rHGH

Recombinant Human Growth Hormones

Onur Akyol, Julian Stalder

Term Paper Biology

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1. Preface

We decided to write our term paper on the synthesis of human growth hormones, because one of us was already thinking once about taking a growth hormone replacement therapy. Growth hormone therapy is a prime example for the application of DNA recombinant technology in pharmaceutical manufacturing, which makes it primarily interesting from a biological/ biotechnological point of view. But since genetic engineering is a relatively young branch of science, hence opening a lot of new possibilities and chances, there are simultaneously new questions and perhaps dangers arising, mostly of social and ethical nature. The use of human growth hormones, particulary, has been a focus of many such controversies. This bioethical aspect was a major point in determining our topic during our decision-making process.

2. Introduction

Growth hormone is a polypeptide hormone, basically stimulating growth, cell reproduction, cell regeneration, the immune system, but also increasing protein synthesis, muscle mass and the mineralization of bones among other functions. When the body does not produce enough growth hormones, we speak of growth hormone deficiency. Growth hormone deficiency can have various effects depending on the age of the affected person. Possible manifestations can be hypoglycemia and micropenis in newborns, growth failure in the childhood. In adults growth hormone deficiency is rather rare: Poor bone density, diminished lean body mass as well as a series of psychological problems including depression and poor memory can be possible symptoms.

Growth hormone deficiency can be treated by growth hormone replacement therapy. This requires artifical synthesis of human growth hormones. Today this is done by genetically modified bacteria. Before recombinant DNA technology was used for the modification of bacteria to produce human growth hormone, the hormone was fabricated by extraction from human hypophyses collected at autopsy. This however led to problems in supply, since up to fifty hypophyses were needed to cover a single year‘s demand and animal growth hormones were not of any use for humans. Then in the late 1970s the breakthrough came: researchers at Genetech - a pioneer biotechnology corporation - had achieved to create human growth hormones. They took the DNA coding for human growth

hormone, which they gained by reverse transcription of the mRNA found in the hypophysis, and inserted it into a plasmid, that was subsequently implanted in escherichia coli bacteria. From 1985 on, recombinant human growth hormone was produced on an industrial scale. Even though the formerly scarce situation in supply changed radically, medicine containing recombinant human growth hormones continued to be highly expensive. This gave reason to criticism for the corporations marketing the drugs and can be described as the first human growth hormone controversy. Later controversies concerning doping and false or exaggerated proclamations about a supposed anti-aging effect of rHGH followed.

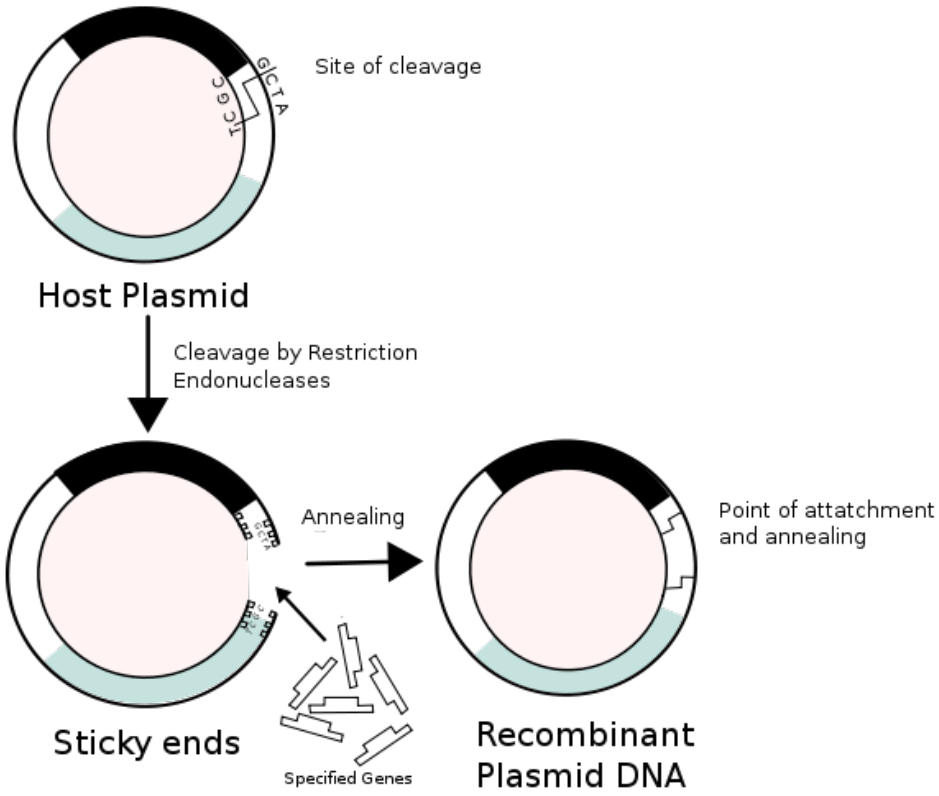
3. Description of Engineering Technique:

The human growth hormone can be produced in other organisms, this functions particularly well in bacteria like for example E. Coli. Almost all bacteria have a structure called plasmid. These plasmids are circular, double-stranded DNA molecules which are seperate from the chromosomal DNA.

The human growth hormone is a protein of 191 amino acids and is normally produced in the human pituitary gland. They are responsible for growth in the human body by increasing the production of proteines. When the hormone is produced in the body, it is attached with a signal peptide with 26 amino acids together with 24 neighbouring amino acids. By the use of restriction enzyme EcoR1 the base sequence is cut in the coding cDNA. This coding cDNA is integrated into the plasmid which is then inserted into the bacteria cell. These bacteria cells are cultured and the hGH can be extracted again.

For this method we often use the bacteria Escherichia Coli because it has been used in laboratories for a long time and because it is easy to handle and to manipulate. This engineering technique is called recombinant DNA technology.

Efforts to produce entirely synthetical human growth hormone failed, since it would be exceedingly circumstantial to synthesize a gene that would later be translated into human growth hormone owing to the considerable lenght of the amino acid sequence of human growth hormone (to be more precise: 191 amino acids, as mentioned above).



A simple example of how a desired gene is inserted into a plasmid.
http://en.wikipedia.org/wiki/File:Recombinant_formation_of_plasmids.svg

4. Interview

We conducted an interview with Prof. Christoph Rehmann-Sutter. He is the head of the Unit for Ethics in the Biosciences at the University of Basel and professor for theory and ethics in the biosciences at the Institute for History of Medicine and Science Research at the University of Luebeck.

If most extremely small children are treated with growth hormones in order to become taller, will what society defines as ‚extremely small' simply go up, opposing the expected social benefit?

CRS: I am also sceptical about the use of growth hormones, but things are not so simple. You will never treat all short children in the world, not all parents will want to treat their shorter children, and you will always know and remember how short children could be. So I don't think that the definition of "extrememly small" will change automatically. And the crucial point is not "social benefit" as you say, but benefit for the

child in the context of society. So it should not be society who benefits but the individual. And there is my question: are we so sure that the individual is always better off if she/he is given GH? I know some extremely short people (with Achondroplasia) who lead a highly important life that they would just not have led if they would be average size. Look out for the name of Tom Shakespeare on Google, for example.

If growth hormones are only accessible within the scope of economic limits, so that only children are treated whose parents can afford it, will shortness become a future marker for lower social rank?
CRS: Yes.

Isn‘t growth hormone treatment a reasonable use of limited healthcare resources, or is the doctor‘s initial responsibility to the patient?
CRS: The decision should always be on the individual patient, not about managing the healthcare budget.

If stimulation tests are used to determine growth hormone deficiency, is it possible, that a child is able to produce enough growth hormones as a reaction to such a stimulation test, but fail to produce enough in everyday life in order to grow normally?
CRS: This seems to be a physiological question that I am not able to answer. I am a philosopher and bioethicist.

If a stimulation test is used to define deficiency, what growth hormone level should be used to define normal?
CRS: The definition of "normal" is always tricky and controversial for good reasons, because there, the social norm kicks in, and at the same time variation and social acceptance of varied embodiements are reduced.

5. Discussion

The use of recombinant DNA technology for the production of human growth hormone has some major advantages compared to the alternatives. The

method is safe and offers a large and abundant production. Bacteria cells are more suitable for the process than mammalian cells since those show difficulties in maintenance and have lower yields. Bacteria like E. Coli are worldwide available and well suited for mass production. Critics of this method say that the purpose of producing recombinant hGH is for the pharmaceutical companies to have a high profit. Also the medical use of recombinant human growth hormone is very expensive. There are some ethical issues with the use of human growth hormones in general. If as an example you consider the shortest 1% of the population to have a sickness and you treat them, the problem is not solved. It is just transferred to the next group of people which subsequently will become the shortest, some critics say.

The long term use of growth hormones is not well studied but from experience there are unpleasant effects like diabetes or joint pain. When it comes to the treatment of children with growth deficiencies a n increased risk of colon cancer and Hodgkin's Disease has been observedGrowth hormones have been used by professional athletes before the invention of rHGH but it was only after it was invented that its abuse started to spread to athletes of all levels. It is mainly used in power sports and often in combination with other performance enhancing drugs. The actual effectiveness of HGH to increase athletic performances is very unclear. It is believed to have an impact on muscle mass and injury resistance but recent studies showed that the use of HGH had a negative impact on stamina, so it is possible that the use of growth hormones is contra productive.Growth hormones are today used in the field of life extension but again there is a lot of controversy. Anti-aging therapies with growth hormones could be dangerous for the patient and the desired positive effect has not been proven. Studies have only been made with animals and there the results were divergent.Scientists believe that the impact of recombinant DNA in general will become more important. This technique may be applied in many different domains like medicine, agriculture (crops, livestock). However some people are concerned about possible negative impacts. Viruses and bacteria could become to medication like antibiotics. Also there is an ethical dilemma, the technique could be used to voluntarily harm people.HGH is a relatively young discovery and still shows a very high potential.HGH is hoped to be very effective against all diseases connected with aging in the future. It also improves cardiac function and it may be helpful against cardiac diseases. All in

all HGH shows extremely great promise for physical and mental well-being in the future.There are also downsides to treatment with HGH. It could cause severe damages to the body and have negative side effects, so a complete physical examination before the treatment makes sense.

6. Summary

Growth hormones are important for various functions, and deficiency can have diverse effects. It can be treated. Today treatment consist of external insertion of human growth hormones into the body. These hormones are also referred to as recombinant human growth hormones, because they are produced with recombinant DNA technology, wherby the DNA coding of human growth hormone is inserted into a plasmid. The introduction of recombinant DNA technology has solved former problems regarding supply, however new problems develop: (r)HGH continues especially to arouse social and ethical concerns.

7. References

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