复印件样张五

第八章　第三节　强心苷类化合物

Chapter 8，Section 3　Cardiac Glycosides

Revised text

改写双语教材（授课 20 分钟内）

一、What is Cardiac glycosides （ 强心苷概述 ）

1．Identification

Cardiac glycosides are a group of plant constituents used in the treatment of cardiac failure. They are glycosides with sugar residues linked to the C-3-OH groups of the cardiac steroid aglycones .

1．定义

强心苷（cardiac glycosides）是生物界中存在的一类对心脏有显著生理活性的甾体苷类，是由强心苷元（cardiac aglycones）与糖缩合的一类苷

2．Biological Activity

Cardiac failure can be described as the inability of the heart to pump blood effectively at a rate that meets the needs of the metabolizing tissues. This occurs when the muscles that perform contraction and force the blood out of heart are performing weakly. Thus cardiac failures primarily arise from the reduced contractility of heart muscles, especially the ventricles. Reduced contraction of heart leads to reduced heart output but new blood keeps coming in resulting in the increase in heart blood volume. The heart feels congested. Hence the term congestive heart failure.

2．生物活性

强心苷是一类选择性作用于心脏的化合物，能加强心肌收缩性，减慢窦性频率，影响心肌电生理特性。临床上主要用于治疗慢性心功能不全，以及一些心率失常如心房纤颤、心房扑动、阵发性室上性心动过速等心脏疾患。据报道，某些强心苷有细胞毒活性，动物试验表明可抑制肿瘤。此外，强心苷类化合物有一定的毒性，它能兴奋延髓极后区催吐化学感受区而致恶心、呕吐等胃肠道反应，能影响中枢神经系统产生眩晕、头痛等症。

二, chemical structures and classification （强心苷的结构与分类）

Cardiac glycosides are composed of two structural features：aglycone and sugar

moieties.

强心苷由强心苷元与糖缩合而成。

1. The strucure of aglycone

The cardiac aglycone is the steroid compounds with an unsaturated lactone ring attached to the C-17 of the steroid backbone. The structural feature is as following:

(1) A unique set of fused ring system that makes the aglycone moiety structurally distinct from the other more common steroid ring systems. Rings A/B and C/D are commonly cis fused while rings B/C are all trans fused.

(2) The substituted groups at C-10, C-13 and C-17 positions are all β -conformation. The substituted groups at C-10 position can be methyl or hydroxy methyl, at C-13 is methyl group and at C-17 is definitely an unsaturated lactone ring. There are also many substitutes groups at other position of backbone, Among them there is usually a 3β hydroxy group via which sugar residues are linked glycosidically to the cardiac steroid aglycones.

1. 苷元部分的结构

天然存在的强心苷元是 C_{17} 侧链为不饱和内酯环的甾体化合物。其结构特点如下：

（1）甾体母核 A、B、C、D 四个环的稠合方式为 A/B 环有顺、反两种形式，但多为顺式；B/C 环均为反式；C/D 环多为顺式。

（2）C_{10}、C_{13}、C_{17} 的取代基均为 β 型。C_{10} 为甲基或醛基、羟甲基、羧基等含氧基团，C_{13} 为甲基取代，C_{17} 为不饱和内酯环取代。C_3、C_{14} 位有羟基取代，C_3 羟基多数是 β 构型，少数是 α 构型，强心苷中的糖均是与 C_3 羟基缩合形成苷。C_{14} 羟基为 β 构型。母核其它位置也可能有羟基取代，一般位于 1β、2α、5β、11α、11β、12α、12β、15β、16β，其中 16β-OH 有时与小分子有机酸，如甲酸、乙酸等以酯的形式存在。在 C_{11}、C_{12} 和 C_{19} 位可能出现羰基。有的母核含有双键，双键常在 C_4、C_5 位或 C_5、C_6 位。

2. The classification of aglycone

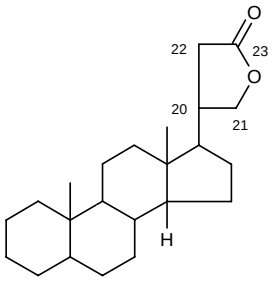
Two classes have been observed in nature cardiac aglycone - the cardenolides and the bufadienolides (see figure below). The cardenolides have an unsaturated butyrolactone ring while the bufadienolides have an a-pyrone ring.

The lactone moiety at C-17 position is an important structural feature. The size and degree of unsaturation varies with the source of the glycoside. Normally two classes have been observed in nature cardiac aglycone - the cardenolides(A-type) and the bufadienolides (B-type)(see figure below). The cardenolides have a 5-membered unsaturated lactone ring while the bufadienolides have 6-membered unsaturated lactone ring. And usually plant sources provide a 5-membered unsaturated lactone ring while animal sources give a 6-membered unsaturated lactone ring.

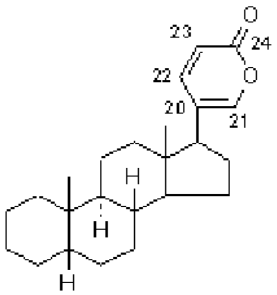
2. 苷元的分类

根据 C_{17} 不饱和内酯环的不同，强心苷元可分为两类。①C_{17} 侧链为五元不

饱和内酯环（△$^{\alpha\beta}$-γ-内酯），称强心甾烯类（cardenolides），即甲型强心苷元。在已知的强心苷元中，大多数属于此类。②C_{17}侧链为六元不饱和内酯环（△$^{\alpha\beta,\gamma\delta}$-δ-内酯），称海葱甾二烯类(scillanolides)或蟾蜍甾二烯类(bufanolide)，即乙型强心苷元。自然界中仅少数苷元属此类，如中药蟾蜍中的强心成分蟾毒配基类。



cardenolides（强心甾烯类）



bufanolides（蟾蜍甾二烯类）

3. The sturctures of sugar moieties

About 20 types of sugar(saccharide) residues were found in cardiac glycosides, most commonly used include L-rhamnose, D-glucose, D-digitoxose, D-digitalose, D-digginose, D-sarmentose, L-vallarose, and D-fructose. These sugars predominantly exist in the cardiac glycosides in the β-conformation.

The types of sugar found in cardiac glycosides can be devided in 3 types: 2,6-dideoxysugar moiety, 6-deoxysugar moiety and normal sugar moiety. The special one is 2,6-dideoxysugar moiety, such as digitoxose which occur only in cardiac glycosides.

Usually the sugar chain is attached to the 3β-OH group. There are one to 5 sugars moieties in the sugar chain in most cardiac glycosides. These sugars predominantly exist in the cardiac glycosides in the β-conformation.

There are 3 sorts of sugar chains:

A - type: aglycone-(2,6-dideoxy sugar)x-(D-glucose)y

B - type: aglycone-(6-deoxy sugar)x-(D-glucose)y

C - type: aglycone- (D-glucose)y

3．糖部分的结构

构成强心苷的糖有 20 多种。根据它们 C_2 位上有无羟基可以分成α-羟基糖（2-羟基糖）和α-去氧糖（2-去氧糖）两类。α-去氧糖常见于强心苷类，是区别于其它苷类成分的一个重要特征。

（1）α-羟基糖： 除 D-葡萄糖、L-鼠李糖外，还有 6-去氧糖如 L-夫糖（L-fucose）、D-鸡纳糖（D-quinovose）、D-弩箭子糖（D-antiarose）、D-6-去氧阿洛糖（D-6-deoxyallose）等；6-去氧糖甲醚如 L-黄花夹竹桃糖（L-thevetose）、D-洋地黄糖（D-digitalose）等。

（2）α-去氧糖： 有 2，6-二去氧糖如 D-洋地黄毒糖（D-digitoxose）等；2，6-二去氧糖甲醚如 L-夹竹桃糖（L-oleandrose）、D-加拿大麻糖（D-cymarose）、D-迪吉糖（D-diginose）和 D-沙门糖（D-sarmentose）等。

3．苷元和糖的连接方式　强心苷大多是低聚糖苷，少数是单糖苷或双糖苷。通常按糖的种类以及和苷元的连接方式，可分为以下三种类型：

I　型：苷元-（2，6-去氧糖）$_x$—（D-葡萄糖）$_y$ ，如紫花洋地黄苷 A（purpurea glycoside A）。

II 型：苷元-（6-去氧糖）$_x$—（D-葡萄糖）$_y$ ，如黄夹苷甲（thevetin A）。

III 型：苷元-（D-葡萄糖）$_y$ ， 如绿海葱苷（scilliglaucoside）。

植物界存在的强心苷，以 I、II 型较多，III 型较少。

三、Structure - Activity Relationships of cardiac glycoside (强心苷的结构与活性的关系)

The aglycone part is key to activity. The active intensity is depended on the streo structure of backbone, the type of unsaturated lactone ring and the substitutes attached to the backbone. The sugar moiety has no effect itself but can modified the strength caused by the aglycone.

大量的研究证明，强心苷的化学结构对其生理活性有较大影响。强心苷的强心作用取决于苷元部分，主要是甾体母核的立体结构、不饱和内酯环的种类及一些取代基的种类及其构型。糖部分本身不具有强心作用，但可影响强心苷的强心作用强度。强心苷的强心作用强弱常以对动物的毒性（致死量）来表示。

1, The steroid backbone

Usually steroid backbone has rings A/B and C/D in cis fused system while rings B/C are all trans fused system. This will let the "backbone" U shape which is very important to activity. Usually, conversion to C/D ring trans fusion are inactive. Conversion to A/B trans system leads to a marked drop in activity although not mandatory A/B cis fusion is important.

1. 甾体母核

甾体母核的立体结构与强心作用关系密切的是 C/D 环须顺式稠合。一旦这种稠合被破坏，将失去强心作用。若 C_{14} 羟基为 β 构型时即表明 C/D 环顺式稠合，若为 α 构型或脱水形成脱水苷元，则强心作用消失。A/B 环为顺式稠合的甲型强心苷元，必须具 C_3-β 羟基，否则无活性。A/B 环为反式稠合的甲型强心苷元，无论 C_3 是 β -羟基还是 α -羟基均有活性。

2, unsaturated lactone ring

The α、β-unsaturated lactone ring to C-17 in β-conformation plays an important role in receptor binding. Saturation of the lactone ring, attacheing to C-17 in α-conformation or the ring broken dramatically reduced the biological activity.

2. 不饱和内酯环

C_{17} 侧链上 α、β-不饱和内酯环为 β-构型时，有活性；为 α 构型时，活性减弱；若 α、β 不饱和键转化为饱和键，活性大为减弱，但毒性也减弱；若内酯环开裂，活性降低或消失。

3, sugar moiety

Although the sugar moiety is not necessary to activity directively. It appears to be important for the partitioning and kinetics of action. When a sugar residue attached to aglycone, it will inhance the hydrophilic property of molecule, the the toxic will become less.

Therefore, when sugar chain grows longer, although the activity is become weaker, the molecule become more safe since the aglycone partion in the whole molecule become less.

3. 糖部分

强心苷中的糖本身不具有强心作用，但它们的种类、数目对强心苷的毒性会产生一定的影响。一般来说，苷元连接糖形成单糖苷后，毒性增加。随着糖数的增多，分子量增大，苷元相对比例减少，又使毒性减弱。

四、TCM contains cardiac glycosides 含强心苷的中药举例

Digitalis lanata is belonged to Scrophularia family.It has been using for hundreds of years on treatment of cardiac failure. The active components in *Digitalis lanata* are cardiac glycosides. Totally over 30 cardiac glycosides have been found in the leaves of the plant. Among them, the lanatosides A an C are the most rich ones.

In pharmaceutical industry, the cardiac glycosides from *Digitalis lanata* are as the main source of the drugs cedilanid-D and digoxin.

（一）毛花洋地黄

毛花洋地黄（*Digitalis lanata*）是玄参科植物，在临床应用已有百年历史 ,至今仍是治疗心力衰竭的有效药物, 其叶富含强心苷类化合物，达 30 余种，多为次生苷。属于原生苷的有毛花洋地黄苷甲、乙、丙、丁和戊（lanatoside A、B、C、D、E），以苷甲和苷丙的含量较高。此外，还含叶绿素、树脂、皂苷、蛋白质、水溶性色素、糖类等杂质和可水解原生苷的酶。

毛花洋地黄是制备强心药西地蓝（cedilanid-D）（又称去乙酰毛花洋地黄苷丙）和地高辛（digoxin）（又称异羟基洋地黄毒苷）的主要原料。