Saudi Pharmaceutical Journal (2014) **22**, 3–16

King Saud University

Saudi Pharmaceutical Journal

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REVIEW

Targeting cancer using cholesterol conjugates

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Received 17 December 2012; accepted 10 January 2013
Available online 31 January 2013

KEYWORDS

Cholesterol;
Anticancer;
Drug delivery systems

Abstract Conjugation of cholesterol moiety to active compounds for either cancer treatment or diagnosis is an attractive approach. Cholesterol derivatives are widely studied as cancer diagnostic agents and as anticancer derivatives either in vitro or in vivo using animal models. In largely growing studies, anticancer agents have been chemically conjugated to cholesterol molecules, to enhance their pharmacokinetic behavior, cellular uptake, target specificity, and safety. To efficiently deliver anticancer agents to the target cells and tissues, many different cholesterol–anticancer conjugates were synthesized and characterized, and their anticancer efficiencies were tested in vitro and in vivo.

Contents

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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.jsps.2013.01.003

1. Introduction

According to the cancer incidence and survival report 2007 by the Saudi cancer registry (scr.org.sa), 12,309 cancer cases were diagnosed in Saudi Arabia in 2007 (Saudi Arabia's population at that time was approximately 17 million). Breast cancer ranked first in incidence (13.8%), followed by colorectal (9.9%), non-Hodgkin lymphoma (NHL) (7.7%), thyroid (6.4%), leukemia (6.2%), liver (4.8%), and lung cancer (4.5%). The top five cancers in females were breast, thyroid, colorectal, NHL, and leukemia; in males, the top five cancers were colorectal, NHL, leukemia, lung, and liver. Moreover, cancer is the second most common cause of death in the US, exceeded only by heart disease, accounting for nearly 1 of every 4 deaths (American Cancer Society, 2012).

Cholesterol is a neutral lipid that plays an essential role in the maintenance of the integrity of biologic membranes and serves as a precursor in the synthesis of many endocrine mediators. It is also synthesized in mammalian cells via the mevalonate pathway. Recent clinical has demonstrated a possible linkage of cholesterol to prostatic cancer and benign prostatic hyperplasia. Accumulation of cholesterol within the lipid raft component of the cellular plasma membrane may stimulate signaling pathways that promote prostate tumor growth and progression. In addition, cholesterol-lowering drugs, such as statins, have exhibited some promising results for these prostatic diseases (Yat-Ching, 2011). Herein, we shed light upon the anticancer activity of various cholesterol conjugates that have been published in the literatures.

2. The biological properties of cholesterol

Distribution of cholesterol in human organs and tissues varies (Fig. 1) (Alanazi et al., 2003). Cholesterol serves many biological functions. Depending on the cell types, cholesterol content of cell membranes varies (Yeagle, 1988). The membranes of most cells have an intermediate cholesterol/phospholipid ratio

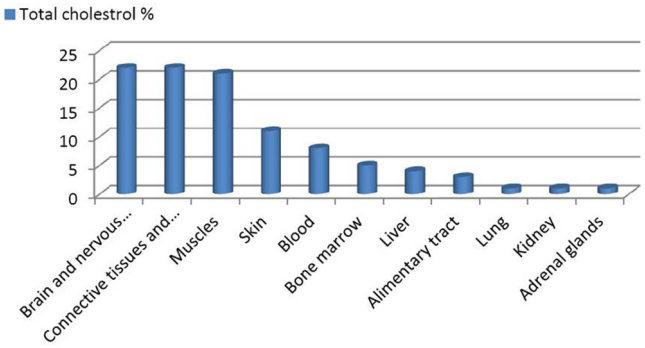

Figure 1 Distribution of cholesterol in human organs and tissues.

and possess both protective and metabolite-transport functions. Cell membranes with a high cholesterol ratio, such as those in the epidermis layer of the skin, have high stability and relatively low permeability, reflecting their major functionality as a protective barrier (Yeagle, 1988; Proksch, 1990). Membranes of the intracellular organelles, such as mitochondria, have a low cholesterol ratio and, thus, are fluidic and permeable (Yeagle, 1988). The total amount of cholesterol bound to lipoproteins in blood circulation is normally about 150–200 mg per 100 ml of serum. The body obtains cholesterol from two routes, either from dietary sources or from *de novo* biosynthesis.

Various lipoproteins act as primary carriers in cholesterol transport through blood circulation. Dietary cholesterol is transported from the intestine to the liver in large lipoprotein particles. The liver secretes very low density lipoproteins (VLDL), containing cholesterol and is partially converted into low density lipoprotein (LDL) through the action of lipoprotein lipase. LDL carries cholesterol from the liver to body tissues while high density lipoprotein (HDL) transports cholesterol from various tissues back to the liver (Alanazi et al., 2003).

Cholesterol is the sole precursor to all steroid hormones. These steroids include glucocorticoids responsible for blood sugar regulation, mineralcorticoids that regulate mineral balance and blood pressure and sex hormones responsible for many functions. Cholesterol is the precursor to a hormone called pregnenolone, which has not only its own functions but also be the precursor to all other steroid hormones. Pregnenolone is converted into progesterone, a sex hormone, which in turn is converted into cortisol, which regulates inflammation and blood sugar, aldosterone, which regulates mineral balance and blood pressure, or testosterone, a type of sex hormone referred to as an androgen, which regulates libido, muscle mass, and plays other roles. In females, and to a lesser degree in males, testosterone is further modified, undergoing conversion to estradiol, a different type of sex hormone called an estrogen (Hume and Boyd, 1978). Many neurotransmitter receptors are created with cholesterol, and maintained with the aid of cholesterol (Fantini and Barrantes, 2009; Baier and Barrantes, 2007; Barrantes, 2010). Our nerve cells require cholesterol to function and maintain fluidity (Barres and Smith, 2001). The central nervous system (CNS) comprises the highest concentration of cholesterol in the body, over any other organ (Dietschy and Turley, 2004). For the *in vivo* synthesis of Vitamin D from the Sun, cholesterol is needed (Bouillon et al., 1995). Bile salts are amphipathic derivatives of cholesterol, and are needed to emulsify dietary fats so they can be digested properly (Denniston et al., 2007).

3. Serum cholesterol and cancer risk

For males with low serum cholesterol levels it has been noted that about 30% increased risk of cancer is expected. For