

DIE HAPPY? -- LIVE LONGER? or how to manipulate the GH/IGF-1 axis?

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A major topic in today's research field is health and ageing. Modern society is obsessed with anti-ageing therapies and potions. Vitamins, mineral supplements, and anti-oxidants are frequently used to stay young forever. Besides changes in our appearance, our interior also changes with age: elderly people are more susceptible to diseases like cancer and diabetes. Therefore, with an ageing population, it is interesting to find out how people age with the least problems. In other words: how can we age healthy?

As we all know and may be afraid of, wrinkles and memory loss are signs of ageing. These changes are a consequence of changes from the inside of the body. What mechanisms cause these phenomena? And how is ageing regulated?

Apparently Growth Hormone (GH) and its signaling molecule Insulin like Growth Factor 1 (IGF-1) play an important role in aging and its manifestations. The paradoxes in this field are numerous and an enormous amount of research is aimed at unraveling components of the pathway and their exact roles in diverse processes.

Figure 1 illustrates in which processes GH might play a role.



GH is implicated as a main regulator of longevity. GH signals directly via the GH receptor and indirectly by inducing IGF-1. IGF-1 on its turn is also associated with longevity. Both GH and IGF-1 are important regulators of muscle and skeletal development. The GH/IGF-1 pathway is believed to be the most fundamental determinant of body size and is implicated in many more physiological and disease processes.

GH and IGF-1 are important regulators of longitudinal growth. Research in fruit flies and mice has also shown a role for these hormones in ageing. Mutant mice deficient of GH live longer than their wild-type counterparts. In humans the relation between GH/IGF-1 and ageing is not that straight-forward. In humans GH and IGF-1 levels decline with age and GH deficient patients usually have a shorter life because of increased cardiovascular mortality, like patients with giant growth (acromegaly) who have increased GH levels. Figure 1 illustrates other processes in which GH might play a role during ageing. In addition, GH deficient people show several characteristics of ageing, as opposed to GH deficient mice that actually live longer.

The main difference between GH-deficient mice and humans is insulin sensitivity. Human GH deficient patients are usually obese with corresponding insulin resistance whereas GH deficient mice show insulin sensitivity. Insulin resistance increases the risk of several age-related diseases and increases oxidative damage by increased levels of insulin (hyperinsulinemia) and increased levels of glucose (hyperglycemia). Oxidative damage that occurs after Reactive Oxidative Species (ROS) generation is also known as an important determinant of ageing, because of the extensive damage it can do. In addition, oxidative damage is related to cancer. GH and especially IGF-1 are now also related to cancer. High IGF-1 blood levels are associated with an increased risk on several cancers, whereas increased production of GH by mammary cells is implicated in mammary carcinoma.

GH is now often used as anti-ageing medicine, whereas the role of GH in this process is dual. On the one hand low GH levels lead to an increase in weight, a reduction in muscle strength, insulin resistance and a putative increase in lifespan. On the other hand, higher GH levels are associated with reduced weight and increased physical strength, improved psychological well-being, and possibly reduced lifespan. The effectiveness of GH treatment in healthy elderly is thus debated. Treatment has limited beneficial effects, whereas adverse effects are common.

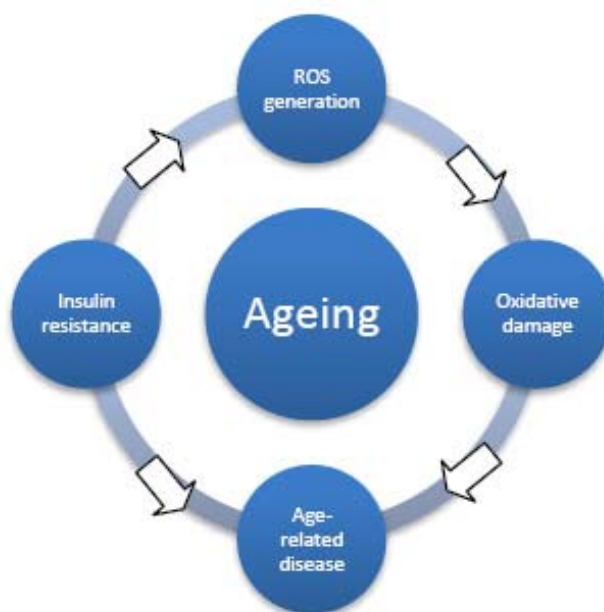


Figure 2: This scheme shows changes that come with age, perhaps causing the phenotype of ageing. GH is involved in all aspects. Arrows indicate relations between the boxes. ROS: Reactive Oxidative Species.

Taken together, in humans the influence of GH on lifespan has not yet been elucidated. To use GH safely as an anti-ageing medicine, more research is needed. Differences in the role of GH in the ageing process of mice and man may give indications on important mechanisms in ageing.

GH AND AGEING: THE CONTROVERSY

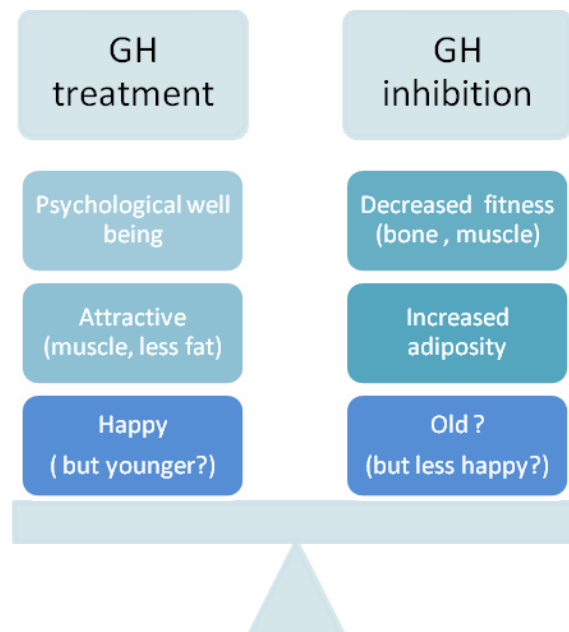
Although ageing is a continuous process of life starting on our first day, the way people deal with this process is fascinating: The first half of our life is the offensive part: we grow up, reproduce, and raise our children. These processes take place in the presence of high levels of GH and IGF-1. Then we come into the second half in which we switch to the survival mode: our GH and IGF-1 levels decline and our bodies try to reduce the damage done at the expense of fitness.

Indeed, longevity is thought to be associated with processes of damage reduction. Extended longevity originates from several basic mechanisms including enhanced insulin sensitivity and the corresponding reduced insulin levels, alterations in sugar and fat metabolism, decreased generation of Reactive Oxidative Species, enhanced resistance to stress, reduced oxidative damage and a delayed onset of age-related disease. These mechanisms are all inter-related and GH and IGF-1 affect all aspects (Figure 2).

However, the effects of GH and IGF-1 signaling are complicated by the multiplicity of their function. GH has a dual function in ageing in that it regulates adiposity, bone composition and cognitive function, but also plays a role in oxidative damage and insulin resistance. High levels of GH/IGF-1 are associated with increased fitness, and a feeling of well-being, whereas the process of ageing, at least in mice, seems to be accelerated by the presence of high GH and high levels of IGF-1. In man there is less evidence for a relation between GH/IGF-1 levels and ageing.

The complexity of the GH pathway lies in that it affects so many processes. If one process is optimal at a certain concentration of GH (for example protection to DNA damage), than other processes may be negatively affected (for example an increase of adipose tissue) with corresponding adverse effects. This paradox explains the difficulty to use GH as an anti-ageing medicine. GH treatment is a trade-off

Fig. 3. Possible positive and negative effects of GH treatment in healthy elderly. More research is needed to verify the effects of GH in man.



between increased fitness and possibly a shorter life. However, the latter aspect has not been proven yet. This will also be extremely difficult to prove in humans, because we often die of age-related diseases that may but may just as well not be a consequence of GH treatment/GH deficiency.

In addition, GH treatment has not always proven to be useful. Often, fitness is not really improved, although adiposity is reduced and muscles have enlarged. Besides limited beneficial effects, several adverse effects were observed. GH treatment can thus not yet be advised as an effective anti-ageing drug. In mice GH deficiency was shown to extend lifespan. In man GH deficiency is associated with an increased risk on cardio-vascular disease and adiposity. Thus, for now GH replacement or inhibition does not seem to be useful in the treatment of ageing. For this, more research will be inevitable.

OUR RESEARCH ON THE DEGRADATION OF THE GROWTH HORMONE RECEPTOR

Our research focuses on the GH sensitivity of cells. The effect of GH depends on the number of GH receptors that are present on all cells of the body. Once a GH molecule binds to the GH receptor on a cell somewhere in the body, signals are transmitted to the DNA in the nucleus and the necessary actions are initiated. This will eventually lead to an increased pace of life, depicted at the left side of figure 3. On the other hand, if the number of GH receptors is decreased, the body is in a state of GH-insensitivity, and GH will have little effect throughout the whole body. This will result in a situation depicted in the right panels of figure 3.

In addition, in severe diseases (body stresses) like cancer, aids, and during long hospitalization, the number of GH receptors is decreased, and the body becomes GH-insensitive due to the metabolic stress that comes with these conditions. There is sufficient GH, but the cells are unable to respond, like is the case in diabetes type 2. This leads to muscle wasting (cachexia) and life-threatening conditions due to respiratory and cardiac insufficiency.

In many conditions discussed above, GH injections are neither effective nor healthy. This is also due to the extremely complicated activities of GH that are fine-tuned in the body in a gender-dependent fashion. The only way to address the conditions depicted in figure 3 as well as in cachectic situations is [to regulate the GH sensitivity](#) of cells in the human body, in other words: to regulate the number of GH receptors on the cell surface. The number of GH receptors is clearly regulated by its degradation. Therefore, our research concentrates on the [degradation](#) of the GH receptor.

In general, it is difficult to study the degradation of cell surface (membrane) proteins. These molecules serve many causes; they act as the antennas of the cells sensing stressors and changes in the environment and are able to transmit these changes into the cell's interior. Levels of the many sensors, transporters and receptors are individually, precisely and timely regulated. In many cases ubiquitylation, often in combination with phosphorylation are key regulatory systems. For the GH receptor we have identified the proteins that can either act to rapidly destroy or to stabilize the GH receptors. If protein A binds to the receptor, the GH receptor is stable and the cells are GH sensitive; however, if protein B binds, the receptors are rapidly destroyed rendering the cells GH-insensitive. In our studies we try to understand how the activities of the proteins A and B are coordinated: how does stress affect the activities of A and B?? The most advanced methods are used in our studies. Once we know the molecular details of these actions we will develop drugs that can regulate the number of GH receptors on the cell surface and as such regulate GH-sensitivity of cells.

Insight in the way the GH is degraded is important for science and is a great project to teach and inspire young people to become the next generation of prominent European scientists. This project also serves the society. Society is not interested in cellular effects, but wants to know what happens to fitness, appearance, and life span. However, cellular and molecular aspects are the key to help to understand systemic effects and to determine central drug targets.

At the European level, Rubicon supports this important project which is carried out in close collaboration between Academia and Industry, and aims at a new generation of drugs to improve quality of life.