Journal of Photochemistry and Photobiology B: Biology 124 (2013) 1–19

Contents lists available at SciVerse ScienceDirect

Journal of Photochemistry and Photobiology B: Biology

journal homepage: www.elsevier.com/locate/jphotobiol

Short Review

Drug–DNA interactions and their study by UV–Visible, fluorescence spectroscopies and cyclic voltametry

Muhammad Sirajuddin [1], Saqib Ali *, Amin Badshah [2]

Department of Chemistry, Quaid-i-Azam University, Islamabad 45320, Pakistan

ARTICLE INFO

Article history:
Received 7 February 2013
Received in revised form 26 March 2013
Accepted 28 March 2013
Available online 6 April 2013

Keywords:
Drug–DNA interaction
UV–Visible spectroscopy
Fluorescence spectroscopy
Cyclic voltammetry

ABSTRACT

The present paper review the drug–DNA interactions, their types and applications of experimental techniques used to study interactions between DNA and small ligand molecules that are potentially of pharmaceutical interest. DNA has been known to be the cellular target for many cytotoxic anticancer agents for several decades. Understanding how drug molecules interact with DNA has become an active research area at the interface between chemistry, molecular biology and medicine. In this review article, we attempt to bring together topics that cover the breadth of this large area of research. The interaction of drugs with DNA is a significant feature in pharmacology and plays a vital role in the determination of the mechanisms of drug action and designing of more efficient and specifically targeted drugs with lesser side effects. Several instrumental techniques are used to study such interactions. In the present review, we will discuss UV–Visible spectroscopy, fluorescence spectroscopy and cyclic voltammetry. The applications of spectroscopic techniques are reviewed and we have discussed the type of information (qualitative or quantitative) that can be obtained from the use of each technique. Not only have novel techniques been applied to study drug–DNA interactions but such interactions may also be the basis for the development of new assays. The interaction between DNA and drugs can cause chemical and conformational modifications and, thus, variation of the electrochemical properties of nucleobases.

© 2013 Elsevier B.V. All rights reserved.

Contents

* Corresponding author. Tel.: +92 51 90642130; fax: +92 51 90642241.
E-mail addresses: m.siraj09@yahoo.com (M. Sirajuddin), drsa54@yahoo.com (S. Ali), aminbadshah@yahoo.com (A. Badshah).
[1] Tel.: +92 51 90642208; fax: +92 51 90642241.
[2] Tel.: +92 51 90642131; fax: +92 51 90642241.

1011-1344/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jphotobiol.2013.03.013

1. Introduction

DNA is present in body in the form of a double helix (Fig. 1A), where each strand is composed of a combination of four nucleotides (a nucleotide is a nucleoside with one or more phosphate groups covalently attached to the 3′- and/or 5′-hydroxyl group(s)), adenine (A), thymine (T), guanine (G) and cytosine (C) (Fig. 1B). Within a strand these nucleotides are connected through phosphodiester (deoxyribose sugars joined at both the 3′-hydroxyl and 5′-hydroxyl groups to phosphate groups in ester links is called phosphodiester linkage) linkages (Fig. 1C). The two strands are held together primarily through Watson Crick hydrogen bonds where A forms two hydrogen bonds with T and C forms three hydrogen bonds with G (Fig. 1D) [1–3]. The region where the two strands are close to each other (deep–narrow) is called minor grove while the region where they are away from each other (shallow–wide) is called major groove.

2. Drug–DNA interactions

DNA is the pharmacological target of many of the drugs that are currently in clinical use or in advanced clinical trials. Targeting DNA to regulate cell functions by modulating transcription (gene expression and protein synthesis) or by interfering with replication (a major step in cell growth and division) seems logical, intuitively appealing and conceptually straightforward. Small ligand molecules bind to DNA and artificially alter and/or inhibit the functioning of DNA. These small ligand molecules act as drug when alteration or inhibition of DNA function is required to cure or control a disease [4].

The study of interaction of drug with DNA is very exciting and significant not only in understanding the mechanism of interaction, but also for the design of new drugs. However, mechanism of interactions between drug molecules and DNA is still relatively little known. It is necessary to introduce more simple methods for investigating the mechanism of interaction. By understanding the mechanism of interaction, designing of new DNA-targeted drugs and the screening of these in vitro will be possible [5].

3. Types of Drug–DNA interaction

There are primarily three different ways by which anticancer drugs interact with DNA (Scheme 1), (i) through control of transcription factors and polymerases. Here, the drugs interact with proteins that bind to DNA, (ii) through RNA binding to DNA double helix to form nucleic acid triple helix structures or RNA hybridization (sequence specific binding) to exposed DNA single strand forming DNA–RNA hybrids that may interfere with transcriptional activity and (iii) through binding of small aromatic ligand molecules to DNA double helical structures. The binding of small molecules to DNA involves electrostatic interaction, intercalation between base pairs and minor and major DNA grooves binding interaction [6].

4. Modes of Drug–DNA binding

There are two modes of drug–DNA binding, covalent and non-covalent. Some examples of DNA-interacting agents are given in Table 1[7].

4.1. Covalent mode of binding

Many anticancer drugs in clinical use function by interacting with DNA, not only those that bind to DNA through non-covalent interactions but also those that form covalent adducts such as via alkylation or inter- and intrastrand crosslinking [8]. The covalent mode of binding of drug–DNA is irreversible and invariably causes the complete inhibition of DNA processes and subsequent cell death (if the reaction is not directly chemically reversible). A major advantage of covalent binders is the high binding strength. Moreover, covalent bulky adducts can cause DNA backbone distortion, which in turn can affect both transcription and replication, such as by disrupting protein complex recruitment [9].

Cis-platin [*cis*-dichlorodiammineplatinum(II)] is a famous covalent binder used as an anticancer drug, and makes an intra/interstrand cross-link through the chloro groups with the nitrogens on the DNA bases (Scheme 2).

The covalent attachment of organic intercalators to transition metal complexes, producing metallointercalators, can lead to novel DNA interaction that affect biological activity. Metal complexes having σ-bonded aromatic side arms can acts as dual-function complexes: they bind to DNA both by metal coordination and through intercalation of the attached aromatic ligand. These aromatic side arms introduce new mode of DNA binding, involving mutual interactions of functional groups held in close proximity [10].

The covalent binders are also called alkylating agents due to adduct formation because they are used in cancer treatment to attach an alkyl group (C_nH_{2n+1}) to DNA [11].

4.1.1. Alkylating agents

DNA alkylating agents have been used as anticancer agents by producing significant DNA damage to kill cancer cell [12]. Alkylating agents involve reactions with guanine in DNA. However, some alkylating drugs exert their strongest effects through alkylation of other positions and other types of cross-links. These drugs add methyl or other alkyl groups onto molecules where they do not belong. This in turn inhibits their correct utilization by base pairing and causes a miscoding of DNA. Alkylating agents can interact *via* three mechanisms.

In the first mechanism, an alkylating agent attaches alkyl groups to DNA bases. This alteration results in the DNA being fragmented by repair enzymes in their attempts to replace the alkylated bases.

A second mechanism by which alkylating agents cause DNA damage is the formation of cross-links, bonds between atoms in the DNA. In this process, two bases are linked together by an alkylating agent that has two DNA binding sites. The cross-linking of the two strands of DNA produced by the bifunctional alkylating agents prevents the use of that DNA as a template for further DNA and RNA synthesis leading to inhibition of replication and transcription and, then, to cell death. A large number of chemical compounds are alkylating agents under physiological conditions, and a variety of such compounds have exhibited antitumor activity.

The third mechanism of action of alkylating agents causes the mispairing of the nucleotides leading to mutations. The alkylating agents, by chemical interactions, form covalent links with DNA. This causes "mistakes" in the DNA that may result in mispairing, substitutions, or excision. The cellular response of these mistakes may inhibit DNA synthesis and proliferation or they may result in apoptosis (process of programmed cell death that may occur in multinuclear organisms) [11].

Alkylating drugs are the oldest class of anticancer drugs still commonly used; they play an important role in the treatment of several types of cancers. Most alkylating drugs are monofunctional methylating agents (e.g., temozolomide [TMZ], N-methyl-N′-nitro-N-nitrosoguanidine [MNNG], and dacarbazine), bifunctional alkylating agents such as nitrogen mustards (e.g., chlorambucil and cyclophosphamide), or chloroethylating agents (e.g., nimustine [ACNU], carmustine [BCNU], lomustine [CCNU], and fotemustine) [13]. The alkylation of N3 of guanine by (+)-CC1065 (antitumor antibiotic) is shown in Scheme 3 [14]. (+)-CC1065 induces both DNA bending toward the minor grooves and widing equivalent to about one base pair per covalent alkylation event. (Scheme 4)

Download English Version:

https://daneshyari.com/en/article/30355

Download Persian Version:

https://daneshyari.com/article/30355

Daneshyari.com