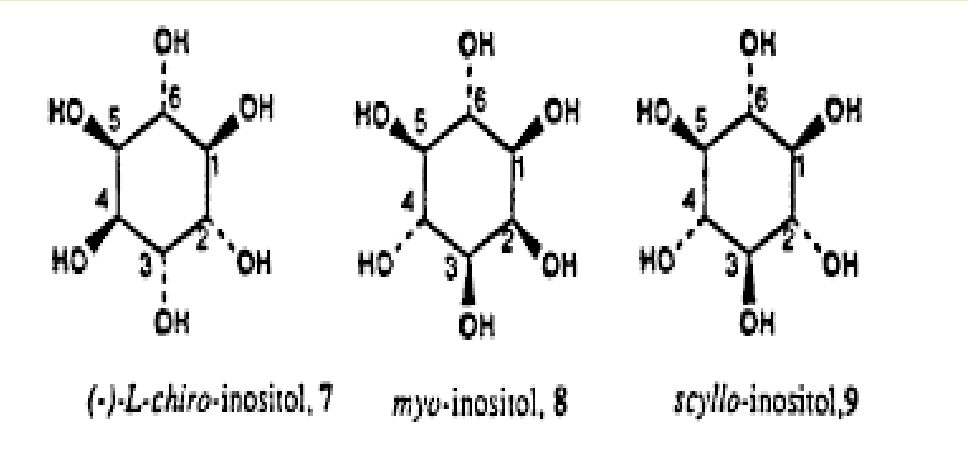
- Split Peas 45
- Fava beans 40
- Canned Refried Beans 38
- Adzuki beans 35
- Black Beans 35
- White Beans 35
- Hummus 35
- Garbanzos 33
- Kidney beans 32
- Sprouted Lentils 30
- Lentils 29
- Mung Beans 25
- Soy beans 18
- Green Beans 15
- Bean sprouts 15
- Tempeh 15
- Tofu 15
- Carob powder 15

LEGUMES FOR DYSGLYCEMIA

- **Regular consumption of legumes is recommended, as beans are high in complex carbohydrates, fiber, and saponins, all of which are of value for diabetics.**

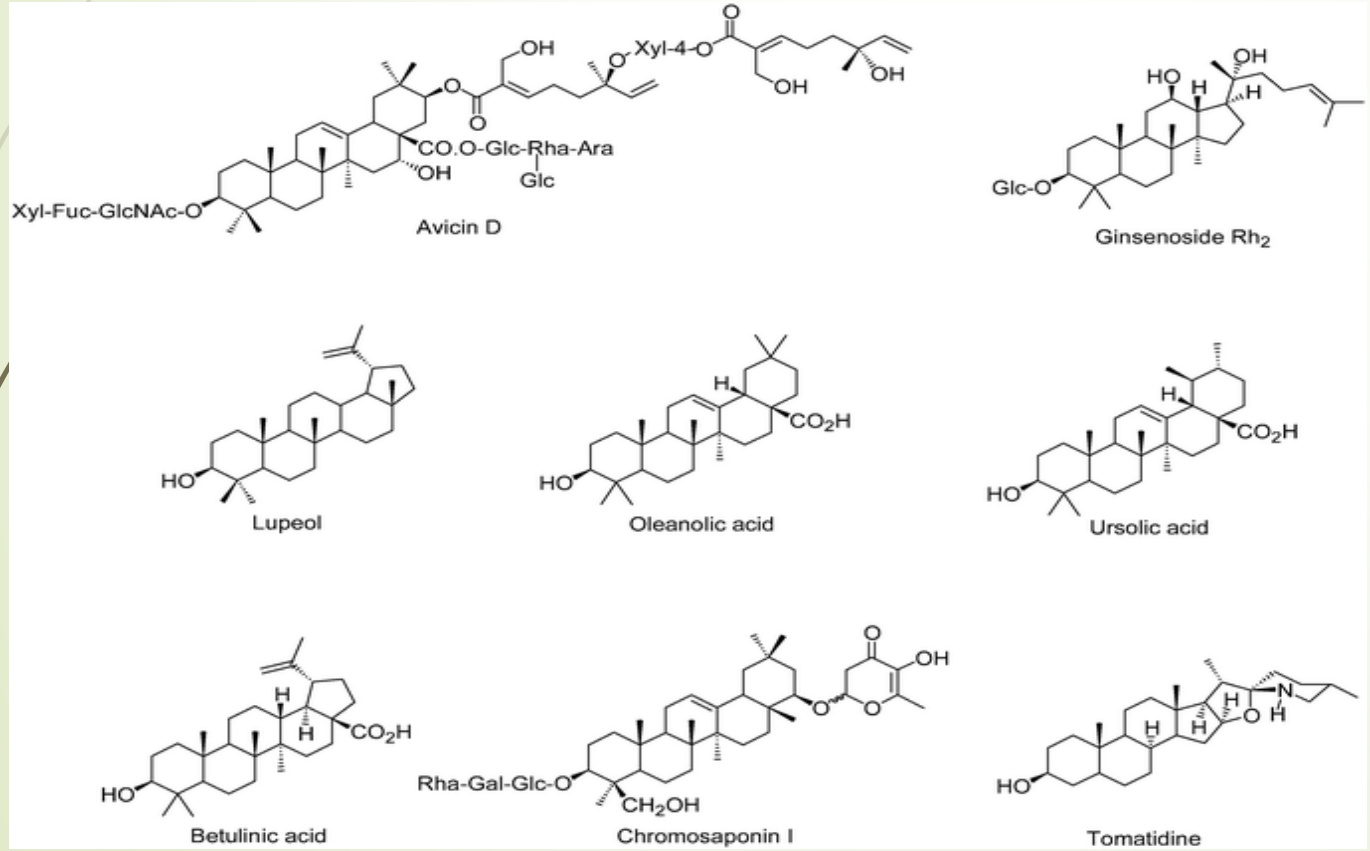
Lancet, 1981, i pp 1-5, *A high carbohydrate leguminous fiber diet improves all aspects of diabetic control*
Simpson, Simpson, and Lousley

- **Legumes are also high in magnesium and D-Chiro-Inositol, two substances of great value for insulin resistance and women with PCOS.**



LEGUMES FOR DYSGLYCEMIA

Saponins in legumes lower both blood fats and sugar.



- **J Med Food.** 2004 Spring;7(1):67-78. *Saponins from edible legumes: chemistry, processing, and health benefits.* Shi J, Arunasalam K, Yeung D, Kakuda Y, Mittal G, Jiang Y.
- **Protocol J of Bot Med**,Vol 1, Num 3 "*Antidiabetic plants and their active constituents*", Marles, RJ, Farnsworth, NR
- **Am J Clin Nutr.,** 1980, 33, pp 1,729-33 *Diabetic diets: high carbohydrate combined with high fiber.* Jenkins, D., WoleverT., Bacon, S.,

VEGETABLES

Potatoes, baked	100
Potatoes, boiled	84
Carrots, cooked	80
Squash	75
Rutabaga	72
Beets, cooked	64
Pumpkins	64
Corn	55
Sweet Potatoes	54
Parsnips	52
Yam	51
Peas	44
Tomato Sauce	35
Coconut	35
Carrots, raw	30
Beets, raw	30
Bean Sprouts	25
Artichoke	15
Celery	15
Broccoli	15
Cauliflower	15
Cucumber	15
Eggplant	15
Green beans	15
Lettuce	15
Snow Peas	15
Bell Peppers	15
Tomatoes	15
Zucchini	15
Summer Squash	15
Radishes	15
Arugula	15
Asparagus	15
Mushrooms	15
Asparagus	15

FRUITS

- Watermelon 90
- Dates 70
- Pineapple 66
- Raisins 64
- Canned Fruit in Syrup 60
- Apricots 57
- Strawberries 56
- Papaya 55
- Mango 55
- Orange Juice 54
- Banana 51
- Persimmons 50
- Grapes 46
- Orange 43
- Apple Juice 42
- Plum 39
- Apple 36
- Pear 35
- Pomegranates 35
- Stewed Apples, Applesauce 35
- Passion fruit 35
- Nectarines 35
- Most Dried Fruits 35
- Tangerines 30
- Peach 28
- Grapefruit 25
- Blackberries 25
- Blueberries 25
- Raspberries 25
- Gooseberries 25
- Cherries 22
- Rhubarb 15

DAIRY PRODUCTS and ALTERNATIVES

Rice Milk	84
Coconut Milk	40
Soy Milk	36
Chocolate Milk	34
Low Fat Fruit Yogurt	33
Skim Milk	32
Almond Milk	30
Oat milk	30
Cottage Cheese	30
Whole Milk	27

Beverages

Beer	110
Soda Pop	80
Mango Juice	55
Cranberry Juice (Unsweetened)	50
Orange juice	45
Grapefruit juice	45
Carrot Juice	40
Tomato Juice	35
1/2 water, 1/2 Juice drinks	20
Water	0
Herbal Teas	0

The Consumption of Simple Sugars

- The advent of processed sugars is a relatively new phenomena and the average consumption has increased dramatically with each generation for the past several hundred years.
- Sucrose and other simple sugars can be as much as 15% of the overall diet, and even higher for some people.
- The use of high fructose corn syrup has also increased significantly in the last generation or two alone.
- A single soda may have some 10 tsp of sugar in it, often in the form of high fructose corn syrup.

- Some sources have estimated the annual consumption of high fructose corn syrup per capita to be well over 60 pounds!
- There is a clear correlation between the consumption of simple sugars such as sucrose and purified fructose and the development of diabetes.

AGES – Advanced Glycation End Products

- Advanced glycation end products (AGE) form naturally when many foods are cooked at high temperatures or industrially processed.
- AGEs contribute to diabetes and insulin resistance.
- A high-AGE diet in animals damages the pancreas and kidneys and shortens the lifespan.
- AGEs are especially formed when foods are fried, broiled and roasted compared with the water-based cooking methods of poaching, steaming, boiling, and stewing.

Diabetes Metab (Paris)
2001, 27, 535-542

REVIEW

ADVANCED GLYCATION END PRODUCTS, THEIR RECEPTORS AND DIABETIC ANGIOPATHY

J.L. WAUTIER (1), P.J. GUILLAUSSEAU (2)

SUMMARY - The role of chronic hyperglycemia in the development of diabetic microvascular complications and in neuropathy has been clearly established by intervention studies. However, the biochemical or cellular links between elevated blood glucose levels, and the vascular lesions remain incompletely understood. This review focuses on the consequences of hyperglycemia on the formation of advanced glycation end-products (AGEs), and on the role of AGEs and of their specific receptors (RAGE) in the functional and anatomical alterations of the vascular wall. AGEs are formed during the Maillard reaction by the binding of aldoses on free NH_2 groups of proteins, which, after a cascade of molecular rearrangements, result in molecules of brown color and specific fluorescence. Experimental studies have indicated that the binding of AGEs to RAGE activates cells, particularly monocytes and endothelial cells. Activated endothelial cells produce cytokines, and express adhesion molecules and tissue factor. The role of AGEs in increased oxidative stress, and in the functional alterations in vascular tone control observed in diabetes, in part related to a reduction in nitric oxide, is also discussed. The microvascular retinal, glomerular and nerve lesions induced by experimental diabetes in animals are prevented by an inhibitor of AGEs formation, aminoguanidine. The administration in diabetic animals of recombinant RAGE, which hinders AGEs-RAGE interaction, prevents hyperpermeability and vascular lesions. These data suggest a central role of AGEs and RAGE in the development of chronic complications of diabetes.

Key-words: diabetic angiopathy, hyperglycemia, advanced glycation end-products, receptor for advanced glycation end-products (RAGE), glycoxidation.

RÉSUMÉ - **Produits de la glycation avancée et angiopathie diabétique.**
Les mécanismes responsables des lésions micro et macrovasculaires et nerveuses observées au cours du diabète sucré ont fait l'objet de multiples hypothèses, la majorité d'entre elles essayant d'établir un lien entre l'hyperglycémie et l'angiopathie. Les travaux récents mettent l'accent sur le rôle délétère des produits de la glycation avancée (AGEs), conséquence de l'hyperglycémie. Lors de la réaction de Maillard ou glycation, les oses se lient au NH_2 libre des lysines puis une succession de réactions d'oxydation et de réarrangements moléculaires aboutit aux AGEs. La liaison des AGEs à leur récepteur spécifique (RAGE), entraîne une activation cellulaire en particulier endothéliale et macrophagique, qui produit des cytokines et du facteur tissulaire. Les AGEs sont ainsi à l'origine de formes réactives de l'oxygène et provoquent des modifications du contrôle du tonus vasculaire. Les lésions vasculaires observées chez les animaux diabétiques peuvent être prévenues par des inhibiteurs de la formation d'AGEs ou en empêchant l'interaction AGE-RAGE par l'injection de RAGE recombinant. L'ensemble de ces faits expérimentaux suggère le rôle central des AGE dans le déterminisme de l'angiopathie diabétique.

Mots-clés : angiopathie diabétique, hyperglycémie, produits de la glycation avancée, récepteurs des produits de la glycation avancée (RAGE), glyco-oxydation.

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Received : May 30th, 2001

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AGES – Advanced Glycation End Products

- Glycation or glycosylation involves the fusion of proteins to sugars in foods.
- While these substances smell and taste great, they may contribute to inflammatory processes in the body.
- When the blood sugar is already high, the consumption of glycation products may be particularly disease promoting.
- Furthermore when antioxidant nutrients in the body are low, AGE products may be even more damaging.
- Therefore consuming antioxidant nutrients such as Vitamin C, Vitamin E, and Beta carotene, which happens naturally when eating a diet rich in whole fresh vegetables, may help reduce the harmful effects of eating foods cooked at high temperatures.

Including Raw Foods in the Diet

- Raw Food enthusiasts point to research on advanced glycation products produced by cooking foods as one of many reasons to eat more raw foods.
- Cooking of foods destroys many enzymes and breaks down some of the more heat sensitive vitamins such as vitamin C.
- Frying foods of course adds to the fat content of the meal.
- Cooking foods also promotes the formation of cancer-forming agents in many meats when they are barbecued or roasted.

SNEAKY SUGARS

In an attempt to not put "sugar" on the ingredient list of a product label, some manufacturers will use a long list of synonyms. Watch out for these words as they are all various forms and guises of sugar.

- Dextrin, Dextrose, Maltodextrin
- Malt, Barley Malt, Maltose
- Corn Syrup, Corn Sweetener
- Evaporated Cane Juice
- Fructose, High Fructose Corn Syrup
- Invert Sugar, Raw Sugar, Turbinado sugar, Cane Sugar
- Lactose, Xylose, Sucrose, Saccharose
- Rice Syrup
- Agave Nectar

GET RID OF THE SODA POP RIGHT NOW!

- A 10 ounce can of soda contains the equivalent of about 10 packets of sugar
- A 20 ounce bottle around 17-20 packets of sugar
- Gulping down one of the super-sized monster drinks provides the equivalent of 30 or 40 packets of sugar!

- Soft drink consumption has increased dramatically in the last several decades beginning with widespread ad campaigns of the 1960s.
- Consumption of soda and sugar laden "fruit" drinks and punches are associated with an increased risk of obesity.

J Am Diet Assoc. 2007 Jun;107(6):924-34; *Regular sugar-sweetened beverage consumption between meals increases risk of overweight among preschool-aged children.* Dubois L, Farmer A, Girard M, Peterson K.

CLINICAL STUDIES ON SODA POP

- **A study on the prevalence of obesity in the state of California reported that those who drink soda at all (occasionally) are 15% more likely to be obese than people who drink no soda.**
- **Those who drink 1 or more sodas each day are 27% more likely to be obese than those who drink no soda.**
- **One study linked the consumption of soda in the African-American preschool aged population to obesity.**
- **Soda pop consumption is also linked to an increased risk of dental cavities in children.**

- **Policy Brief UCLA Cent Health Policy Res**. 2009 Sep;(PB2009-5):1-8. *Bubbling over: soda consumption and its link to obesity in California*. Babey SH, Jones M, Yu H, Goldstein H.
- **Obesity (Silver Spring).** 2009 Jun;17(6):1262-8. *Obesity and sugar-sweetened beverages in African-American preschool children: a longitudinal study*. Lim S, Zoellner JM, Lee JM, Burt BA, Sandretto AM, Sohn W, Ismail AI, Lepkowski JM.
- **Gen Dent.** 2003 Jan-Feb;51(1):30-6. *Soft drink consumption and caries risk in children and adolescents*. Shenkin JD, Heller KE, Warren JJ, Marshall TA.

A HIGH FIBER DIET (HFD)

- A high fiber intake is highly recommended to help slow the uptake of sugars into the blood stream and blunt the glucose curve.
- *Guar gum* and *pectin* fibers have a positive effect on blood sugar control.
- *Pectin* is found in the cell walls of all types of fruits and vegetables.
- *Guar gum* is a fiber extracted from algae and seaweed, and commonly used in the food industry as thickener and stabilizing agent.

- One study found consuming from 14 to 26 grams of guar per day resulted in a lowered insulin requirement and a reduced amount of sugar spilled over into the urine in human diabetic subjects.

Gut. 1983 September; 24(9): 798–802. *Effect of acarbose, pectin, a combination of acarbose with pectin, and placebo on postprandial reactive hypoglycaemia after gastric surgery.* P A Speth, J B Jansen, and C B Lamers

WHY CUT DOWN ON THE REFINED CARBS?

- Carbohydrates turn into sugar in the body and sugar requires insulin to enter cells. Reducing your intake of refined carbohydrates can reduce the sugar load in the body and improve insulin sensitivity.
- Carbohydrates contribute every bit as much to the accumulation of fat in the body as eating fat itself.
- Carbohydrates contribute to high cholesterol every bit as much as eating fat or cholesterol itself.
- Studies have shown that eating a low refined carbohydrate diet can help you lose more weight than an indiscriminate calorie restricted diet.

The High Carbohydrate High Fiber Diet (HCF)

- The High Carbohydrate High Fiber Diet (HCF) has been shown to be more advantageous than simple fiber supplementation.
- Don't be fooled by the name. This "High Carbohydrate" diet doesn't mean a high bread diet; it means a high complex carbohydrate diet, meaning lots of vegetables.
- While the HCF is more stringent than the diets recommended by the ADA, it is also more effective.

50 FIBER-RICH FOODS

THIS LIST IS FOR INFORMATIONAL AND ENTERTAINMENT PURPOSES ONLY AND IS NOT MEANT TO BE A SUBSTITUTE FOR MEDICAL ADVICE, DIAGNOSIS, OR TREATMENT.

FRUITS

Prunes	7.7 g per cup
Pear	5.1 g
Mango	3.3 g
Apple	3.3 g
Raspberries	8 g per cup
Raw blackberries	3.8 g per half cup
Raw strawberries	3.3 g per cup
Raisins, seedless	5.4 g per cup

BREADS

Rye	5.6 g for 2 slices
Bran flakes	5.2 g per cup
Wheat bread	5.2 g for 2 slices

NUTS & SEEDS

Almonds	3.5 g per oz (24 nuts)
Pistachios	3 g per oz (47 nuts)
Peanuts	4.6 g per 2 oz (56 nuts)
Walnuts	4 g per 2 oz (30 halves)
Pecans	5.4 g per 2 oz (40 halves)

LEGUMES

Navy beans	19 g per cup	Lima beans, cooked	6.6 g half cup
Pinto beans, cooked	15.4 g per cup	Split peas, cooked	16.3 g per cup
Kidney beans	13 g cup		
Baked beans, canned	5.2 g half cup		
Lentils, cooked	7.8 g half cup		
Black beans, cooked	7.5 g half cup		

MEALS & CANNED FOOD

Half cup bean with ham soup	19 g
One cup whole wheat pasta and a half cup broccoli	9 g
Tomato paste, canned	5.4 g per half cup
Pumpkin, canned	13 g per half cup

Chart from www.doctoroz.com

The High Carbohydrate High Fiber Diet (HCF)

- The carbohydrate portion of this diet must be of the very best quality and does not refer to sugars or processed starches.
- The carbohydrate portion of this dietary regimen is intended to be comprised of whole foods, not flours, breads, and refined vegetable or cereal grain starches.

- The HCF recommends that 70 to 75% of calories come from whole vegetables, fruits, and grains,
- 15-20% from protein,
- 5-10% from fat,
- and that 15-20 grams of fiber per day be included.

Linum ussitatissimum and Plantago Seeds

- Psyllium and Flax seeds are high in fiber and help control blood glucose and blood lipids, mainly via a mechanical mechanism where emptying of the stomach is slowed and glucose curves are blunted because sugars, fats and calories are simply trapped in the fiber bolus.
- Replacing some of the flour in recipes with wheat germ, flaxseed meal, oat bran etc. will increase the nutritional profile and fiber content of the recipe and lower the glycemic index of the food.

BREAD/CRACKER SUBSTITUTE

- 1/2 cup raw sunflower seeds
- 1/2 cup raw pumpkin seeds
- 1/2 cup raw whole almonds
- 1 1/2 cups old fashioned oats
- 4 TBS chia seeds
- 1/4 cup psyllium husks
- 1 tsp salt
- 1 tsp pepper and/or spices
- 1/4 cup coconut oil, melted
- 1 TBS maple syrup
- 1 1/2 cups water

Let sit several hours or overnight, then bake 45 minutes and 325. Slice and freeze, toast individual pieces when ready to eat.

FLAXSEED MEAL
Linum usitatissimum

- **Flax seeds contain good quality essential fatty acids and the seed coat is high in lignans, credited with their own health benefits for heart disease, and metabolic syndrome.**

- **Nutr Rev.** 2010 Oct;68(10):571-603. *Dietary lignans: physiology and potential for cardiovascular disease risk reduction*. Peterson J, et al.
- **Nutrition.** 2008 Jan;24(1):23-30. *Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial.* Dodin S, et al
- **Appl Physiol Nutr Metab**. 2009 Apr;34(2):89-98.*A randomized controlled trial of the effects of flaxseed lignan complex on metabolic syndrome composite score and bone mineral in older adults.* Cornish SM, et al

FLAX SEEDS AND FLAX MEAL

- Flax seeds have help lower elevated blood glucose and cholesterol in Type II Diabetics.

- Flax lignans are also credited with many anti-cancer and hormonal balancing effects.

- PLoS One. 2007 Nov 7;2(11):e1148. *Effects of a flaxseed-derived lignan supplement in type 2 diabetic patients: a randomized, double-blind, cross-over trial.* Pan A, et al
- Br J Nutr. 2008 Jun;99(6):1301-9. *Dietary flaxseed lignan extract lowers plasma cholesterol and glucose concentrations in hypercholesterolaemic subjects.* Zhang W, et al.
- Br J Nutr. 2010 Apr;103(7):929-38. *Health effects with consumption of the flax lignan secoisolariciresinol diglucoside.* Adolphe JL, rt al.

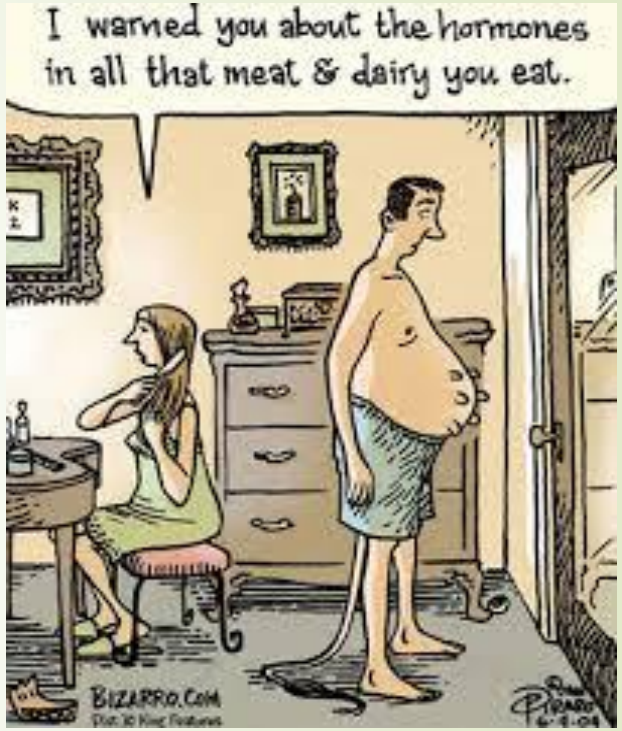
Plantago lanceolata and ovata
Psyllium seeds and seed powder

Plantago lanceolata and ovata
Psyllium seeds and seed powder

HORMONAL INFLUENCES ON GLYCEMIC CONTROL

GROWTH HORMONES AND DYSGLYCEMIA

- Animal products may be high in hormones such as GH as cattle are supplemented aiming to produce more milk, lay more eggs, or reach profitable weight more quickly.
- These hormones remain in the meat and milk and have hormonal effects in the humans when consumed, and contribute to the hormonal load in the body.
- Some states allow the use of GH and some states have banned the use of hormones in dairy cattle.

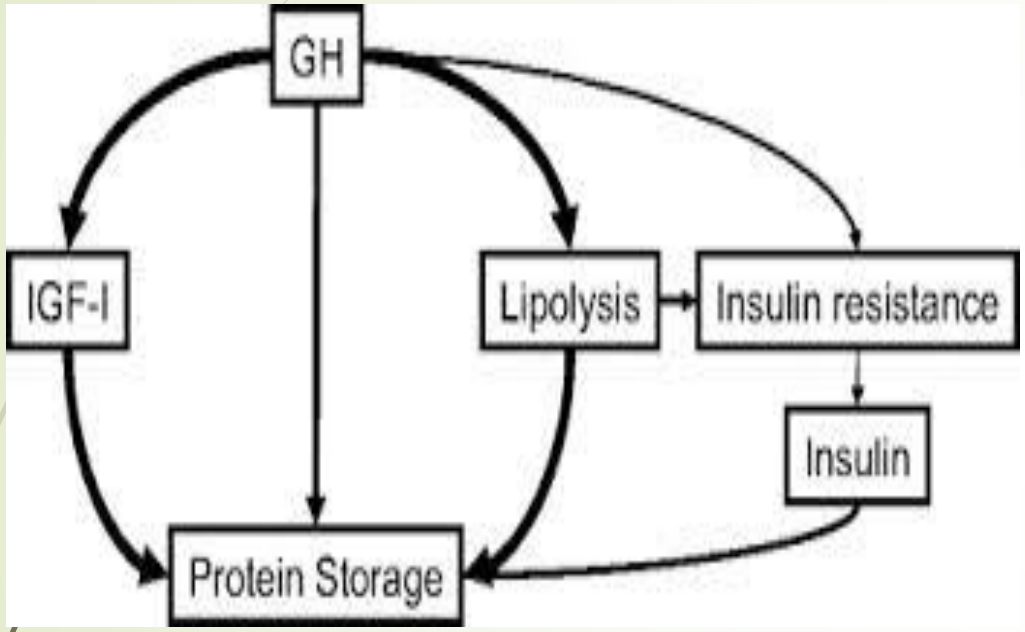


Int J Cancer. 2011 Jun 29. doi: 10.1002/ijc.26265. *Milk, dairy intake and risk of endometrial cancer: A twenty six-year follow-up.* Davaasambuu G, Cui X, Feskanich D, Hankinson SE, Willett WC.

Growth hormones

- In 1993, the FDA approved recombinant bovine growth hormone (rBGH), a synthetic cow hormone that spurs milk production when injected into dairy cows.
- Farmed Fish are also given growth hormones.
- By itself, rBGH has no discernible *acute* effect in humans
- Of greater concern is that manipulating growth hormones in animals and fish cows promotes *insulin-like growth factor* (IGF), which may reach up to 10 times more IGF than other milk.

GROWTH HORMONES AND IGF



- **Higher blood levels of IGF from ingested meat, farmed fish, eggs, and diary products has been associated with an increased risk of insulin resistance and diabetes.**
- **IGF is also associated with an increased risk of breast, prostate, and other cancers in humans.**
- **In a 2004 study, patients with above-average IGF levels had nearly a 50% higher risk of prostate cancer and a 65% higher risk of hormone-dependent premenopausal breast cancer than people with below-average levels.**

Int J Cancer. 2014 Jun 1;134(11):2683-90. *Insulin-like growth factor I and risk of breast cancer by age and hormone receptor status-A prospective study within the EPIC cohort.* Kaaks R1, ET AL.

GROWTH HORMONES AND DYSGLYCEMIA

Endocrine, vol. 6, no. 1, 47–52, February 1997 0969–711X/97/6:47–52/$9.50

Human Growth Hormone Fragment ($hGH_{44–191}$) Produces Insulin Resistance and Hyperinsulinemia but Is Less Potent than the 22 kDa hGH in the Rat

Manthinda Hettiarachchi, Allan Watkinson, Kin-Chuen Leung, Yagya N. Sinha, Ken K. Y. Ho, and Edward W. Kraegen

Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, NSW Australia

A 17 kDa fragment of human growth hormone (22 kDa hGH), identified as $hGH_{44–191}$, has lower binding affinity for growth hormone receptors (GHRs), but has been reported to be more potent in producing glucose intolerance in yellow obese mice. Our aim was to investigate this anomaly by comparing acute development of hyperinsulinemia and insulin resistance ("diabetogenic activity") during $hGH_{44–191}$ or 22 kDa hGH infusion in normal rats. Fasted awake male rats (350–370 g) were infused via a carotid cannula with saline (CON), 22 kDa hGH (at 0.125 μg/min), or $hGH_{44–191}$ (at 0.64 or 0.32 μg/min) for 5.75 h. Over the last 2 h, a euglycemic hyperinsulinemic clamp (insulin infusion rate 0.25 U/kg/h) was performed. After 3.75 h infusion, 22 kDa hGH at 0.125 and $hGH_{44–191}$ at 0.64 μg/min produced basal (preclamp) hyperinsulinemia compared to CON. During the clamp, insulin resistance was consistently produced by 22 kDa hGH at 0.125 and $hGH_{44–191}$ at 0.64 μg/min compared to CON. Using specific radioimmunoassays for 22 kDa hGH and $hGH_{44–191}$, we determined that under conditions of equivalent diabetogenic activity, molar circulating levels of $hGH_{44–191}$ were 50–60-fold higher than 22 kDa hGH. It was concluded that whereas 22 kDa hGH and $hGH_{44–191}$ are both capable of generating acute hyperinsulinemia and insulin resistance in the normal rat, the diabetogenic potency of $hGH_{44–191}$ is not enhanced compared to 22 kDa hGH, and that diabetogenic potency is in accord with the reported lower binding affinity of $hGH_{44–191}$ to the GHR.

Key Words: Hyperinsulinemia; glucose clamp; insulin resistance; glucose infusion rate (GIR).

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Author to whom all correspondence and reprint requests should be addressed: Dr. Edward Kraegen, Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, NSW Australia 2010. E-mail: e.kraegen@garvan.unsw.edu.au

Introduction

As well as its growth promoting activity, human growth hormone (22 kDa hGH) possesses diabetogenic activity *(1–4)*. Acute and chronic elevation of 22 kDa hGH have been shown to cause insulin resistance and hyperinsulinemia in humans and animals *(1–4)*. It has also been demonstrated that different fragment forms of hGH exist in humans in addition to the 22 kDa form *(5)*, and that these exhibit varying degrees of diabetogenic activity *(5–6)*.

One particular fragment of hGH, $hGH_{44–191}$, which is devoid of 43 amino acid residues from the amino terminal end, has recently been demonstrated not only to exist in the human pituitary gland and serum *(7)*, but also to be 10 times more potent in causing glucose intolerance in yellow obese mice compared to the 22 kDa form *(8)*. Paradoxically, in a recent study by Rowlinson et al. *(9)*, comparing the in vitro binding affinities of $hGH_{44–191}$ with 22 kDa hGH to the growth hormone receptor (GHR), it was found that $hGH_{44–191}$ had a much lower binding affinity for GHRs. Furthermore, the lower binding affinity was in accord with lower growth promoting activity of $hGH_{44–191}$ in vitro as well as in vivo *(8)* compared to 22 kDa hGH. The authors, therefore, thought that the apparent anomaly of greater diabetogenic activity, but lower GHR binding of $hGH_{44–191}$ compared with 22 kDa hGH should be investigated. This would provide information as to the likelihood or otherwise that the diabetogenic action of $hGH_{44–191}$ was mediated via GHR binding.

Therefore, in this study the aim was to compare the diabetogenic activity of infusions of $hGH_{44–191}$ and 22 kDa hGH in chow-fed rats by examining effects on the basal insulin level and also on insulin sensitivity with the euglycemic hyperinsulinemic clamp.

Materials and Methods

Experimental Animals

All surgical and experimental procedures performed were approved by the Garvan Institute of Medical Research, St. Vincent's Hospital Animal Experimentation Ethics

REVIEW ARTICLE

Drug Safety 2002; 25 (3): 199-212
0114-5916/02/0003-0199/$25.00/0

Growth Hormone Therapy and its Relationship to Insulin Resistance, Glucose Intolerance and Diabetes Mellitus

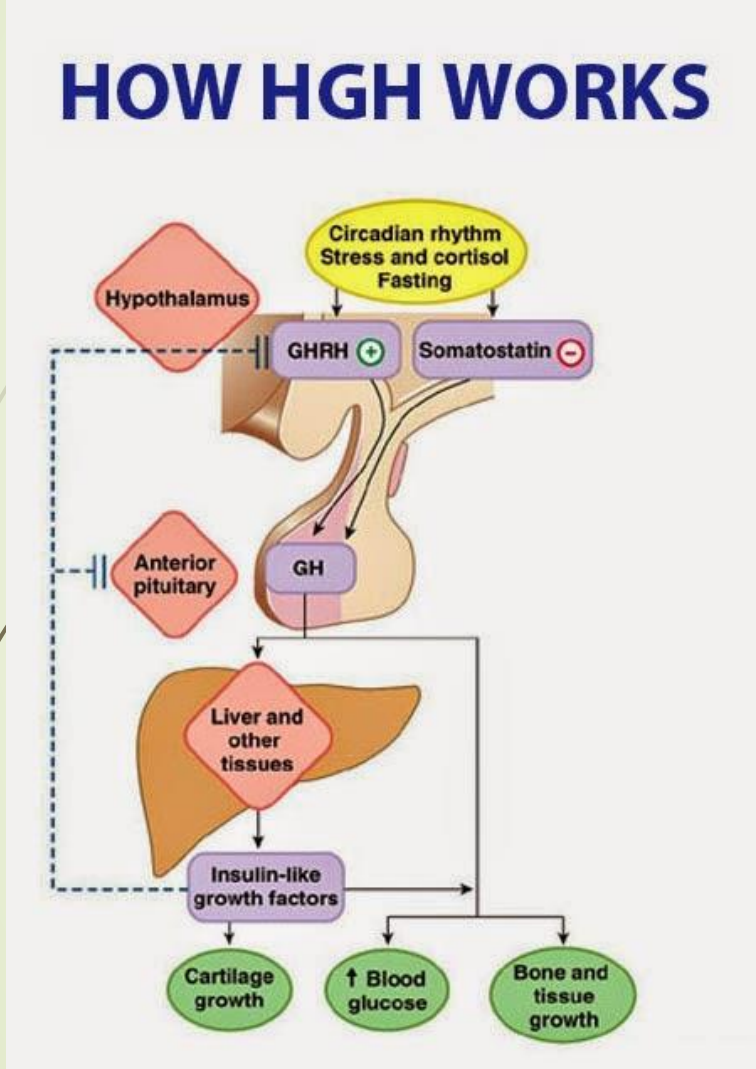
A Review of Recent Evidence

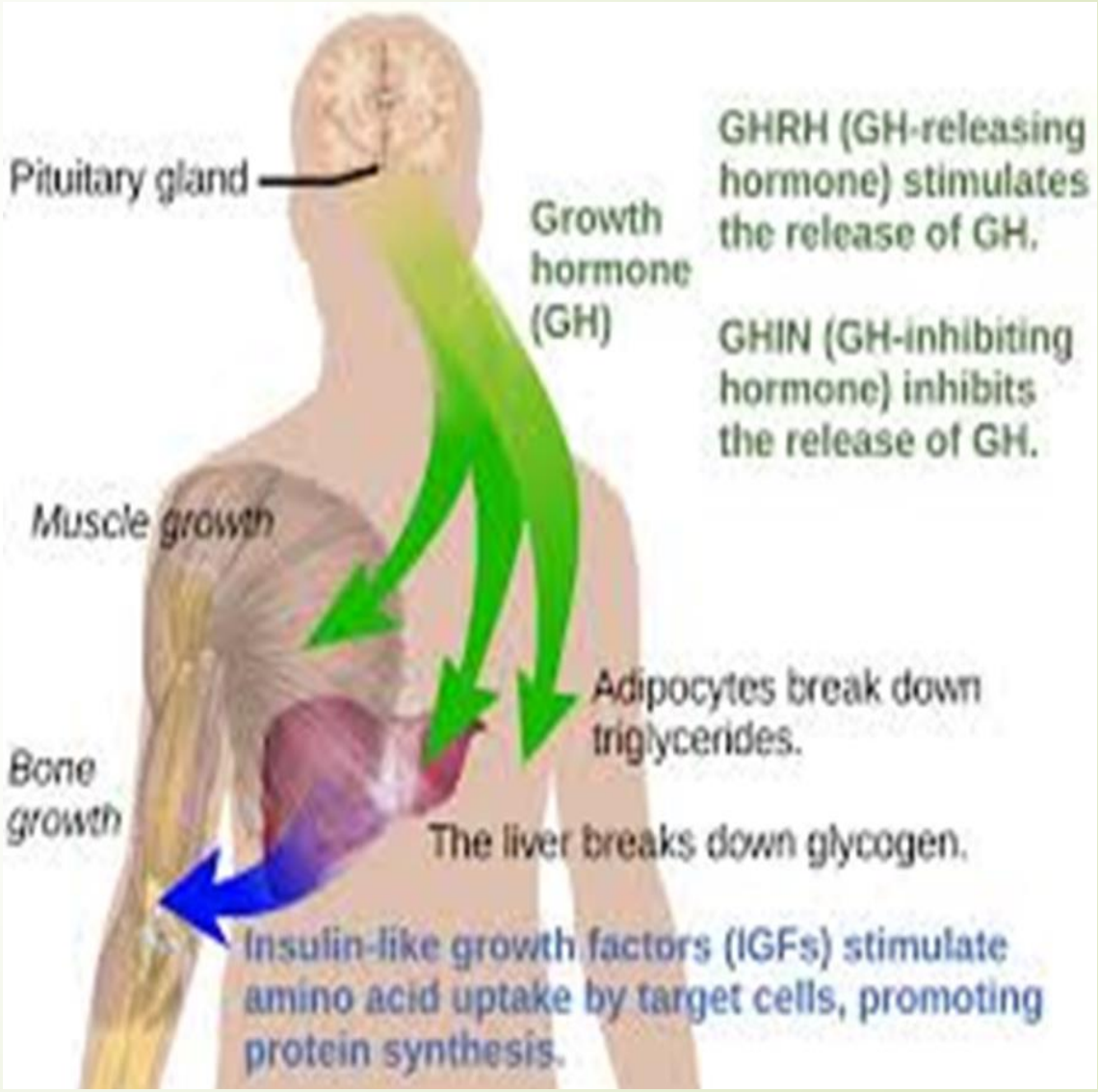
William Jeffcoate

Department of Diabetes and Endocrinology, City Hospital, Nottingham, England

Contents

GROWTH HORMONES AND DYSGLYCEMIA





GROWTH HORMONES AND DYSGLYCEMIA

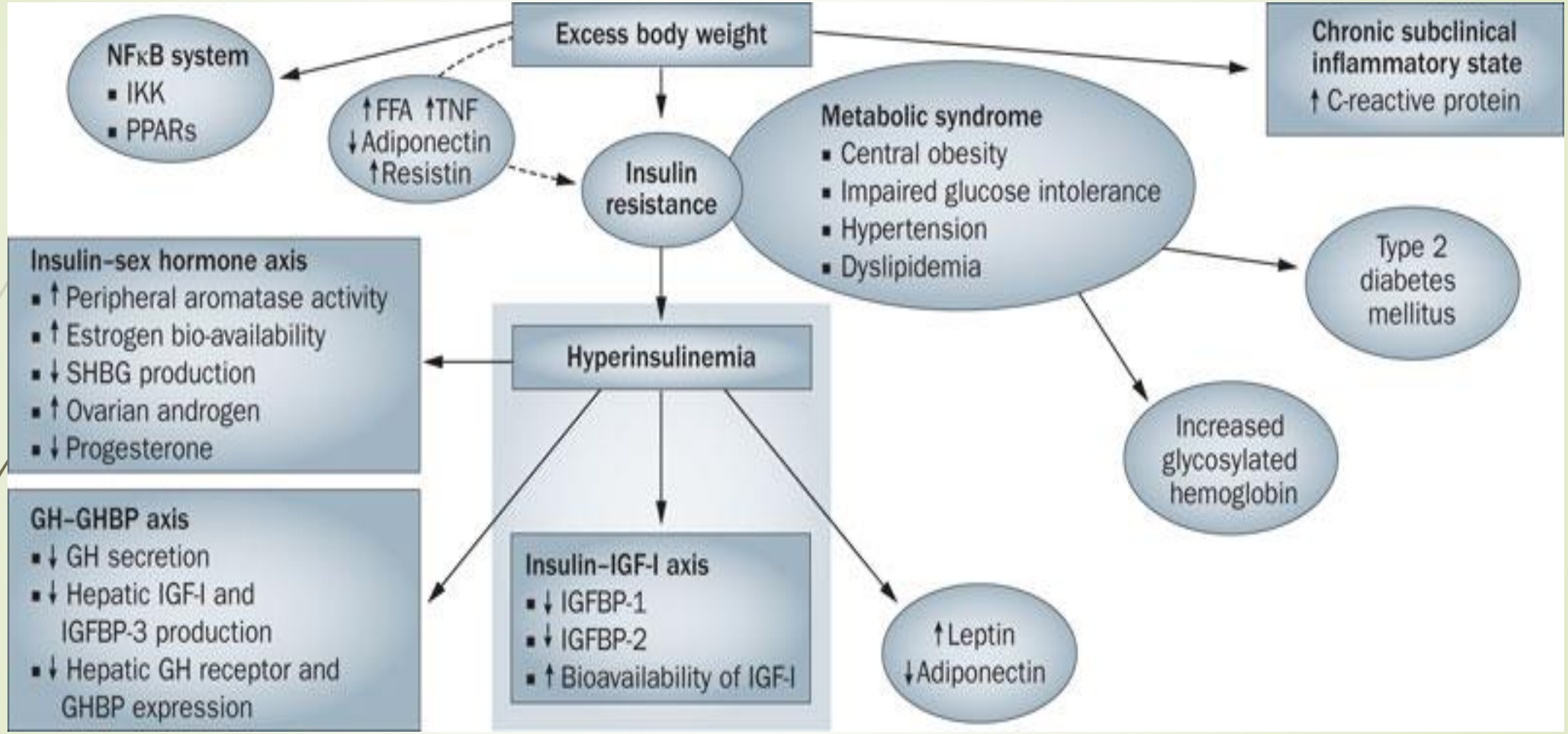


Image from www.nature.com

PESTICIDES AND HORMONE BALANCE

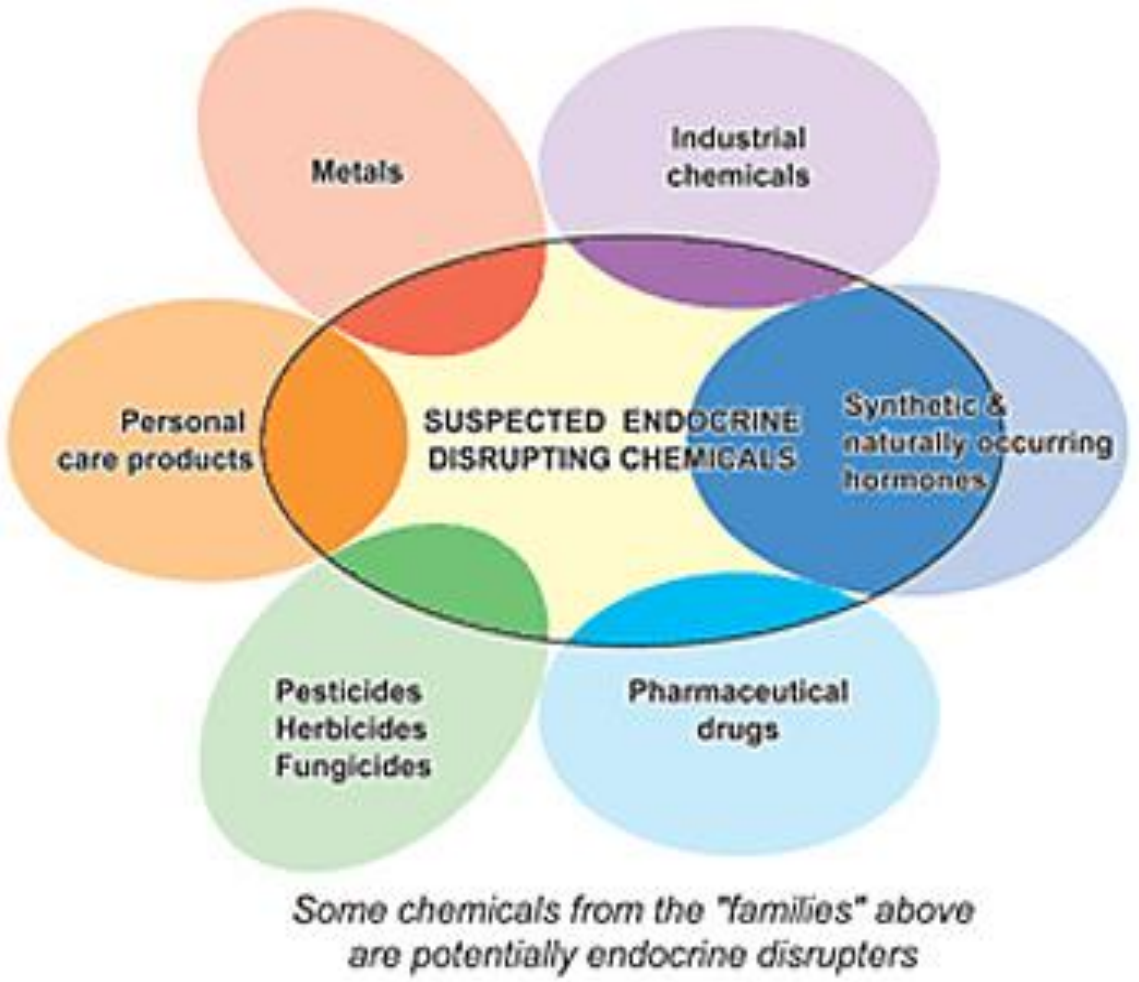
Pesticides may have hormonal effects in human tissues.

Pesticides interfere with:

- **Hormone synthesis,**
- **Hormone release and storage,**
- **Hormone transport about the body,**
- **Hormone clearance from the body,**
- **Hormone receptors, and t**
- **Thyroid function.**

- **Reprod Toxicol**. 2011 May;31(4):574-84. *Assessment strategies and decision criteria for pesticides with endocrine disrupting properties relevant to humans*. Marx-Stoelting P, Pfeil R, Solecki R, Ulbrich B, Grote K, Ritz V, Banasiak U, Heinrich-Hirsch B, Moeller T, Chahoud I, Hirsch-Ernst KI.
- **Reprod Biol Endocrinol.** 2006; 4: 30. *Pesticide exposure: the hormonal function of the female reproductive system disrupted?* Reini W Bretveld,Chris MG Thomas Paul TJ Scheepers, Gerhard A Zielhuis,

PESTICIDES AND HORMONE BALANCE



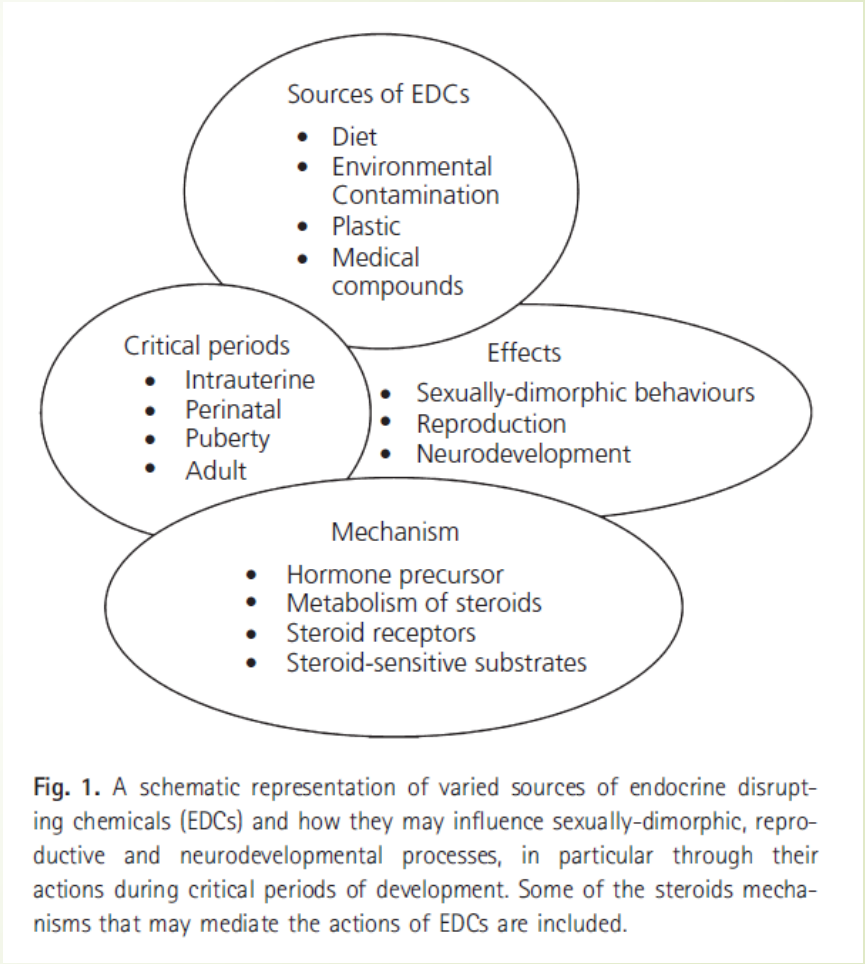


Fig. 1. A schematic representation of varied sources of endocrine disrupting chemicals (EDCs) and how they may influence sexually-dimorphic, reproductive and neurodevelopmental processes, in particular through their actions during critical periods of development. Some of the steroids mechanisms that may mediate the actions of EDCs are included.

Image from www.precisionnutrition.com

PRODUCE THAT MAY BE HIGH IN PESTICIDES

THE DIRTY DOZEN

- Peaches
- Apples
- Sweet bell peppers
- Celery
- Nectarines
- Strawberries
- Cherries
- Pears
- Imported grapes
- Spinach
- Lettuce
- Potatoes

ENDOCRINE DISRUPTORS

- Numerous environmental chemicals in addition to pesticides, bind to estrogen receptors and disrupt our reproductive and hormonal systems.

- Many man-made chemicals are "endocrine disruptors" due to the many ways that they interfere with normal endocrine and reproductive functions.

- Amphibians are especially affected as most live in chemical laden rivers, streams and wetlands.

ENDOCRINE DISRUPTORS and DIABETES

SCIENCE CHINA
Chemistry

• ARTICLES •
• SPECIAL TOPIC • Research Progress of Persistent Organic Pollutants

May 2010 Vol.53 No.5: 1003–1009
doi: 10.1007/s11426-010-0143-7

Understanding the endocrine disruption of chiral pesticides: The enantioselectivity in estrogenic activity of synthetic pyrethroids

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[1]*College of Biological and Environmental Engineering, Zhejiang University of Technology, Hangzhou 310032, China*
[2]*Key Laboratory of Environmental Remediation and Ecosystem Health, Ministry of Education; College of Environmental and Resource Sciences, Zhejiang University, Hangzhou 310029, China*

Received January 13, 2010; accepted February 22, 2010

Synthetic pyrethroids (SPs), a family of chiral insecticides consisting of multiple stereoismers, have been regarded as estrogenic endocrine-disrupting chemicals (EDCs). In this study, we applied the yeast two-hybrid and molecular docking (MD) assay to assess the enantioselective estrogenic activities of three commonly used SPs, bifenthrin (*cis*-BF), permethrin (PM) and fenvalerate (Fen). The β-galactosidase analyses indicated that all of the testing pyrethroids displayed significant ($p<0.05$) enantioselectivity. The results showed that the estrogenic potential of *cis*-BF was mainly attributed to 1*S*-*cis*-BF. Neither PM nor Fen showed estrogenic effects. However, two stereoisomers of PM possessed estrogenic potential activities. α*R*-2*R*-Fen and α*S*-2*S*-Fen also induced the β-galactosidase activity. The inability to initiate the reporter gene expression by the racemic chemicals may be due to the low ratios of these isomers or the antagonism among them. The strong hydrophobic interaction and the hydrogen bond between positive estrogenic isomers and ERα support our biological testing results. This research demonstrated that the enantioselective estrogenic activity of chiral SPs was due to selective binding between their isomers and the ERα receptor. The data suggests that enantioselectivity of these chiral pesticides is significant to their estrogenic activities.

enantioselectivity, synthetic pyrethroids (SPs), endocrine disruption, yeast, molecular docking

1 Introduction

Since the enantioselective biodegradation of organochlorine pesticide α-hexachlorocyclohexane was observed in the 1990s [1, 2], research has focused on the enantioselectivity in terms of environmental safety of chiral pesticides. Significant differences between enantiomers of synthetic pyrethroids (SPs) and organophosphates were observed in their acute toxicity to the freshwater invertebrates [3, 4]. The individual stereoisomers of chiral pesticides also induced differential effects of various chronic toxicities, including enantioselective endocrine disruption [5, 6], embryo developmental toxicity [7, 8], genotoxicity [9], cytotoxicity [9] and immunotoxicity [10]. In addition, the enantioselective reproductive toxicity of SPs in *daphnia magna* has been reported [11, 12]. Therefore, it is significant to evaluate the enantioselectivities of stereoisomers in terms of environmental safety, ecotoxicological and health risks.

Synthetic pyrethroids (SPs) are commonly used pesticides for controlling agricultural and indoor insects. Synthetic pyrethroids account for about 20% of all agricultural insecticides applied to U.S. crop lands [13], and approximately 70% of total pyrethroids used in California [14]. As the second generation of SPs with a broad spectrum of insecticidal and acaricidal activity, bifenthrin (*cis*-BF), permethrin (PM) and fenvalerate (Fen) are used to control a wide range of insect pests in a variety of applications [15]. Because all these pyrethroids contain two or three chiral

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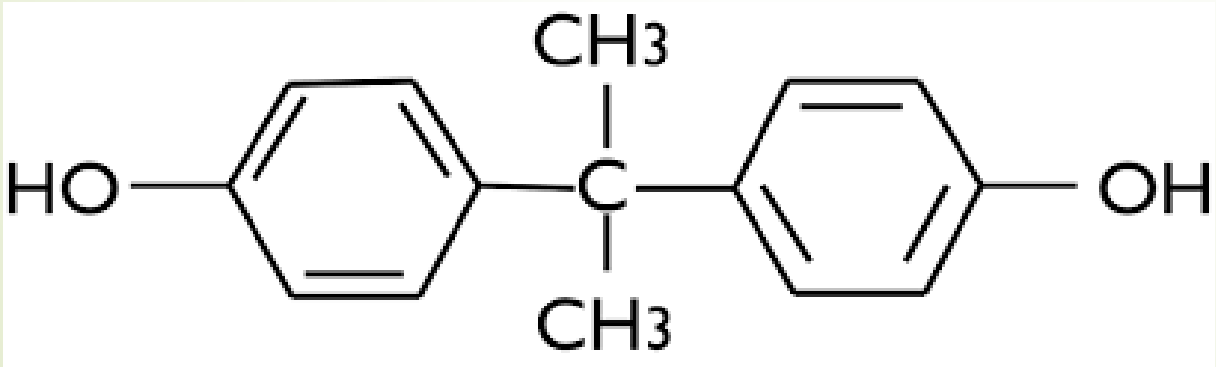
†Authors with equal contribution to this work.

REVIEWS

Endocrine disruptors in the etiology of type 2 diabetes mellitus

BISPHENOLS AND ENDOCRINE BALANCE

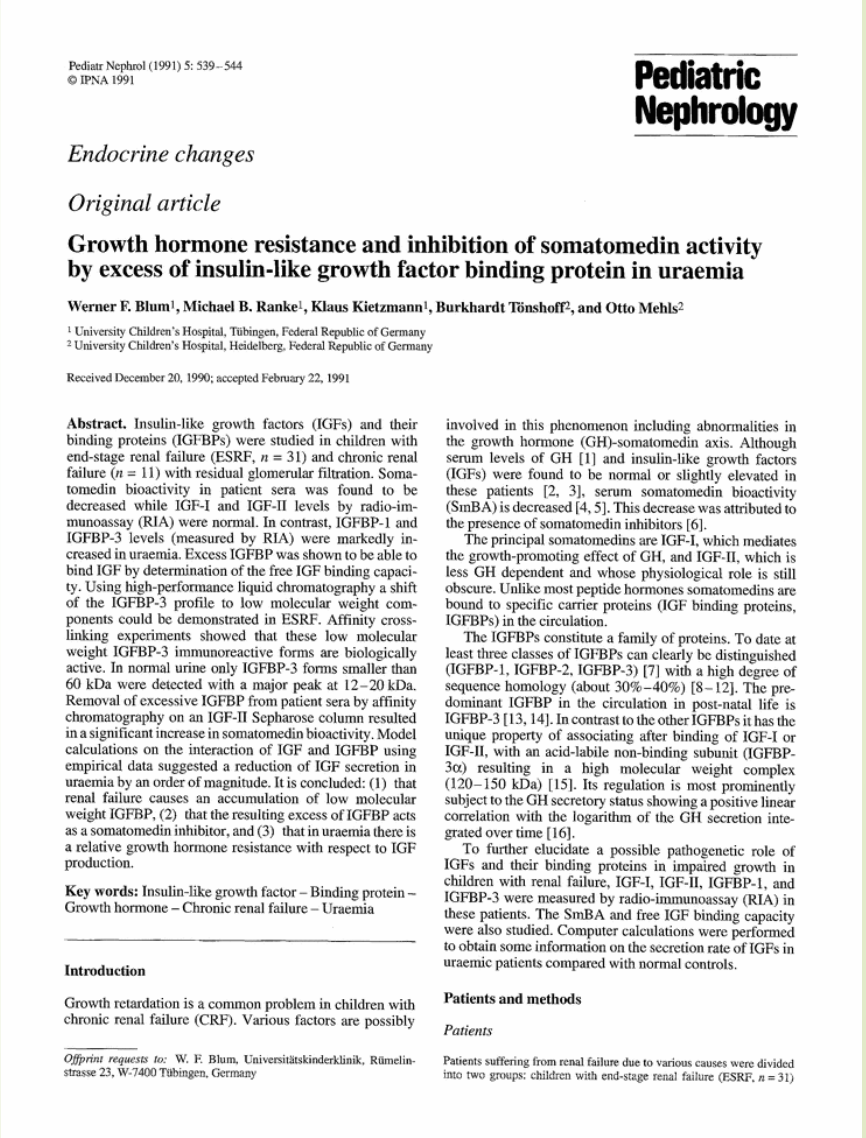
- **Bisphenols are Endocrine Disruptors and associated with PCOS.**
- **Bisphenols are a large group of chemicals and it is thought that all human beings have regular and substantial exposure.**
- **Bisphenols are known to bind to estrogen receptors.**



- **Indian J Endocrinol Metab.** 2011 Apr-Jun; 15(2): 143–144. *Endocrine disruptors: Ubiquitous, yet less known*Dilip Gude
- **Environ Health Perspect.** 2010 August; 118(8): 1055–1070. *Urinary, Circulating, and Tissue Biomonitoring Studies Indicate Widespread Exposure to Bisphenol A* Laura N. VandenbergIbrahim Chahoud, Jerrold J. Heindel, Vasantha Padmanabhan, Francisco J.R. Paumgartten,and Gilbert Schoenfelder
- **Environ Health Perspect.** 2010 September; 118(9): 1267–1272. *Bisphenol AF Is a Full Agonist for the Estrogen Receptor ERa but a Highly Specific Antagonist for ERβ* Ayami Matsushima, Xiaohui Liu, Hiroyuki Okada, Miki Shimohigashi,Yasuyuki Shimohigashi

Insulin-Like Growth Factor and Insulin Resistance

- One of the main hormones given to dairy cattle to increase milk production is IGF-1, Insulin-like growth factor. This hormone has sometimes been called an "insulin-like" hormone.
- Europe, Canada, New Zealand, Australia, and Japan have banned its use and therefore US milk and cheese cannot legally be imported to these nations.
- The consumption of IGF-1 has been linked to hormonal cancers and other hormonal imbalances.
- Consumer advocate groups have complained for decades that US labeling laws to do not require dairies or producers to label clearly when a dairy product contains added hormones.



Pediatr Nephrol (1991) 5: 539–544
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Pediatric Nephrology

Endocrine changes

Original article

Growth hormone resistance and inhibition of somatomedin activity by excess of insulin-like growth factor binding protein in uraemia

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[1] University Children's Hospital, Tübingen, Federal Republic of Germany
[2] University Children's Hospital, Heidelberg, Federal Republic of Germany

Received December 20, 1990; accepted February 22, 1991

Abstract. Insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) were studied in children with end-stage renal failure (ESRF, $n = 31$) and chronic renal failure ($n = 11$) with residual glomerular filtration. Somatomedin bioactivity in patient sera was found to be decreased while IGF-I and IGF-II levels by radio-immunoassay (RIA) were normal. In contrast, IGFBP-1 and IGFBP-3 levels (measured by RIA) were markedly increased in uraemia. Excess IGFBP was shown to be able to bind IGF by determination of the free IGF binding capacity. Using high-performance liquid chromatography a shift of the IGFBP-3 profile to low molecular weight components could be demonstrated in ESRF. Affinity cross-linking experiments showed that these low molecular weight IGFBP-3 immunoreactive forms are biologically active. In normal urine only IGFBP-3 forms smaller than 60 kDa were detected with a major peak at 12–20 kDa. Removal of excessive IGFBP from patient sera by affinity chromatography on an IGF-II Sepharose column resulted in a significant increase in somatomedin bioactivity. Model calculations on the interaction of IGF and IGFBP using empirical data suggested a reduction of IGF secretion in uraemia by an order of magnitude. It is concluded: (1) that renal failure causes an accumulation of low molecular weight IGFBP, (2) that the resulting excess of IGFBP acts as a somatomedin inhibitor, and (3) that in uraemia there is a relative growth hormone resistance with respect to IGF production.

Key words: Insulin-like growth factor – Binding protein – Growth hormone – Chronic renal failure – Uraemia

Introduction

Growth retardation is a common problem in children with chronic renal failure (CRF). Various factors are possibly involved in this phenomenon including abnormalities in the growth hormone (GH)-somatomedin axis. Although serum levels of GH [1] and insulin-like growth factors (IGFs) were found to be normal or slightly elevated in these patients [2, 3], serum somatomedin bioactivity (SmBA) is decreased [4, 5]. This decrease was attributed to the presence of somatomedin inhibitors [6].

The principal somatomedins are IGF-I, which mediates the growth-promoting effect of GH, and IGF-II, which is less GH dependent and whose physiological role is still obscure. Unlike most peptide hormones somatomedins are bound to specific carrier proteins (IGF binding proteins, IGFBPs) in the circulation.

The IGFBPs constitute a family of proteins. To date at least three classes of IGFBPs can clearly be distinguished (IGFBP-1, IGFBP-2, IGFBP-3) [7] with a high degree of sequence homology (about 30%–40%) [8–12]. The predominant IGFBP in the circulation in post-natal life is IGFBP-3 [13, 14]. In contrast to the other IGFBPs it has the unique property of associating after binding of IGF-I or IGF-II, with an acid-labile non-binding subunit (IGFBP-3α) resulting in a high molecular weight complex (120–150 kDa) [15]. Its regulation is most prominently subject to the GH secretory status showing a positive linear correlation with the logarithm of the GH secretion integrated over time [16].

To further elucidate a possible pathogenetic role of IGFs and their binding proteins in impaired growth in children with renal failure, IGF-I, IGF-II, IGFBP-1, and IGFBP-3 were measured by radio-immunoassay (RIA) in these patients. The SmBA and free IGF binding capacity were also studied. Computer calculations were performed to obtain some information on the secretion rate of IGFs in uraemic patients compared with normal controls.

Patients and methods

Patients

Patients suffering from renal failure due to various causes were divided into two groups: children with end-stage renal failure (ESRF, $n = 31$)

Offprint requests to: W. F. Blum, Universitätskinderklinik, Rümelinstrasse 23, W-7400 Tübingen, Germany

Insulin-Like Growth Factor and Insulin Resistance

AUTHOR COPY ONLY

Review

insulin resistance and cancer:
the role of insulin and IGFs

Insulin-Like Growth Factor Binding Protein-3 Induces Insulin Resistance in Adipocytes In Vitro and in Rats In Vivo

Insulin-Like Growth Factor and PCOS

- **Cattle may develop a PCOS-like disease when given hormones.**
- **The metabolic imbalances in women with PCOS may cause them to tolerate IGF-1 poorly and regular exposure to the hormone may contribute to cyst formation.,**
- **Women with PCOS have been found to have higher levels of IGF-1 than other women.**

- **Anim Reprod Sci. 1999** Aug 16;56(3-4):211-22. *Insulin resistance: the link between metabolic disorders and cystic ovarian disease in high yielding dairy cows?* Opsomer G, Wensing T, Laevens H, Coryn M, de Kruif A
- **J Clin Endocrinol Metab**. 2007 Jul;92(7):2726-33. *Insulin and insulin-like growth factor stimulation of vascular endothelial growth factor production by luteinized granulosa cells: comparison between polycystic ovarian syndrome (PCOS) and non-PCOS women.* Stanek MB, Borman SM, Molskness TA, Larson JM, Stouffer RL, Patton PE.
- **Gynecol Endocrinol**. 2011 Feb;27(2):86-90. *Serum and follicular fluid levels of IGF-II, IGF-binding protein-4 and pregnancy-associated plasma protein-A in controlled ovarian hyperstimulation cycle between polycystic ovarian syndrome (PCOS) and non-PCOS women.* Zhong G, Chen B.
- **Sichuan Da Xue Xue Bao Yi Xue Ban**. 2006 Nov;37(6):882-5. *The relationship between leptin, insulin-like growth factor-1 (IGF-1) and hyperinsulinemia of patients with polycystic ovarian syndrome*. Xu LZ, Li R, Sun ZJ, Han DW, Qiu DS.

Insulin-Like Growth Factor and PCOS

Arch Gynecol Obstet (1987) 241: 33–35

Archives of Gynecology and Obstetrics

Insulin-like Growth Factor-Binding Protein PP12 in Ovarian Cyst Fluid

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[1] Department I of Obstetrics and Gynecology, Helsinki University Central Hospital, Helsinki, Finland,
[2] Department of Obstetrics and Gynecology, University of Pécs, Pécs, Hungary

Summary. Elevated levels of insulin-like growth factor-binding protein (IGF-bp) were recently found in the serum of patients with ovarian tumors. We studied the concentration of IGF-bp in cyst fluids of 37 women operated on for benign or malignant ovarian cysts. The levels were elevated (> 47 µg/l) in 6 of 28 benign, but in none of the nine malignant ovarian cysts. The highest IGF-bp concentration (447 µg/l) was observed in a benign serous cystadenoma.

Key words: IGF-binding protein – Placental protein 12 – Ovarian tumors

Introduction

Insulin-like growth factors (IGFs) are bound to binding proteins which appear in serum as 34K and 150K forms (D'Ercole 1985). Both are capable of binding IGF-I, and the 34K protein appears in unsaturated form in the circulation (Furlanetto 1986). Recently, Iino et al. (1986) reported elevated levels of the 34K IGF-bp, previously designated as placental protein 12 (PP12) (Koistinen et al. 1986), in the serum of 64% of patients with ovarian cancer. This prompted us to study the levels of IGF-bp in malignant and benign ovarian cyst fluids.

Material and Methods

Cyst fluid was obtained from 37 women who underwent surgery for cystic ovarian tumor(s). Twenty-eight of the cysts were benign including follicular cysts ($n = 11$), luteal cysts ($n = 2$), serous papillary cystadenomas ($n = 9$) and mucinous cystadenomas ($n = 6$). Nine of the tumors were malignant: five were serous papillary cystadenocarcinomas, three were mucinous cystadenocarcinomas, and one was a tubovillous carcinoma (Table 1).

Offprint requests to: Professor Markku Seppälä, Department I of Obstetrics and Gynecology, Helsinki University Central Hospital, SF-00290 Helsinki, Finland

Molecular Cancer

BioMed Central

Research

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Insulin-like growth factor binding protein 2 promotes ovarian cancer cell invasion

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Address: [1]Departments of Pathology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas, 77030, USA, [2]Department of Gynecologic Medical Oncology, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, Texas, 77030, USA, [3]Molecular Therapy Research Center, Samsung Medical Center, Seoul, 135–710, Korea and [4]Institute of Signal Processing, Tampere University of Technology, Tampere, Finland

Email: Eun-Ju Lee - lej1943@yahoo.com; Cristian Mircean - mirceanc@cs.tut.fi; Ilya Shmulevich - is@ieee.org; Huamin Wang - hmwang@mdanderson.org; Jinsong Liu - jliu@mdanderson.org; Antti Niemistö - ant@cs.tut.fi; John J Kavanagh - jkavanag@mdanderson.org; Je-Ho Lee* - jeholee@unitel.co.kr; Wei Zhang* - wzhang@mdanderson.org

* Corresponding authors

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Accepted: 02 February 2005

This article is available from: http://www.molecular-cancer.com/content/4/1/7

Abstract

Background: Insulin-like growth factor binding protein 2 (IGFBP2) is overexpressed in ovarian malignant tissues and in the serum and cystic fluid of ovarian cancer patients, suggesting an important role of IGFBP2 in the biology of ovarian cancer. The purpose of this study was to assess the role of increased IGFBP2 in ovarian cancer cells.

Results: Using western blotting and tissue microarray analyses, we showed that IGFBP2 was frequently overexpressed in ovarian carcinomas compared with normal ovarian tissues. Furthermore, IGFBP2 was significantly overexpressed in invasive serous ovarian carcinomas compared with borderline serous ovarian tumors. To test whether increased IGFBP2 contributes to the highly invasive nature of ovarian cancer cells, we generated IGFBP2-overexpressing cells from an SKOV3 ovarian cancer cell line, which has a very low level of endogenous IGFBP2. A Matrigel invasion assay showed that these IGFBP2-overexpressing cells were more invasive than the control cells. We then designed small interference RNA (siRNA) molecules that attenuated IGFBP2 expression in PA-1 ovarian cancer cells, which have a high level of endogenous IGFBP2. The Matrigel invasion assay showed that the attenuation of IGFBP2 expression indeed decreased the invasiveness of PA-1 cells.

Conclusions: We therefore showed that IGFBP2 enhances the invasion capacity of ovarian cancer cells. Blockage of IGFBP2 may thus constitute a viable strategy for targeted cancer therapy.

Background

Ovarian cancer is the most lethal gynecological malignancy. Indeed, epithelial ovarian cancer is detected at a late clinical stage in as much as 75% of patients, in whom the overall survival rate is a dismal 14–30% [1]. Hindering the development of effective treatments for the cancer is

Insulin-Like Growth Factor and PCOS

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Insulin-Like Growth Factor Binding Proteins in Endocrine-Related Neoplasia

Giuseppe Minniti, MD and Youngman Oh, PHD

CONTENTS

INTRODUCTION

The insulin-like growth factor binding proteins (IGFBPs) are components of the IGF signaling system, which is comprised additionally of the IGF-I, IGF-II, and insulin ligands, and a family of transmembrane receptors, including the insulin receptor (IR) and IGF-I and IGF-II receptors (IGF-IR and IGF-IIR) *(1–3)*. Six IGFBPs have been identified, cloned, and sequenced *(3–5)*. They share a high degree of similarity in their primary protein structure, particularly in their N- and C-terminal regions, which are separated by a variable midprotein segment of 55–95 amino acid residues *(5)*. IGFBPs bind IGF-I and IGF-II, but not insulin, with high affinity *(6)*, and are essential to transport IGFs, to prolong their half-lives, and to regulate the availability of free IGFs for interaction with IGFRs, thereby modulating the effects of IGFs on growth and differentiation *(6–10)*. Recent evidence indicates that some IGFBPs may themselves have direct receptor-mediated effects, independent of IGFs. A growing body of data has demonstrated that IGFBP-3 is an important growth-suppressing factor in various cell systems, through an IGF-independent mechanism *(11,12)*. In addition, the recent identification of proteins with significant similarity to IGFBPs in their N-terminal domains suggests the existence of other potential IGFBPs *(13)*. This has led to the concept of an IGFBP superfamily with high- and low-affinity members, capable of influencing cell growth and differentiation by both IGF-dependent and IGF-independent means (Fig. 1, *13–15*).

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Intraovarian IGF-I System

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As the significance of putative intraovarian regulators becomes increasingly recognized, much of the attention centers on insulin-like growth factors (IGFs). Indeed, a large body of evidence now suggests the existence of an intraovarian IGF system complete with ligands, receptors, and binding proteins. More importantly, IGFs have been shown to exert a variety of significant effects at the level of the somatic ovarian cell, raising the possibility of a meaningful in vivo role. The above notwithstanding, there is at this time no compelling evidence to indicate that IGFs (or for that matter any other putative intraovarian regulator) are indispensable to ovarian function. However, a large body of a somewhat indirect nature strongly suggests such a possibility. It is the purpose of this communication to review and summarize key developments in this area.

OVARIAN IGF-I PRODUCTION

Ovarian production of IGF-I was initially suggested by studies revealing that the immunoreactive (i) IGF-I content of porcine follicular fluid substantially exceeded that encountered in serum (1). Further evidence consisted of the demonstration of cycloheximide-inhibitable, gonadotropin-dependent (and estradiol-dependent) iIGF-I in serum-free media conditioned by cultured porcine granulosa cells (2–3). Although the rat ovarian content of iIGF-I appears to be growth hormone-dependent (4), a direct effect of growth hormone at the level of the rat granulosa cell remains to be demonstrated.

Acknowledgments: Supported in part by NIH Research Grant HD-19998 and USPHS Research Career Development Award 1-K04-HD-00697 from the NICHHD, NIH.

D. W. Schomberg (ed.), *Growth Factors in Reproduction*

AIM FOR CHEMICAL FREE LIVING

- The bottom line is that eating a clean diet, free of pesticides, hormones, and other endocrine disruptors is important to optimal endocrine balance.

- Furthermore, care should be taken in the home and wherever possible to avoid chemicals, cleaning products, garden chemicals, toxic body products, etc.

Image from www.LivingLifeChemicalFree.com

ADRENAL AND THYROID INFLUENCES ON BLOOD SUGAR CONTROL

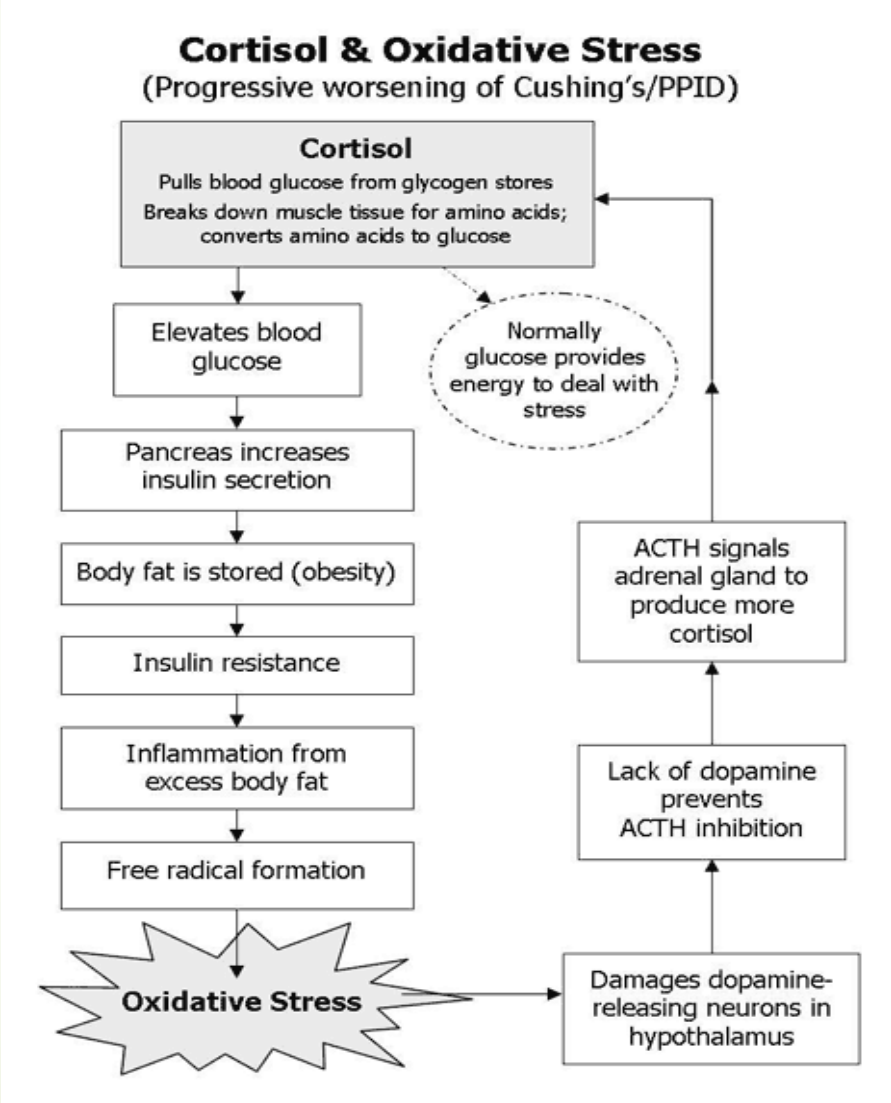
STRESS AND CONTRIBUTE TO INSULIN RESISTANCE

- Adrenergic Signals have significant influences on glucose metabolism.
- Adrenaline and stress hormones lead raise serum glucose, and elevated serum glucose, triggers insulin release.
- Constant Stress = Constant Glucose production = Constant Insulin Release…..and leads to insulin resistance.

- **Am J Physiol Endocrinol Metab**. 2014 Nov 15;307(10):E896-905.*Interleukin-6 amplifies glucagon secretion: coordinated control via the brain and pancreas.* Barnes TM1, Otero YF1, Elliott AD1, et al.

HOW STRESS PROMOTES DYSGLYCEMIA AND OBESITY

- Stress promotes the release of cortisol, which catalyzes carbohydrates and metabolizes fats to provide immediate increases in blood glucose.
- Insulin is released from pancreatic Beta cells increasing appetite.
- Stress therefore can increase oxidative load in the body and contribute to "inflammaging".



HYPOGLYCEMIA COMPLEXITIES

- Severe calorie restriction skipping meals is not necessarily helpful for losing weight or treating diabetes.
- Hypoglycemic episodes induce a surge of sympathetic activity that may contribute to vascular injury.
- Animal studies suggest that adrenoreceptor agonism contributes to thickening of the tunica intima.
- Stress can use up blood glucose, shunting circulation to the heart and muscles
- Even momentary hypoglycemia may trigger great surges in insulin, adrenalin, and cortisol release.

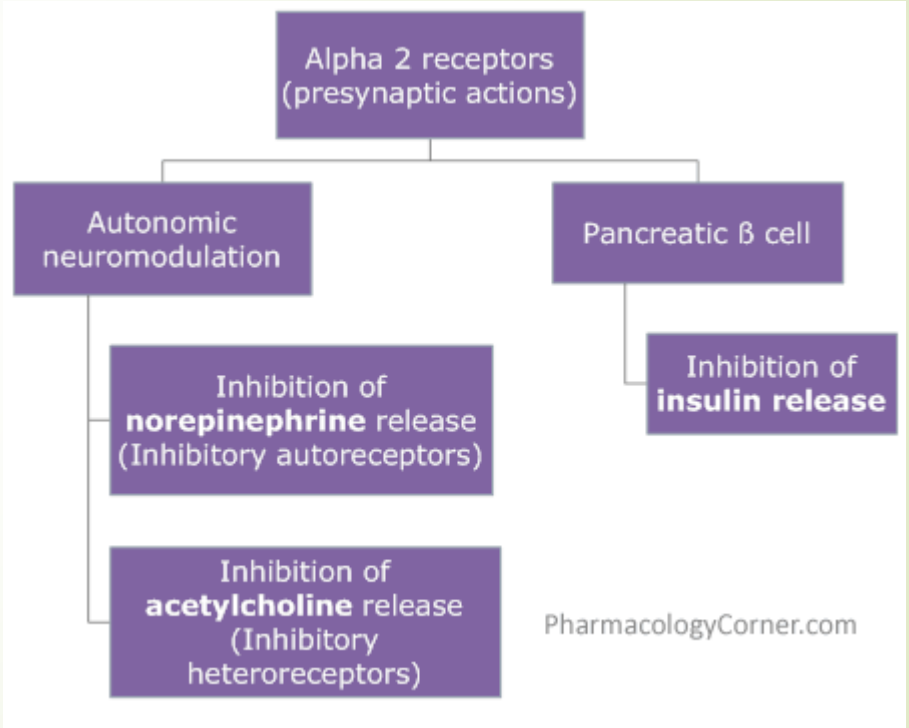
SYMPATHETIC SIGNALING AND GLYCEMIC CONTROL

- Adrenergic blockade has been shown to enhance insulin response.
- Constant stress and "sympathetic overdrive" may suppress insulin release, and contribute to hyperglycemia.
- Nervine herbs, Relaxation, Stress Reduction may therefore improve glycemic control

- **J Dev Orig Health Dis.** 2013 Oct;4(5):402-10. *Elevated plasma norepinephrine inhibits insulin secretion, but adrenergic blockade reveals enhanced β-cell responsiveness in an ovine model of placental insufficiency at 0.7 of gestation*. Macko AR1, Yates DT1, Chen X1, et al
- **Am J Physiol Endocrinol Metab.** 2014 Jan 1;306(1):E58-64. Nov 19.Enhanced insulin secretion responsiveness and islet adrenergic desensitization after chronic norepinephrine suppression is discontinued in fetal sheep. Chen X1, Green AS, Macko AR, et al.

SYMPATHETIC SIGNALING AND GLYCEMIC CONTROL

- The a(2A)-adrenoceptor has been identified as an important regulator of blood glucose homeostasis.
- a(2A)-Adrenoceptors occur on pancreatic β-cells inhibit insulin secretion,
- a(2A)-adrenoceptors occur on sympathetic nerves
- a(2A)-adrenoceptors on adrenomedullary chromaffin cells limit sympathoadrenal output. (Short Feedback Loop)



Adrenal Support Herbs to Improve Glycemic Control

- Because Stress Hormones may contribute to dysglycemia, herbs that blunt stress responses, and HPA activation may be important components of herbal formulas to treat dysglycemia.

- Herbs that help stabilized and regulate the HPA are often referred to as “Adaptogens”, the classic example being ginseng.

Image from pixgood.com

BOTANICAL ADAPTOGENS FOR IMPROVING GLYCEMIC CONTROL

Adaptogens Include the Following Readily Available Herbs:

- *Panax ginseng*
- *Eleutherococcus senticosis*
- *Withania somnifera*
- *Glycyrrhiza glabra*
- *Rhodiola rosea*

Panax ginseng
Ginseng

Glycyrrhiza glabra
Licorice

Rhodiola
Arctic Rose

***Rhodiola rosea* increases plasma β-endorphin secretion from the adrenal glands, in part due to activity at μ-opioid receptors contributing to HPA modulating and hypotensive effects.**

***Rhodiola* increases glycose transporter and regulatory gene expression in skeletal muscle in rats.**

BMC Complement Altern Med. 2014 Jan 13;14:20.
Antihyperglycemic action of rhodiola-aqeous extract in type1-like diabetic rats. Niu CS1, Chen LJ, Niu HS.

INFLAMMATION AND ABERRANT GLUCAGON CONTRIBUTES TO HYPERGLYCEMIA

- Normally glucagon initiates glucose to be produced from glycogen stores.
- Inappropriate glucagon secretion contributes to hyperglycemia in inflammatory disease.
- The proinflammatory cytokine interleukin-6 (IL-6) promotes glucagon secretion via brain signaling loops and via direct action on pancreatic islets, but only in the presence of "stressors" such as adrenaline/epinephrine.

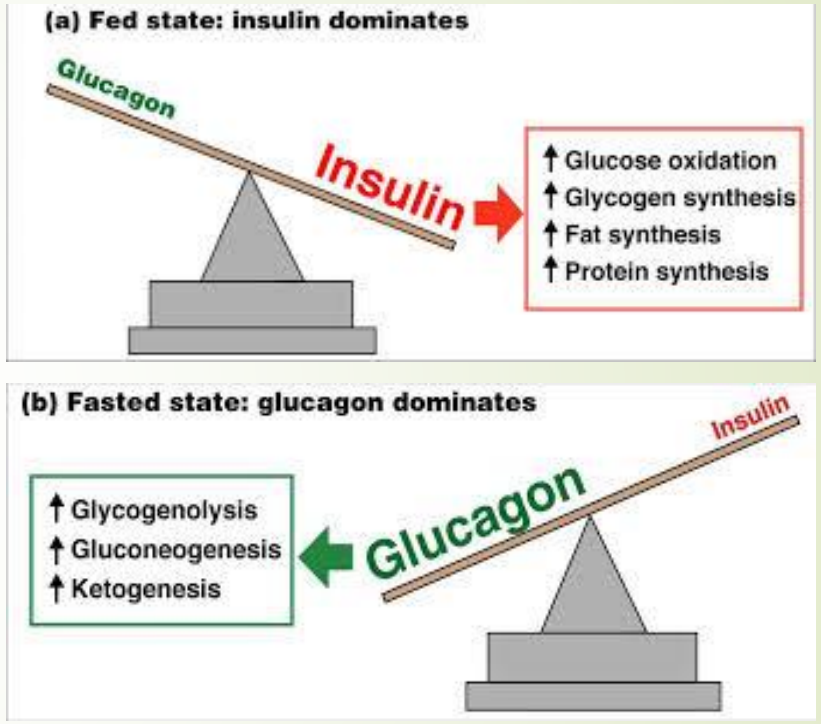


IMAGE FROM AUSTINCC.EDU

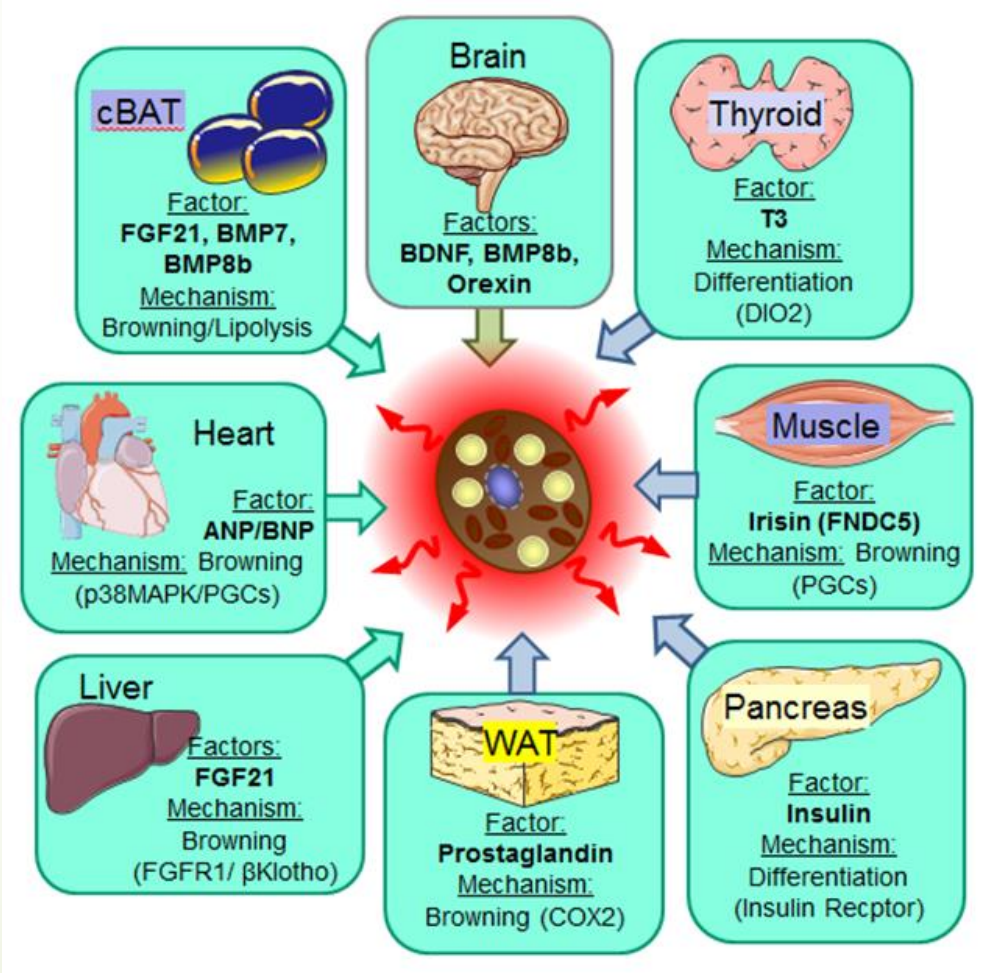
Neuroscience. 2014 Oct 10;278:20-30. *Hindbrain medulla catecholamine cell group involvement in lactate-sensitive hypoglycemia-associated patterns of hypothalamic norepinephrine and epinephrine activity.* Shrestha PK1, Tamrakar P1, Ibrahim BA1

LIVER GLYCOGEN STORES IMPORTANT TO GLYCEMIC CONTROL

- **Glucagon, a counter-regulatory hormone to insulin, serves as a regulator of glucose homeostasis and acts in response to hypoglycemia.**

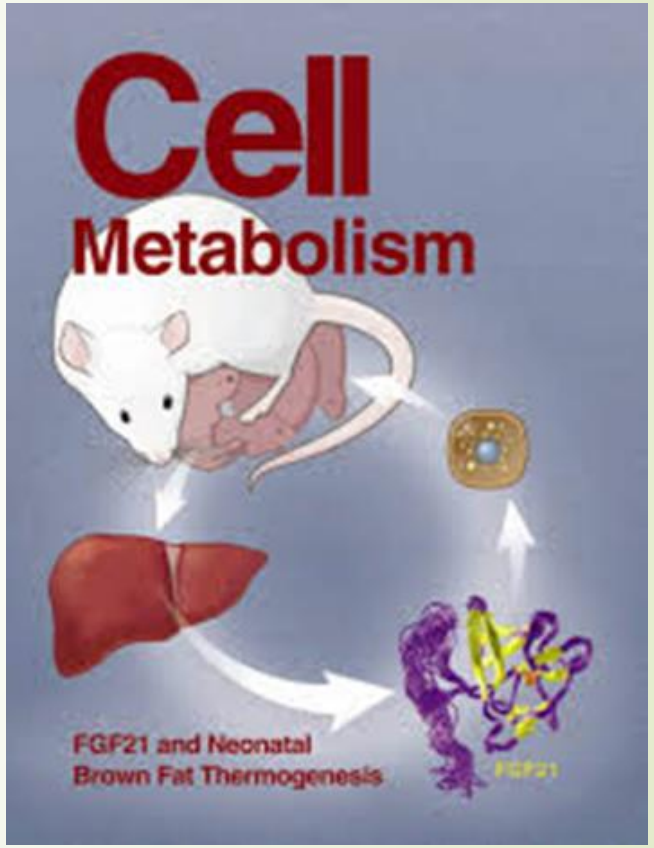
- **Earlier studies have shown that glucagon administration induces thermogenesis in experimental animal models.**

- Yin Yang Glucagon Insulin



LIVER GLYCOGEN STORES IMPORTANT TO GLYCEMIC CONTROL

- **Follow up investigations suggest that glucagon supports BMR via upregulating Fibroblast Growth Factors genes in the liver, in turn optimal carbohydrate metabolism in Brown Adipose cells.**
- **Thus Liver burden can also impair BMR.**
- **Endogenous glucagon is essential for adaptive thermogenesis and involves increasing hepatic Fgf21 production.**



Endocrinology. 2014 Sep;155(9):3484-92. *Glucagon is essential for adaptive thermogenesis in brown adipose tissue.*

LIVER SUPPORTIVE HERBS MAY BE INCLUDED IN PROTOCOLS FOR DYSGLYCEMIA

A group of herbs known as the "Alteratives" are gentle liver supportive herbs.

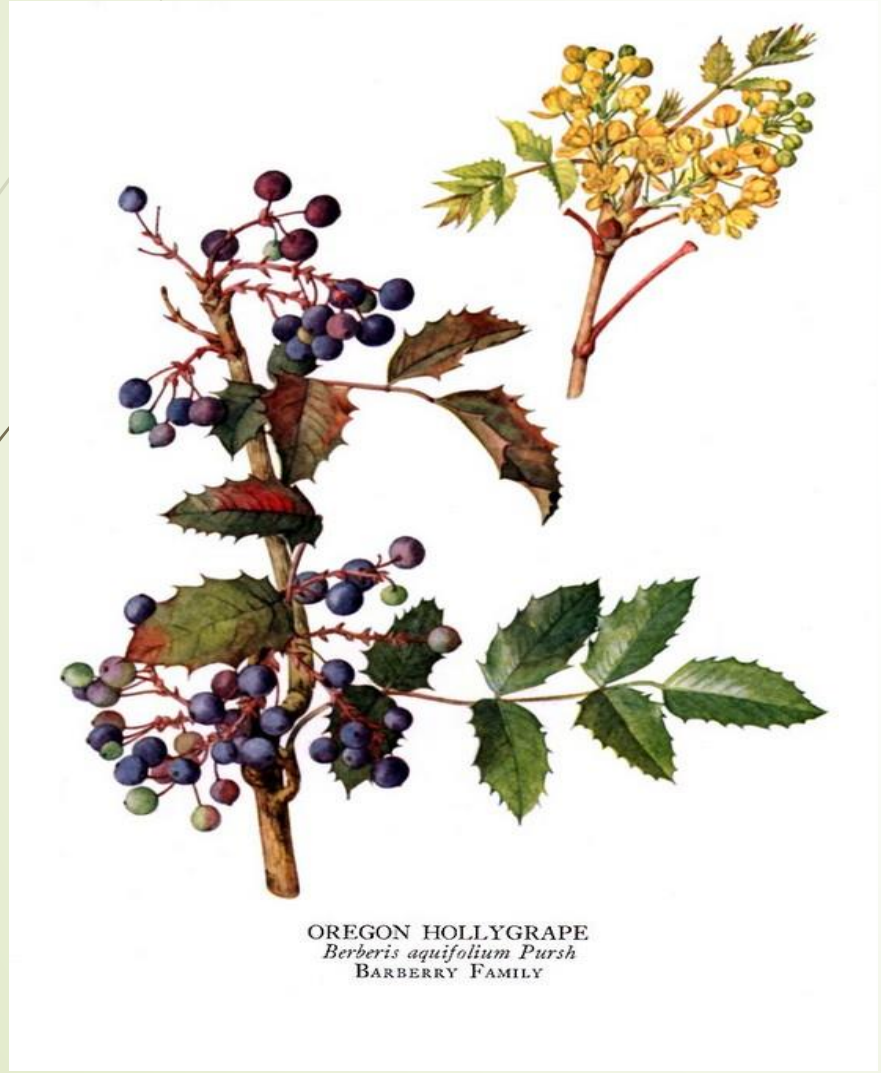
Alterative Herbs Include:

- *Taraxicum officinale*
- *Rumex species*
- *Mahonia aquifolium*
- *Arctium lappa*
- *Curcuma longa*

Taraxicum officinale
Dandelion Leaves and Roots

Rumex species
Yellow Dock, Curly Dock, Crispy Dock

Mahonia aquifolia
Oregon Grape



Arctium lappa
Burdock

Curcuma longa
Tumeric

INDICATIONS FOR EMPHASIZING ALTERATIVES

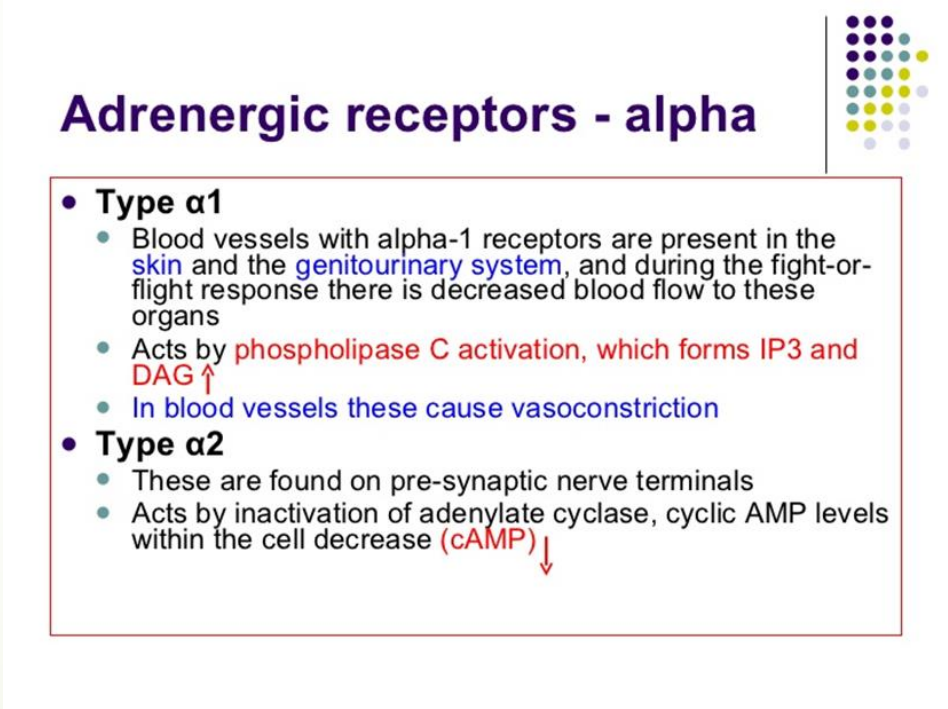
Signs and Sx Indicating the Need for Alterative Herbs:

- Acne and Skin Blemishes
- Constipation
- Dysbiosis, Gas, and Bloating
- Poor Fat Digestion
- PMS, and Hormonal Imbalance
- Hyperlipidemia
- Coated Tongue
- General Vague Malaise

ADRENALIN AND CORTISOL ELEVATIONS AND DYSGLYCEMIA

- Even momentary hypoglycemia may trigger great surges in insulin, adrenalin, and cortisol
- Conversely, cortisol surges may acutely drop blood glycose levels.
- Norepinephrine inhibits insulin secretion and enhances β-cell responsiveness

J Dev Orig Health Dis. 2013 Oct;4(5):402-10. *Elevated plasma norepinephrine inhibits insulin secretion, but adrenergic blockade reveals enhanced β-cell responsiveness in an ovine model of placental insufficiency at 0.7 of gestation*. Macko AR1, Yates DT1, Chen X1, et al



Adrenergic Signaling and Dysglycemia

- **Adrenergic blockade has been shown to enhance insulin response in the pancreas**
- **Normally, Insulin inhibits endogenous glucose production.**
- **However, when adrenergic stimulation is added, glucose production is promoted**
- **β2-adrenergic receptors agonsim in the hypothalamus raises blood glucose in hypoglycemia.**
- **Chronic stress and chronic adrenalin release may keep glucose high and interfere with normal insulin signaling (My conclusion)**
- **Therefore, nervine herbs may be important prongs of glycemic control in some patients.**

- **Am J Physiol Endocrinol Metab.** 2014 Jan 1;306(1):E58-64. Nov 19.Enhanced insulin secretion responsiveness and islet adrenergic desensitization after chronic norepinephrine suppression is discontinued in fetal sheep. Chen X1, Green AS, Macko AR, et al.

- **Diabetologia.** 2013 Nov;56(11):2517-23. *β2-Adrenergic receptor agonist administration promotes counter-regulatory responses and recovery from hypoglycaemia in rats.* Szepietowska B1, Zhu W, Sherwin RS.

NERVINE HERBS

- "Nervines" are an historical classification of botanical medicines that have a tonifying effect on the nervous system.

Botanical Nervines Include:

- *Matricaria chamomilla* - Chamomile
- *Passiflora incarnata* - Passionflower
- *Hypericum perforatum* – St Johnswort
- *Scutellaria lateriflora* - Skullcap
- *Melissa officinalis* – Lemon Balm
- *Nepeta cataria* – Catnip
- *Verbena species* – Verbena
- *Lavendula species* - Lavender

NERVINE HERBS

Nervines are especially indicated in dysglycemia formulas for the following signs and symptoms:

- Stress
- Anxiety
- Poor Sleep
- Muscle Tension, Clenching teeth, H/As
- Irritability
- Hypertension

Matricaria chamomilla
Chamomile

Hypericum perforatum
St Johnswort

Scutellaria lateriflora
Skullcap

Melissa
Lemon Balm

Nepeta cataria
Catnip

Verbena

Lavendula
Lavendar

THERAPEUTIC SUMMARY

BASIC THERAPEUTIC PROTOCOL FOR DYSGLYCEMIA

We have seen how Food, Chemicals, and Stress contribute to Dysglycemia.

Therefore A Basic Protocol for Dysglycemia would include:

- Avoidance of Sugar in all Forms
- Avoidance of Synthetic Chemicals, Pesticides, Bisphenols
- Avoidance or Hormone-laden animal products
- Treat stress, normalize cortisol

Botanical Approaches for Patients with Dysglycemia, Diabetes, Metabolic Syndrome, and CV Disease Risks Include:

- Whole Foods and Good Quality Fats
- Daily Legumes
- High Fiber

Botanical Prescriptions may Include:

- Alteratives
- Adaptogens
- Nervines
- And of course agents that improve glucose metabolism.

THANK YOU!

Dr Jillian Stansbury

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