13.6G: Antisense Agents

LEARNING OBJECTIVES

- Discuss the mechanism of antisense agents and the advantages and disadvantages of antisense therapy.

Antisense agents are synthetic, single-stranded short sequences of DNA bases designed to hybridize to specific sequences of messenger RNA (mRNA) forming a duplex. This DNA-RNA coupling attracts an endogenous nuclease, RNase H that destroys the bound RNA and frees the DNA antisense to rehybridize with another copy of mRNA. In this way, the effect is not only highly specific but prolonged because of the recycling of the antisense DNA sequence. When this agent binds to the pathogen DNA or messenger RNA, the biosynthesis of target proteins is disrupted. Therefore, there are at least two ways in which antisense agents act to effectively reduce the amount of pathogenic protein being synthesized – RNase H based degradation of RNA and prevention of ribosomal assembly and translation. This approach has a great advantage. It prevents a pathogenic protein from being produced, rather than trying to selectively neutralize it once it is made.
Antisense agents can be specifically targeted to genes that control expression of antibiotic resistance mechanisms, thereby potentially restoring an antibiotic-sensitive phenotype to the cell. A limiting factor in their potential application as therapeutic agents for bacterial infections is their poor uptake by bacterial cells. These agents have been successfully developed for the treatment of viral infections such as cytomegalovirus, hepatitis C, and HIV infections. The advantage of antisense therapy is that they can be manufactured fairly fast, they produce a lasting clinical effect, and they are highly specific to the target. Antisense agents also exhibit efficacy in broader clinical applications such as cancer therapy.

Key Points

- Antisense agents have broad applications in several diseases. Their use for treating microbial infections is promising.
- They are synthetic oligonucleotides that can be manufactured quickly and their biological effect is long-lasting.
- Their use for the treatment of antibiotic resistant bacterial infections is possible but limited by their poor uptake by the bacterial cell. Studies are being developed to improve their penetration into the cell.

Key Terms

- messenger RNA: RNA that encodes and carries information from DNA during transcription to sites of protein synthesis to undergo translation in order to yield a protein
- nuclease: Any of several enzymes capable of cleaving the phosphodiester bonds between the nucleotide subunits of nucleic acids.
- hybridize: To combine complementary subunits of multiple biological macromolecules.