Drug Development —— Metformin

AL CHEMISTRY PROJECT

CHUNG PO WAI 7S (9)
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Diabetes type1 vs type2

Type 1 diabetes

- Insulin-dependent
- Caused by the failure of pancreas to produce enough insulin

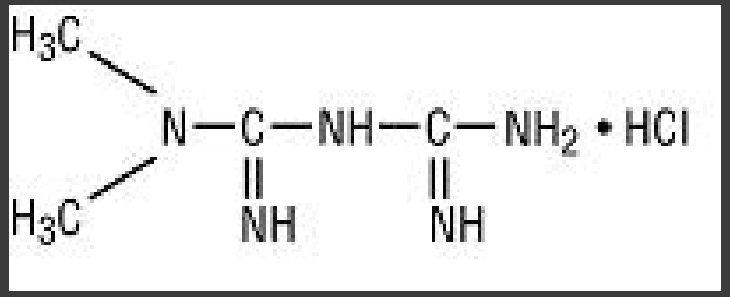
Type2 diabetes

- Insulin-independent
- Caused by the failure of liver and muscle cells to respond to the insulin
- Due to lack of receptor molecules that bind to insulin

Introduction

Metformin (*N*,*N*-dimethylimidodicarbonimidic diamide) is believed to be the most widely prescribed anti-diabetic drug in the world.

- First choice in the treatment for type 2 diabetes.

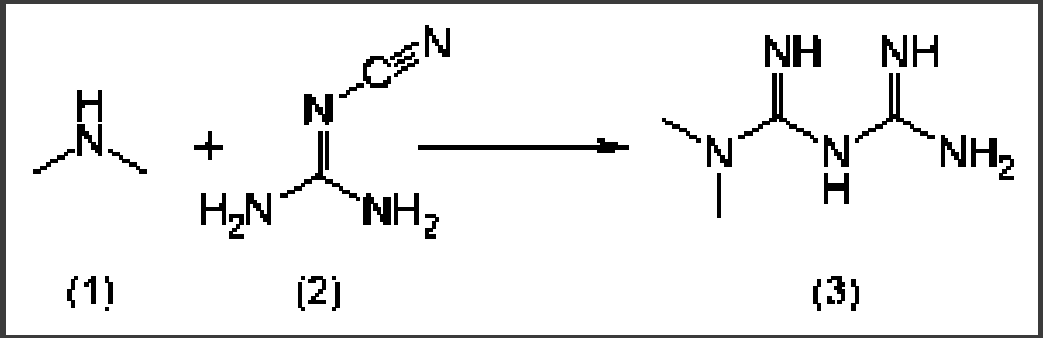


Function

- Suppress hepatic glucose production
- Increase insulin sensitivity
- Enhance peripheral glucose uptake
- Increase fatty acid oxidation
- Decrease absorption of glucose from the gastrointestinal tract

Lead Compound Discovery

1922 ---first discovered as a product in the synthesis of *N*,*N*-dimethylguanidine. (Emil Werner and James Bellandin)



1929 --- found to reduce blood sugar

1929-1949 --- research stopped

1950 --- found not to decrease blood pressure and heart rate in animals

1950 --- a physician, Garcia, used it to treat influenza and discovered it can lower the blood sugar to minimum physiological limit and it is non-toxic.

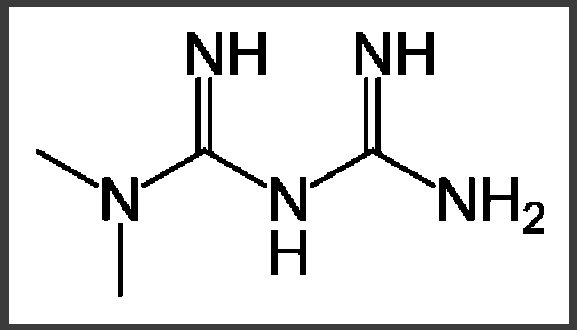
a French diabetologist Jean Sterne tried to re-investigate the blood sugar lowering activity of metformin

Molecular modification

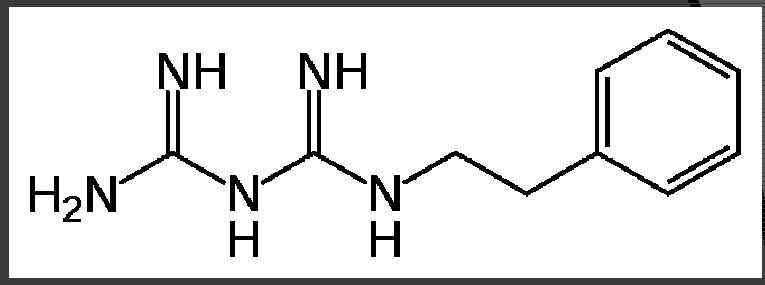
1. Galega officinalis (Goat's rue) was used for diabetes treatment.
2. But it was found to be too toxic
3. Then phenformin derived from Galega officinalis was used.
4. But it was still not safe for human use.
5. Finally metformin which has similar structure to phenformin was used and it is much less toxic.

Galega officinalis flowers

Structure of phenformin and metformin

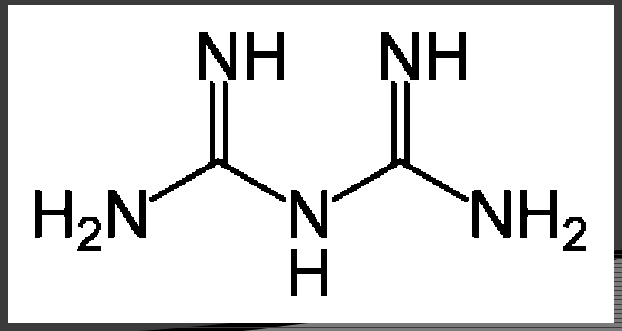


Metformin



Phenformin

They both are the members of **biguanide** and the its structure is shown below:



Formulation development

In diabetes treatment, metformin can:

- decrease glucose (sugar) production in the liver
- decreas absorption of glucose by the intestines

However, metformin also need to use with some other drugs. Here's some examples:

Repaglinide

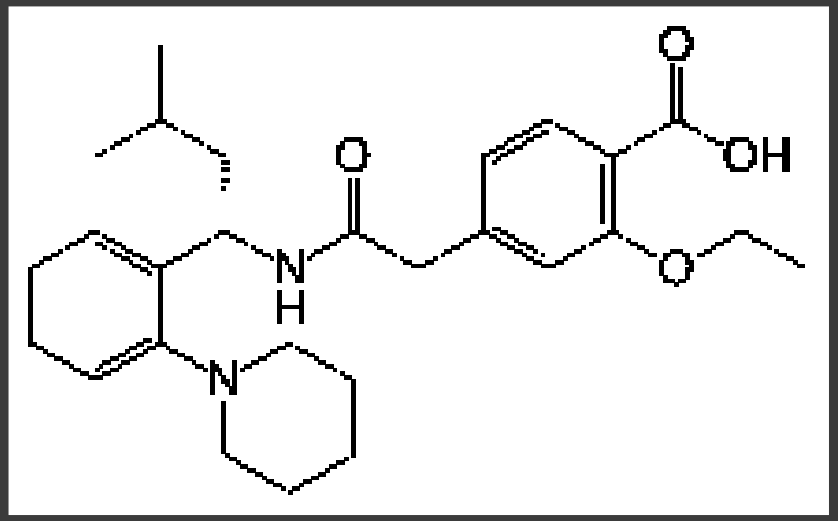
Pioglitazone

Rosiglitazone

Sitagliptin

Repaglinide can:

- lower blood glucose by stimulating the release of insulin from the pancreas



Pioglitazone can:

- reduce insulin resistance in the liver and peripheral tissues
- increase the expense of insulin-dependent glucose
- decrease withdrawal of glucose from the liver
- reduce quantity of glucose, insulin and glycated haemoglobin in the bloodstream

Rosiglitazone can:

- act as insulin sensitizers
- reduce glucose, fatty acid, and insulin blood concentrations
- lower insulin resistance

sitagliptin can:

- work to competitively inhibit the enzyme dipeptidyl peptidase 4 (DPP-4)
- Prevent the break down of GLP-1 and GIP hormones.
- these hormones are then able to potentiate the secretion of insulin and suppress the release of glucagon by the pancreas

Safety test and human trials

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin Levels

Initial and periodic monitoring of hematologic parameters, such as hemoglobin, hematocrit and red blood cell indices, and renal function should be performed

Human trials:

Most Common Adverse Reactions (> 5.0 %) in a Placebo-Controlled Clinical Study of Metformin Hydrochloride Tablets Monotherapy

Adverse Reaction	Metformin Hydrochloride Tablets Monotherapy (n = 141)	Placebo (n = 145)
	% of Patients	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

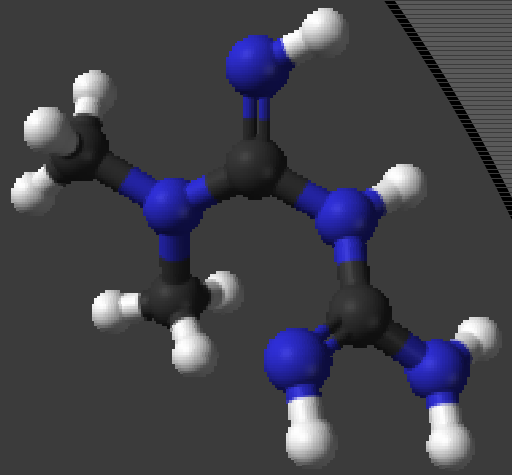
Pediatric Patients:

Metformin hydrochloride tablets USP ：

· effectively lower glucose levels in children (ages 10 to 16 years) with type 2 diabetes

· have not been studied in children younger than 10 years old.

Special conditions:



- have kidney problems
- have liver problems
- have heart failure that is treated with medicines, such as digoxin or furosemide
- drink a lot of alcohol. This means you binge drink for short periods or drink all the time
- are seriously dehydrated (have lost a lot of water from your body)
- are going to have an x-ray procedure with injection of dyes (contrast agents)
- develop a serious condition, such as heart attack, severe infection, or a stroke

Approval for marketing

- described in 1957 and became available in the British National Formulary in 1958.

- first marketed in France in 1979, but did not receive approval by the U.S. Food and Drug Administration (FDA) for Type 2 diabetes until 1994.

1995 - March 3 - **New molecular entity (NME)**

2000- October 13 - **New formulation**

2003- September 11 - **New formulation**

2004- April 28 - **New formulation**

2005- June 3 - **New manufacturer**

2008 - October 20 - **New formulation**

THE END