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Cover Picture:
 CT scan of the pubis shows a slightly-displaced right parasymphseal fracture (arrow). There is no destructive lesion or soft tissue mass detected. The adjacent fascial planes are preserved. (Refer to page 183-186)

AGE-RAGE Interactions: Sticky Sugar Kills

Y C Chee

Ageing is a normal process whose mechanisms are being explored in the hope that life span can be further extended and ageing delayed. The telomerase theory explains why cells finally apoptose. But what explains age-related atherogenesis? Is glucose the culprit?

GLUCOSE & AGES

In its common closed-ring form, glucose (technically D-glucopyranose) is notably unreactive and therefore an excellent reason for evolution to have chosen it from among alternative sugars to be an important cellular fuel. As a cellular fuel, it is the only sugar that circulates in abundance.

Innocuous glucose becomes harmful through its transformation into advanced glycation end products (AGEs) by an intricate, random and primitive process that occurs in all animals and vegetables - a "browning" that requires no enzymatic catalysis but depends merely on temperature and an abundance of reactants.

As AGEs, glucose becomes a molecular glue that makes blood vessels inelastic and stenotic. It also provokes inflammation, activating macrophages and T lymphocytes, which in turn promote the hypertrophy of vascular smooth muscle and extracellular matrix.

We are all familiar with glycosylated or glycated haemoglobin, useful as a marker for the control of diabetes mellitus. However glucose-induced damage affects not just proteins but also other classes of biologic macromolecules, namely fats and nucleic acids. Even our genes are under attack.

THE CHEMICAL PROCESS OF GLYCATION

D-glucopyranose is a six-carbon ring molecule. The first step into AGEs begins when this ring spontaneously comes open, converting it into a linear molecule with an aldehyde at one end. This highly reactive aldehyde is able to hook itself onto any free amino group, such as on collagen. This initial interaction creates a Schiff base which spontaneously rearranges itself into an Amadori product.

We are familiar with HbA₁, an Amadori product in which glucose has hooked itself onto the beta chain of normal haemoglobin. HbA₁ was the first macromolecule recognized more than 20 years ago as a clinically consequential modification mediated solely by the presence of sugar. Today, a long list of molecules is known to be similarly affected ranging from the eye lens protein crystallin (? cause of cataracts) and the connective tissue protein collagen (? cause of diabetic dermopathy) to brain cell substances and lipids.

Physiologically HbA₁ has no immediate significance and the initial events of glucose interaction with any biologic macromolecules are quite

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reversible. A lowered glucose concentration will unhook the sugars from the amino groups to which they have attached themselves. In reverse, a heightened glucose concentration will increase the hookings. Thus, HbA_{1c} is clinically important chiefly as a prognostic marker indicating the patient's past glucose control and the risks that lie ahead.

Continual high sugar concentration allows hooked sugars to remain in place and over a period of days, complex interaction with dehydration, rearrangements and oxidation - reduction reactions occur. These glycation end products become progressively more complex and more irreversible. Lipids like phosphatidyl-ethanolamine and phosphatidylserine - common constituents of biologic membranes - also offer the amino groups required for initial hooking of a sugar⁽¹⁾. Nucleic acids are not spared and nonenzymatic intranuclear glycosylation of chromatin has been reported.

AGE-RAGE INTERACTION

An impact of nonmechanical damage of AGEs is that they can perturb cellular function by binding to a variety of receptors on various cells including macrophages, endothelial cells, smooth muscle, renal and neuronal cells. On macrophages, AGEs activate them and release cytokines which may be part of a system that normally mediates tissue repair and remodeling.

AGEs react with a specific receptor (RAGE) at the vascular endothelium. This AGE-RAGE interaction increases vascular endothelial production of superoxidation and other oxidative products. This interaction at the vascular endothelium is now regarded as a key factor in the accelerated atherogenesis of diabetes. At a developing vascular lesion, the macrophages may stay in place, engulfing modified lipids and releasing cytokines. As they engorge, the cells become the foam cells characteristic of early atherosclerosis. They also trigger a local expansion of both vascular matrix and it produces the smooth muscle cells. The site evolves from a fatty streak into the histologically complex lesion of full-fledged atherosclerosis.

AGEs can be deleterious to the integrity and function of blood vessel walls. By forming AGE cross-bridges among the walls' macromolecules especially of collagen, the normal free sliding of collagen molecules permitting vessel dilation and contraction is prevented. The vessel becomes a stiff, inelastic tube resulting in hypertension and vessel leakiness.

AGE accumulation can cause circulating matter to stick to the blood vessel wall. Trapped cells include platelets and trapped molecules include immunoglobulins and apolipoproteins, some of the latter already modified by glycation of both the lipid and the apoprotein moieties. These modifications may result in non-recognisability by the normal receptor such as LDL receptor, impeding the transfer of circulating lipids out of the blood stream.

AGE receptors are found also on resting CD₄ & CD₈ T lymphocytes and their activation by AGEs may promote a low grade, life-long inflammatory state. It is now thought that the vasculature is prone to seeding now and again by bacterial or viral pathogens or chlamydiae. Each seeding generates inflammation. AGEs are the equivalent of such pathogens.

AGES INGESTED

In addition to the AGEs created internally from circulating glucose, many arrive ready-made in the foods we ingest⁽²⁾. Of ingested AGEs, roughly 10% is absorbed, of which two thirds remains bio-available. One third is released in the urine.

The AGE content of one or another food has no simple relation to its sugar content. The more important relation is with the method of food

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preparation. Some 100 years ago, food chemists had appreciated the changes responsible for increasing the AGE content of food. These changes they term the Maillard reaction⁽³⁾. To us, it is the browning of raw foods by methods, such as roasting or braising - which depend directly on temperature and are greatly increased by long exposure to high heat. Heat creates tastes for which humans in modern societies enjoy. Food manufacturers have pandered to such tastes by increasing the AGE content in foods we eat. For example, roasted duck skin (220°C for 110 minutes) exhibits weight for weight, almost 15 times the AGE content of a doughnut (160°C for 5 minutes). Cooking increased the doughnuts AGE content 24 fold and the duck skin 101 fold.

So what? Should we alter our cooking methods? Is raw food best? Are we ready to be deprived of burger & barbecue? What about the microwave oven? Unfortunately, even microwaving results in AGE increases probably the result of the intense, highly focal heat delivered to foods by microwave. Although browning reaction may be a source of AGEs, many glycated substances have the cross-linking and cell-activating properties of AGEs but without the brown colour.

As usual, what is dangerous is excess. We overeat. We have over processed our foods. Habits need to change.

AGE-BREAKERS

Amnioguanidine is the first drug designed to inhibit glycation reactions⁽⁴⁾. The drug reacts with Amadori products, forestalling their progression to AGEs. It was reported in 1986 with animal studies showing that it works. Human studies are ongoing. Another group called AGE-breakers aim not at preventing glycation but at disrupting AGEs already formed⁽⁵⁾. Animal studies have been promising.

Other approaches? Soluble AGE receptors are being engineered for infusion as AGE decoys.

CONCLUSION

Sugar is sweet. Sugar is sticky. Chronic hyperglycemia leads to glycosylation of proteins, lipids, and nucleic acids resulting in AGEs. AGEs and their consequence may offer a biomolecular explanation for the complications of diabetes including atherogenesis and also for atherogenesis of normative ageing. Many AGEs are man made in vitro and arrive-ready made for ingestion. The way food is prepared may need to be altered.

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