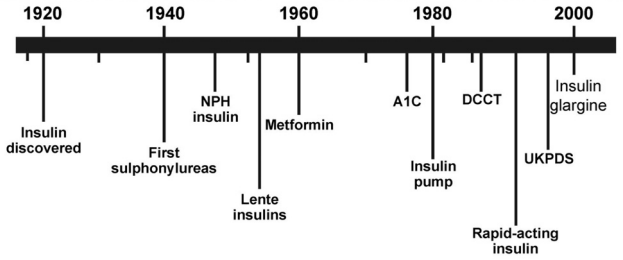
[연수강좌]

당뇨병 치료: Oral Hypoglycemic Agent

최 성 희

서울의대

Milestones in Diabetes Treatment



DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study.

1. Tattersall RB. In: Pickup JC, Williams G, eds. *Textbook of Diabetes*. 3rd ed. Boston, Mass: Blackwell Science; 2003.
2. US FDA Center for Drug Evaluation and Research. Available at: http://www.fda.gov/cder/da/ddpab96.htm. Accessed March 18, 2003.
3. Lantus Consumer Information. Available at: http://www.fda.gov/cder/consumerinfo/druginfo/lantus.htm. Accessed March 18, 2003.

ADA- and AACE/ACE-Recommended Goals for Glycemic Control: A1C, FPG, and PPG

Biochemical Control[1]	Normal[1]	Goal[1]
A1C* (%)	<6.0	<7.0†
FPG (mg/dL) Average preprandial	<100	90-130‡
PPG (mg/dL)	<140	<180§

*Referenced to the nondiabetic range using a DCCT assay.[1]
†AACE/ACE recommendation: ≤6.5%.[2]
‡AACE/ACE recommendation: <110 mg/dL.[2]
§AACE/ACE recommendation: <140 mg/dL.[2]

ADA, American Diabetes Association; AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; FPG, fasting plasma glucose; PPG, postprandial glucose; DCCT, Diabetes Control and Complications Trial.

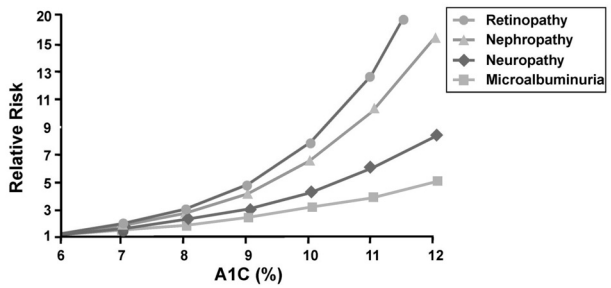
1. ADA. *Diabetes Care.* 2003;26(suppl 1):S33-S50.
2. AACE/ACE. *Endocr Pract.* 2002;8(suppl 1):40-82.

Correlation between A1C level and mean plasma glucose levels

AIC (%)	Mean plasma glucose	
	mg/dl	mmol/l
6	135	7.5
7	170	9.5
8	205	11.5
9	240	13.5
10	275	15.5
11	310	17.5
12	345	19.5

Mean plasma glucose = (HbA1c X 35) - 75

A1C and Relative Risk of Microvascular Complications: DCCT



DCCT, Diabetes Control and Complications Trial.

1. Adapted from Skyler JS. *Endocrinol Metab Clin North Am.* 1996;25:243-254.
2. DCCT. *N Engl J Med.* 1993;329:977-986.
3. DCCT. *Diabetes.* 1995;44:968-983.

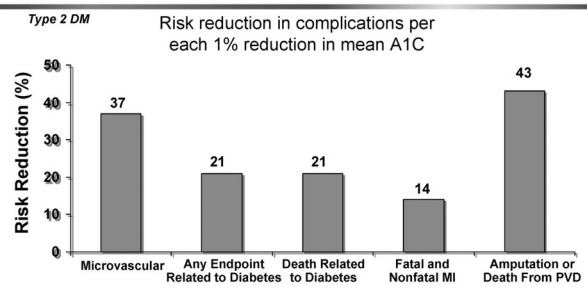
Good Glycemic Control Reduces Incidence of Complications

Complications of diabetes mellitus	Risk reduction by decrease in A1C (%) DCCT[1,2] (9% → 7%)	Ohkubo[3] (9% →7%)	UKPDS[4] (8% → 7%)
Retinopathy	-63%	-69%	-21%
Nephropathy	-54%	-70%	-34%
Neuropathy	-60%	–	–
Macrovascular disease	-41%*	–	-16%*

*Not statistically significant.
DCCT, Diabetes Control and Complications Trial; UKPDS, United Kingdom Prospective Diabetes Study.

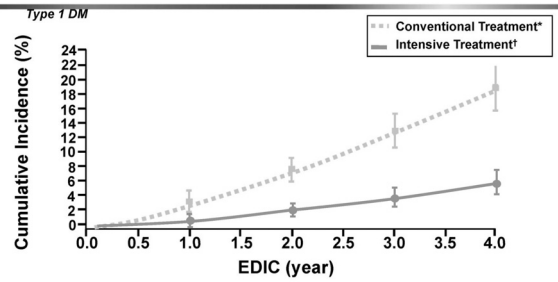
1. DCCT Research Group. *N Engl J Med.* 1993;329:977-986.
2. DCCT Research Group. *Diabetes.* 1995;44:968-983.
3. Ohkubo Y et al. *Diabetes Res Clin Pract.* 1995;28:103-117.
4. UKPDS Group. *Lancet.* 1998;352:837-853.

Correlation of A1C and Complication Risk: UKPDS



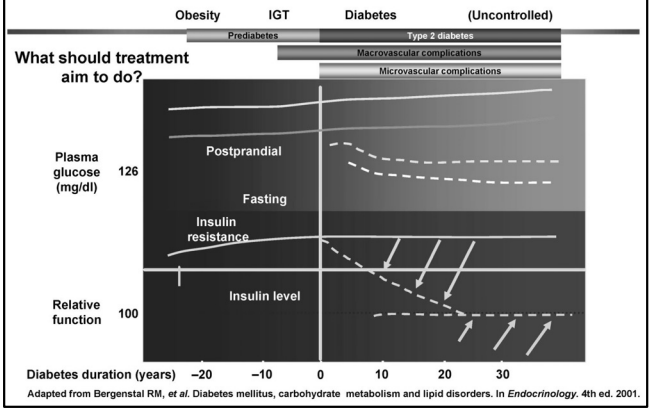
UKPDS, United Kingdom Prospective Diabetes Study; MI, myocardial infarction; PVD, peripheral vascular disease.
Stratton IM et al. *Br Med J.* 2000;321:405-412.

Preservation of Benefit: EDIC Progression of Retinopathy



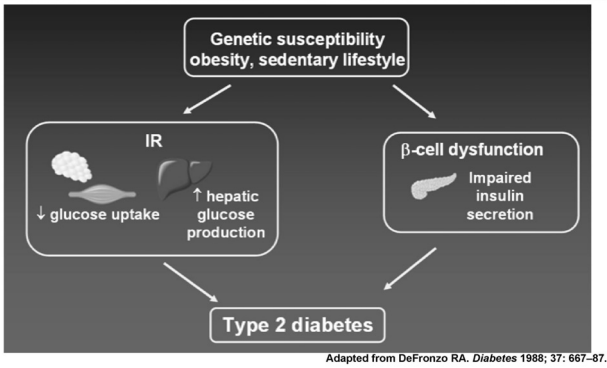
*1-2 insulin injections and 1 urine/blood glucose test daily.
†≥3 insulin injections/pump treatments daily + SMBG + diet + exercise.
EDIC, Epidemiology of Diabetes Interventions and Complications trial; SMBG, self-monitored blood glucose.
DCCT/EDIC Research Group. *N Engl J Med.* 2000;342:381-389.

Modifying disease progression through treatment



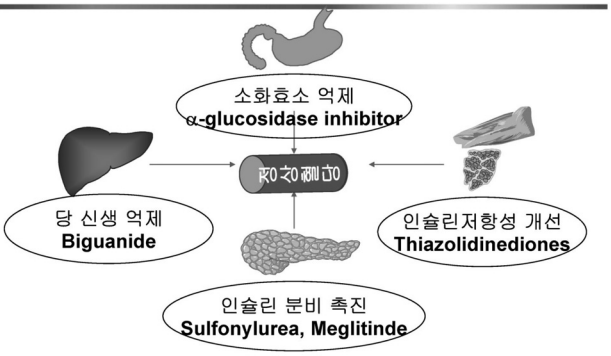
Adapted from Bergenstal RM, *et al.* Diabetes mellitus, carbohydrate metabolism and lipid disorders. In *Endocrinology.* 4th ed. 2001.

Targeting the underlying factors in type 2 diabetes: IR and β-cell dysfunction



Adapted from DeFronzo RA. *Diabetes* 1988; 37: 667–87.

Mechanism of Antidiabetic agents



Adapted from De Fronzo RA. *Diabetes* 1988; **37**:667–687.

약물 선택시 고려사항

1. 환자의 측면:
- 약물의 순응도
- 경제적인 문제

2. 질환의 측면:
- 고혈당의 정도
- 동반질환의 유무
- 합병증의 정도

3. 치료의 측면:
- 약물의 작용기전
- 약물의 부작용

Strategies for the treatment of type 2 DM

- Amelioration of insulin resistance
  - diet, exercise, weight loss
  - metformin, Thiazolidinedione
- Augumentation of insulin Secretion
  - sulfonylurea, meglitinide
- Limitation of postprandial hyperglycemia
  - α-glucosidase inhibitor, Meglitinide

혈당 개선제

- Insulin secretogogues: Sulfonylurea, Meglitinide
- Biguanides
- α-glucosidase inhibitors
- Thiazolidinediones
- Insulin and analogues

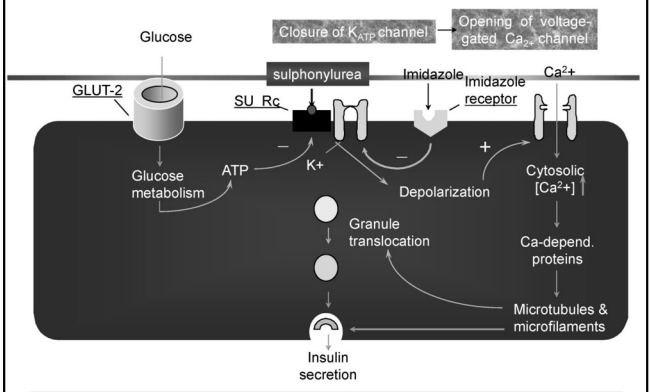


Fig. Sulfonyureas stimulate insulin release through SU receptor.

Sulfonylurea 작용기전

- 췌장에 대한 효과
  베타세포에서 인슐린 분비 증가
- 췌장외에 대한 효과
  - 간의 당 신생 억제
  - 말초조직에서 당 수송 및 섭취 증가

Sulfonylurea 종류

성분명	함량 (mg/dl)	일 사용량 (mg/dl)	작용 시간(h)	횟수	배설경로	특징
Chlorpropamide	250	125-500	60	1	신장	수분저류, 술-안면홍조
Glipizide	5	2.5-40	10-24	1-2	신80/담20	
Glibenclamide	2.5, 5	2.5-15	12-24	1-2	신50/담50	
Gliclazide	40, 80	80-320	12-24	1-2	신70/담30	혈소판 응집억제
Gliquidone	30	15-60	5-7	2-3	신5/담95	신질환시 가능
Gliclazide MR	30	30-120	24	1	신70/담30	*
Glimepiride	2	1-8	16-24	1-2	신60/담40	*

Sulfonylurea 약물 상호 작용

혈당 강하 작용 저하	혈당 강하 작용 증가
Diuretics	Sulfonamides
Diphenylhydantoin	Salicylates
Glucocorticoids	Clofibrate
Lithium	Dicumarol
Rifampin	Monoamine oxidase inhibitors
Isoniazid	NSAIDs
Nicotinic acid	Beta-blockers
	Alcohol

Sulfonylurea 부작용

- 저혈당
- 체중 증가
- 고인슐린혈증
- 위장 장애
- 피부 발진
- 간기능 이상
- 수분저류(only diabinese)

Sulfonylurea 적응증 및 금기

적응증	금 기
40세 이후 발병??	제1형 당뇨병 환자
진단된 지 5년 이내??	임신및 수유부
정상체중, 비만	신질환 (Cr>2.0 mg/dl) gliquidone은 예외
인슐린의 완전결핍 아닌 경우	간질환
	심한 감염, 수술 등 스트레스상태
	약제에 대한 부작용

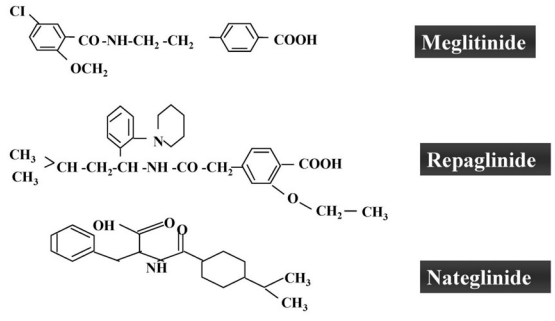
Sulfonylurea 치료실패

- **1차 실패 : 처음부터 설폰요소제 치료에 반응하지 않는 경우(15-20%)**
  원 인; 환자를 잘못 선택
  식사요법을 철저히 하지 않은 환자
- **2차 실패 : 치료 최소 1개월 이상 약제에 잘 반응하다가 더 이상 반응이 없는 경우(5-10%)**
  원 인 ; 잘못된 식사요법, 체중증가
  감염 혹은 스트레스 등의 병발
  혈당을 증가시키는 약제 사용

혈당 개선제

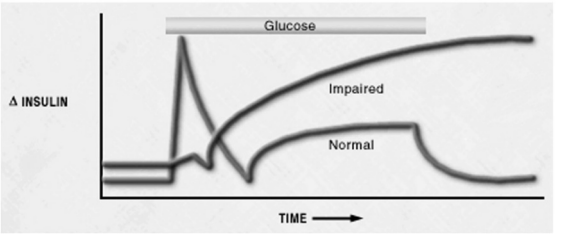
- Insulin secretogogues: Sulfonylurea, Meglitinide
- Biguanides
- α-glucosidase inhibitors
- Thiazolidinediones
- Insulin and analogues

Meglitinides 구조



인슐린의 분비

- **Insulin**분비는 두 단계
  - **1**단계 **:** 혈당 상승 후 즉시 시작 **- 10**분간 지속
  - **2**단계 **:** 혈당이 상승되어 있는 동안 지속됨



Meglitinides 작용기전 및 종류

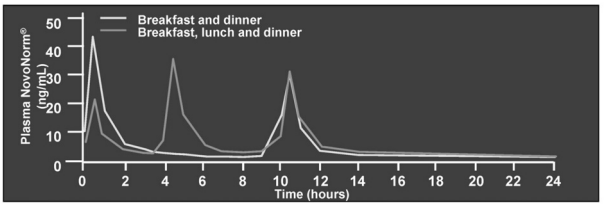
- **Repaglinide : Benzoic acid derivatives**
- **Nategliniides : Phenylalanine derivative**
- **SUR1 receptor**에 결합하여 **1st phage** 인슐린 분비 자극

종 류

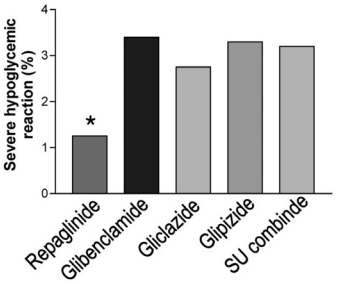
성분명	함량 (mg/dl)	일 사용량 (mg/dl)	Peak (h)	작용 시간(h)	횟수	배설
Repaglinide	0.5, 1	1.5-4	1	<3	식사 횟수	92% 대변 8% 소변
Nateglinide	30, 90	120-360				

Meglitinides 특성

- 식사 직전에 복용 **:** 빠른 흡수
- 식후 혈당 조절
- **No Meal, No Tablet :** 저혈당 적음
- 주로 담즙 배설 **:** 신기능 이상시 사용 가능



Meglitinides Hypoglycemia



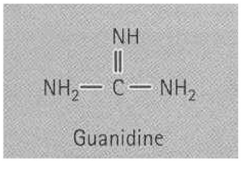
Meta analysis based on 4 one year, comparative double-blind studies

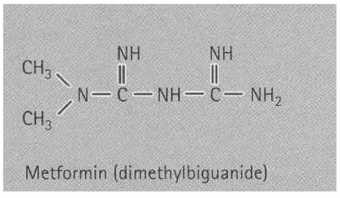
혈당 개선제

- Insulin secretogogues: Sulfonylurea, Meglitinide
- Biguanides
- α-glucosidase inhibitors
- Thiazolidinediones
- Insulin and analogues

Biguanide 종류 및 구조

성분명	함량 (mg/dl)	일일 사용량 (mg/day)	T1/2 (h)	작용 시간(h)	횟수
Metformin	250, 500	500 - 2550	1.7-4.5	12	2-3





Biguanide 특징

- 간의 당신생 억제, 말초조직 인슐린 감수성 증가
- 비만, 인슐린 저항성 환자에서 초기약제로 선택
- 공복시 고혈당 감소에 효과적임.
- 체중 증가가 없고 오히려 다소 체중 감소 유발
- 단독 요법시 저혈당 발생하지 않음
- 심혈관 위험율 감소 : 중성지방, **LDL-C** 감소시킴

Biguanide (Metformin) 금기

- 신기능 이상 : **Cr>1.4(M), 1.5(F) mg/dL**
- 근육량 적은 노인은 정상 **Cr** 이라도 주의
- 울혈성 심부전
- 호흡 부전증
- 간질환
- 젖산혈증 기왕력, 심한 감염, 패혈증
- **Contrast dye** 사용시 일시 중단
- 치료하지 않은 비타민 **B12** 결핍증

Biguanide (Metformin) 부작용

- 소화기계 부작용
- 가장 흔함 : 오심, 구토, 설사, 복부 불쾌감
- 소량부터 서서히 증량하거나, 증상시 감량하면 피할 수 있음
- 금속 맛
- 장기 복용 시-**B12**, 엽산 흡수 장애
- 젖산 혈증: 적음 **(0.03/1000 patients-yr)**

혈당 개선제

- Insulin secretogogues: Sulfonylurea, Meglitinide
- Biguanides
- α-glucosidase inhibitors
- Thiazolidinediones
- Insulin and analogues

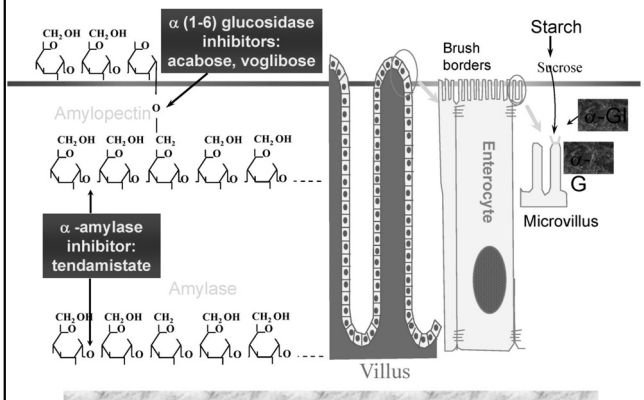


Fig. Starch digestion and its inhibitors.

α-glucosidase inhibitor 특징

- 이당류를 단당류로 분해하는 소장점막의 brush border 효소 억제
- 식후 고혈당에 효과
- 장점 : 단일요법시 저혈당이 없고 혈청 지질농도에 영향이 없음
- 부작용 : 주로 위장증상 (복명, 복부 팽만, 방귀, 설사,)
- 금기 : 염증성 장 질환, 간경변증, s-Cr>2.0 mg/dl
- 종류 : Acarbose, Voglibose, miglitol등

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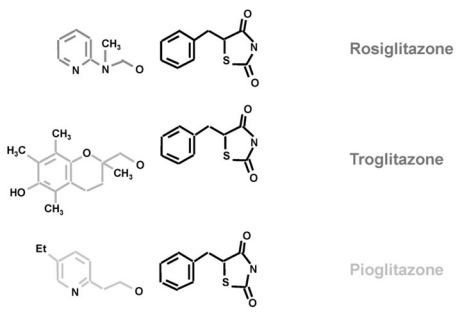
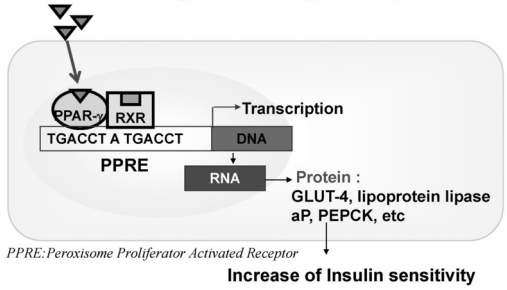
Thiazolidinediones 화학구조



Thiazolidinediones 작용기전

Thiazolidinediones (Rosiglitazone, Pioglitazone)



PPRE:Peroxisome Proliferator Activated Receptor

Increase of Insulin sensitivity

Thiazolidinediones 특징

- 말초조직 인슐린 감수성 증가 **(**메트포르민 보다 **4**배**)**
- 고혈압 및 지질치 개선 효과
- **4**주 이후에 효과**,** 설폰요소제 나 메트포르민보다 혈당강하 효과 적음**-** 단독요법보다 병합요법이 효과적
- 고용량의 인슐린을 사용하는 제**2**형 당뇨병환자에서 인슐린요구량을 감소시킴

Thiazolidinediones 부작용 및 금기

부작용	금 기
▪ 혈액량 증가 **(**부종**)**	▪ 제1형 당뇨병 환자
▪ 체중 증가 **(1-2 Kg)**	▪ 심한 간질환
▪ 간기능 이상	▪ 울혈성 심부전 (3기-4기)
▪ 심비대	▪ 임신 및 수유부
▪ 혈색소 감소	

Site and mode of action

Intestinal agent
- Inhibitors of carbohydrate digestion
- Inhibitors of glucose absorption
- Modulators of incretin hormones

Insulin and insulin-modulating strategies
- Insulin analogs with designer pharmacokinetics
- Alternative insulin delivery methods and routes
- Endogenous insulin secretagogues
- Agents for regeneration of pancreatic β-cells: INGAP
- Insulin mimetics which, though structurally different, act on the insulin receptor

Insulin sensitizers
- Systemic insulin sensitizers
- Hepatic insulin sensitizers
- Global insulin sensitizers (which have systemic and hepatic insulin sensitization properties)

Incretins
- Amylin analogs
- Glucagons-like peptide-1 (GLP-1) agonists and related analogues
- Dipeptidyl peptidase IV inhibitors

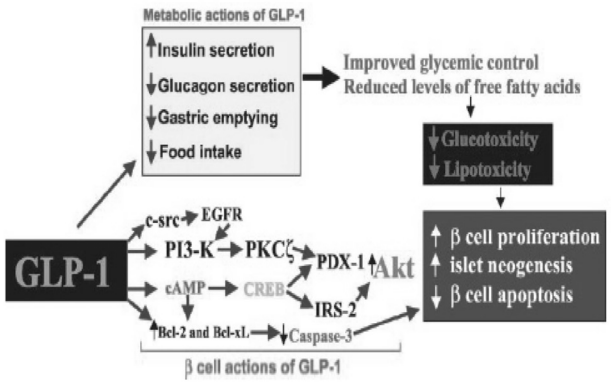
Other agents
- Inhibitors of counter-regulatory hormones
- Antilipolytic agents
- Fatty acid–oxidation inhibitors
- Inhibitors of gluconeogenesis
- Very-low-density lipoprotein synthesis inhibitors
- Glycogenolysis inhibitors
- Antiobesity agents

Effect of 6-Week Course of GLP-1 Infusion in T2DM

GLP-1 as a continuous subcutaneous infusion (using insulin pumps) for 6 weeks

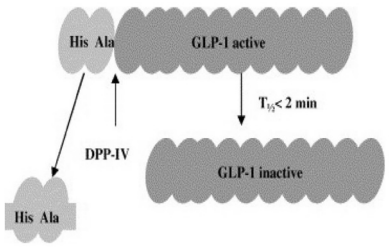
- Lowered fasting plasma glucose by 77mg/dL and 8-hour mean plasma glucose by 100mg/dL
- Decreased A1c levels by 1.3%
- Decreased body weight by 2-3 kg
- Increased insulin sensitivity by 77%

Lancet 359:824-830, 2002



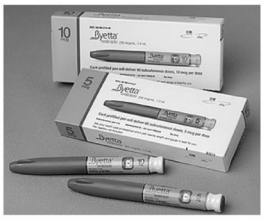
GLP-1

- 30 amino acid polypeptide
- Secreted from L-cells in ileum after meals
- Metabolized by DPP-IV within 2-4 minutes

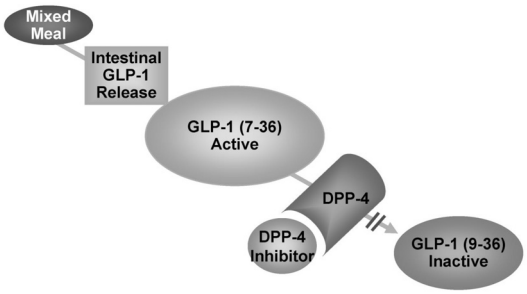


Exenatide

- 5-10 ug twice daily SC injections
- Mainly in postprandial hyperglycemia
- HbA1c: - 1.3% decrease, Wt: - 3.4 kg
- Side effect: N/V
- Approved by FDA in April, 2005



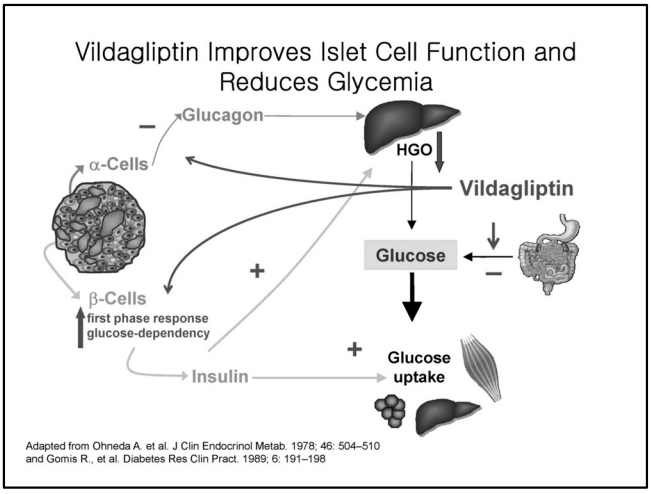
DPP-IV inhibitors



DPP-IV inhibitors ("liptins")

- Vildagliptin (LAF-237) (Galvus®, Norvatis)
- Sitagliptin (MK-0431) (Januvia®, Merck)
- Saxagliptin (BMS-477118) (BMS)
- Others...

1. Reversible product analogue inhibitors (e.g. pyrrolidines, thiazolidines).
2. Covalently modifying product analogue inhibitors (e.g. cyanopyrrolidines).
3. Reversible non-peptidic heterocyclic inhibitors (e.g. Xanthines, aminomethylpyrimidines).


Vildagliptin Improves Islet Cell Function and Reduces Glycemia
Glucagon
HGO
α-Cells
Vildagliptin
Glucose
β-Cells
first phase response
glucose-dependency
Insulin
Glucose
uptake
Adapted from Ohneda A. et al. J Clin Endocrinol Metab. 1978; 46: 504–510
and Gomis R., et al. Diabetes Res Clin Pract. 1989; 6: 191–198