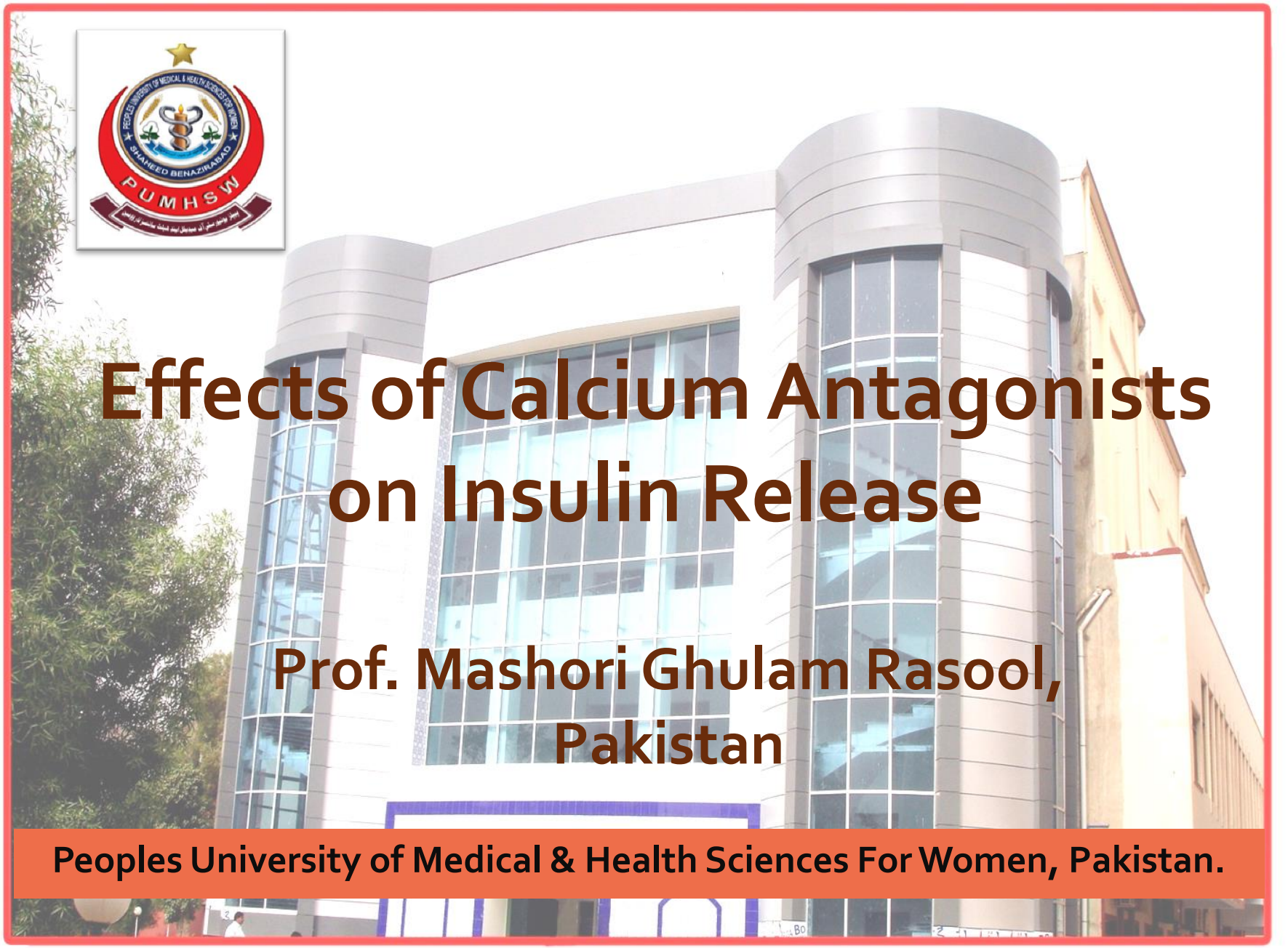


Effects of Calcium Antagonists on Insulin Release

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Introduction

- Cardiovascular diseases are the main cause of death in many countries and pose health problems not only in the developed countries, but also in the developing countries (WHO, 2015).

http://www.who.int/mediacentre/factsheets/fs317/en/)

Introduction

- **Antihypertensive treatment has reduced the incidence of stroke, heart failure and renal failure. However the incidence of coronary heart disease (CHD) is not reduced to the same degree (Wang et. el. 2005) (Europian Society of Cardiology 2014)**

(Wang JG, Staessen JA, Franklin SS, Fagard R, Gueyffier F. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. *Hypertension*. 2005;45:907–913.)
http://www.escardio.org/The-ESC/Press-Office/Press-releases/Last-5-years/Antihypertensive-therapy-reduces-CV-events-strokes-and-mortality-in-older-adult

Introduction

- The main goal in the treatment of Hypertension is to reduce the risk of future cardiovascular morbidity and early death. (Vadera et. el. 2011). Cardiovascular diseases may be related not only to the elevated blood pressure, but also to the other risk factors, including the increase in plasma glucose (Davidson JA, 2009)

1: Vadera R. Does antihypertensive drug therapy decrease morbidity or mortality in patients with a hypertensive emergency? Ann Emerg Med. 2011 Jan;57(1):64-5. doi: 10.1016/j.annemergmed.2010.05.021.
2: Davidson JA, Parkin CG. Is hyperglycemia a causal factor in cardiovascular disease? Does proving this relationship really matter? Yes. Diabetes Care. 2009 Nov;32 Suppl 2:S331-3. doi: 10.2337/dc09-S333. Review.

Introduction

- Treatment of hypertension in most instances is prolonged and often for life. Therefore it is always necessary to identify antihypertensive drugs such as the Calcium Antagonists, which are needed to reduce blood pressure, that may potentially cause deterioration in GI (Jeff Hughes,2007).

Do calcium antagonists contribute to gastro-oesophageal reflux disease and concomitant noncardiac chest pain? British Journal of Clinical Pharmacology, 2007 July 64(1): 83-89.

Introduction

- Several agents advocated as first line drugs in the stepwise antihypertensive therapy have been known to cause carbohydrate intolerance and this has been implicated as a major risk factor in the development of CHD (Suter et. al 1995).

Suter PM, Vetter W. Metabolic effects of antihypertensive drugs. J Hypertens Suppl. 1995 Dec;13(4):S11-7.

Introduction

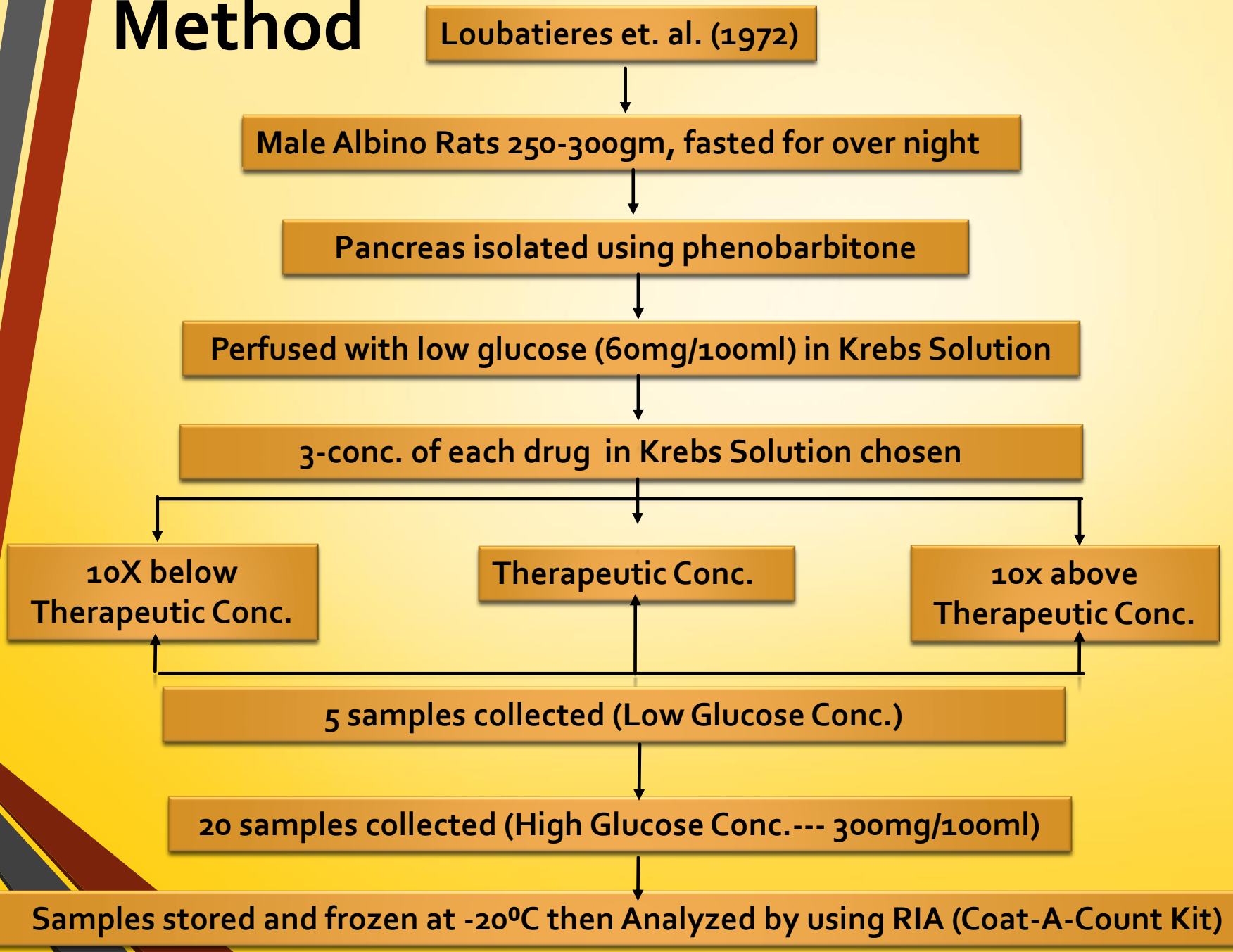
- In the 1990's individualized therapy in the treatment of Hypertension has also been advocated (Ogihara et al 1990), whereby new groups of antihypertensive drugs, such as the Calcium Antagonists may be used as first line therapy (Burnier et al, 2009).

1. Ogihara T, Mikami H. [Pathogenesis and treatment of hypertension]. Rinsho Byori. 1990 May;38(5):559-62. Review. Japanese. :
2. Burnier M, Prujm M, Wuerzner G. Treatment of essential hypertension with calcium channel blockers: what is the place of lercanidipine? Expert Opin Drug Metab Toxicol. 2009 Aug;5(8):981-7. Review.

Objective

- The study relates to evaluate and compare the effects of a number of calcium antagonists of dihydropyridine class on insulin release in rat isolated pancreas.

Method

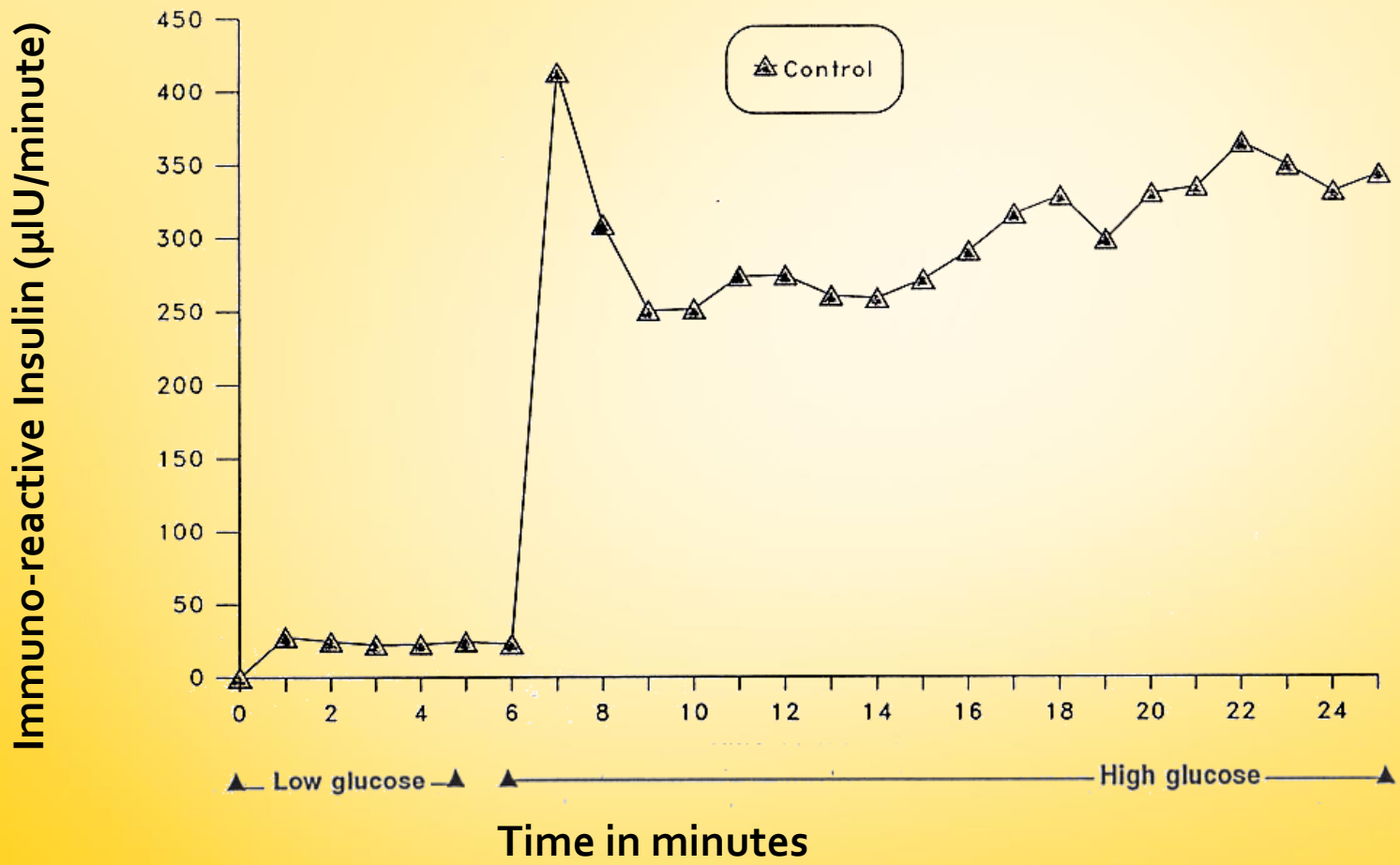

Loubatieres et. al. (1972)
Male Albino Rats 250-300gm, fasted for over night
Pancreas isolated using phenobarbitone
Perfused with low glucose (60mg/100ml) in Krebs Solution
3-conc. of each drug in Krebs Solution chosen
10X below Therapeutic Conc.
Therapeutic Conc.
10x above Therapeutic Conc.
5 samples collected (Low Glucose Conc.)
20 samples collected (High Glucose Conc.--- 300mg/100ml)
Samples stored and frozen at -20⁰C then Analyzed by using RIA (Coat-A-Count Kit)

Method

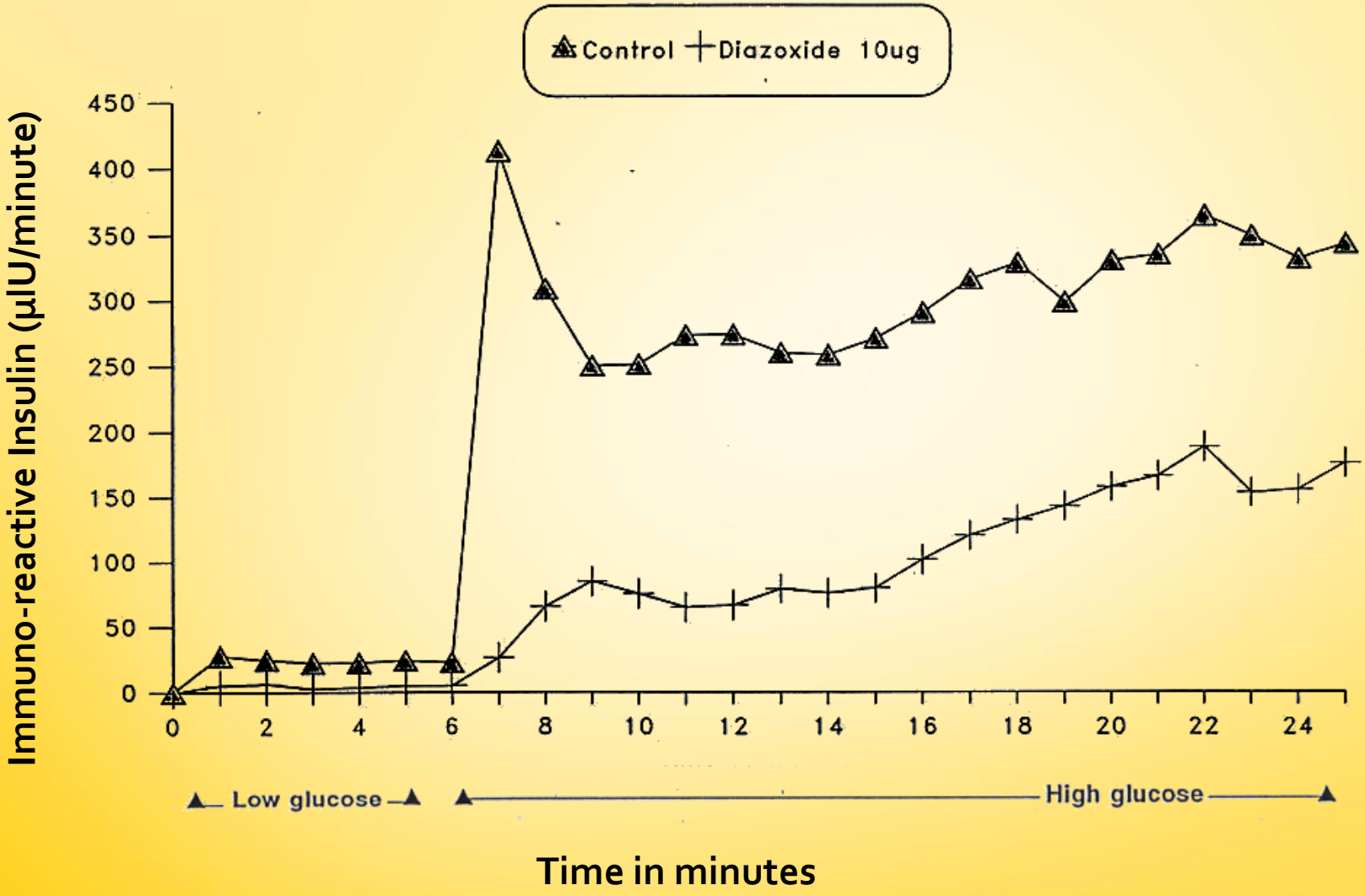
- The concentrations chosen for the drugs were based on the peak serum/ plasma concentration achieved in human with a single therapeutic dose.
- The Concs. of drugs used are shown in Table-I

Table-I: Concentration of Calcium Antagonists used in the Study

Calcium Antagonist	1/10 Peak Plasma Concentration	Peak Plasma Concentration	10x Peak Plasma Concentration
Isradipine	1ng	10ng	100ng
Nicardipine	20ng	200ng	2µg
Amlodipine	0.5ng	5ng	50ng



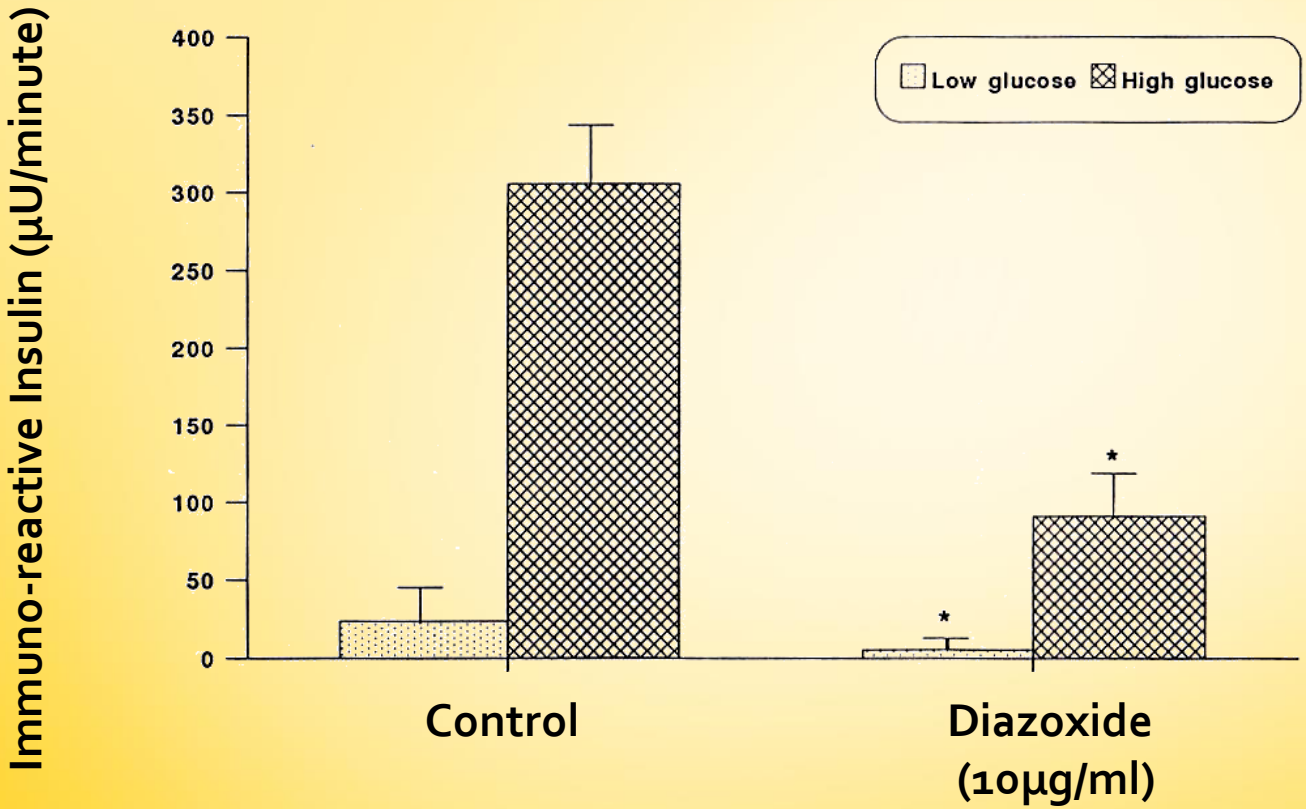
Effects of low (0-5) and high glucose perfusion (6-25 min) on insulin release in normal isolated rat pancreas.



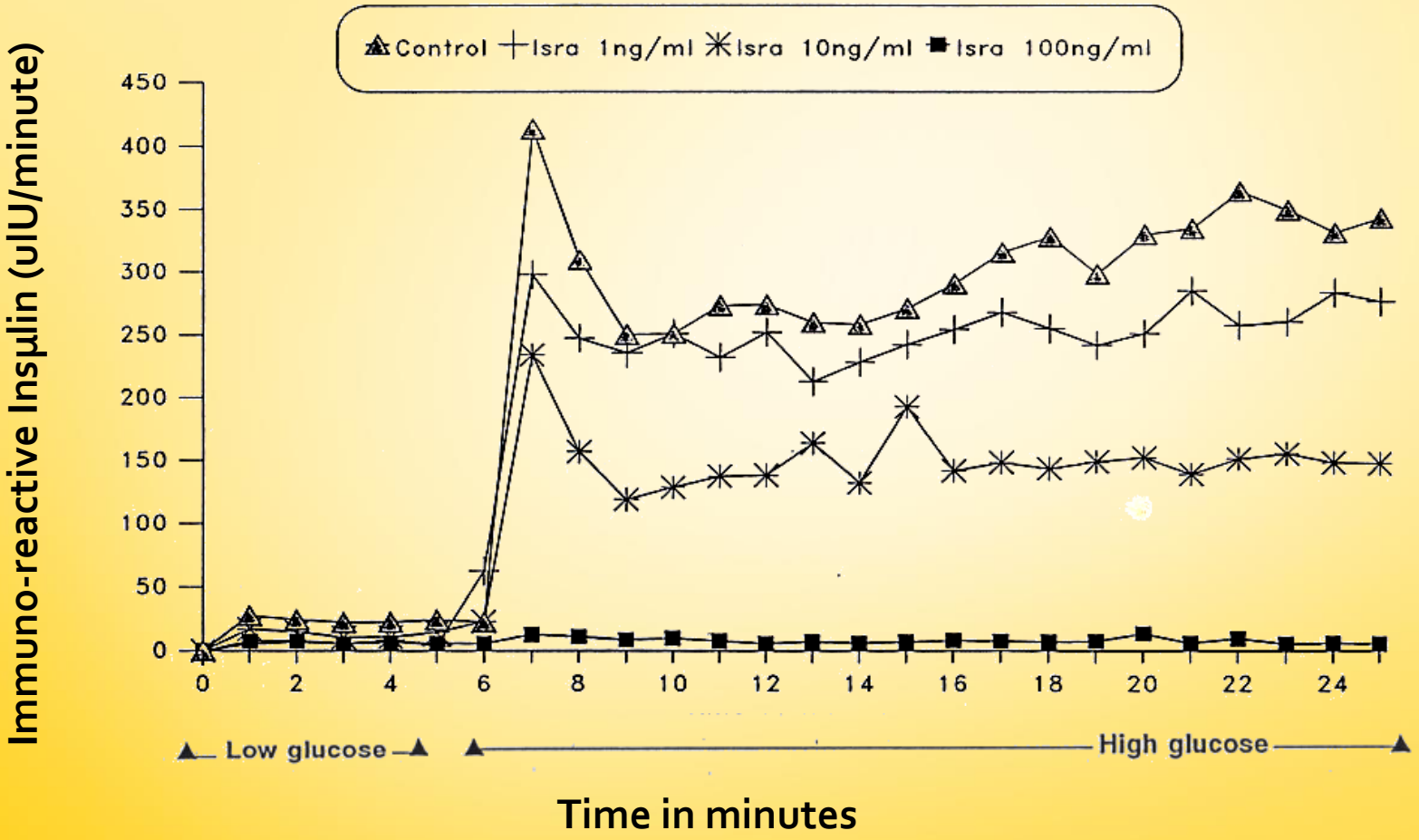
Effect of Diazoxide (10µg/ml) on insulin release (µlU/min) in low and high glucose perfusion in isolated rat pancreas (n=6)

Method

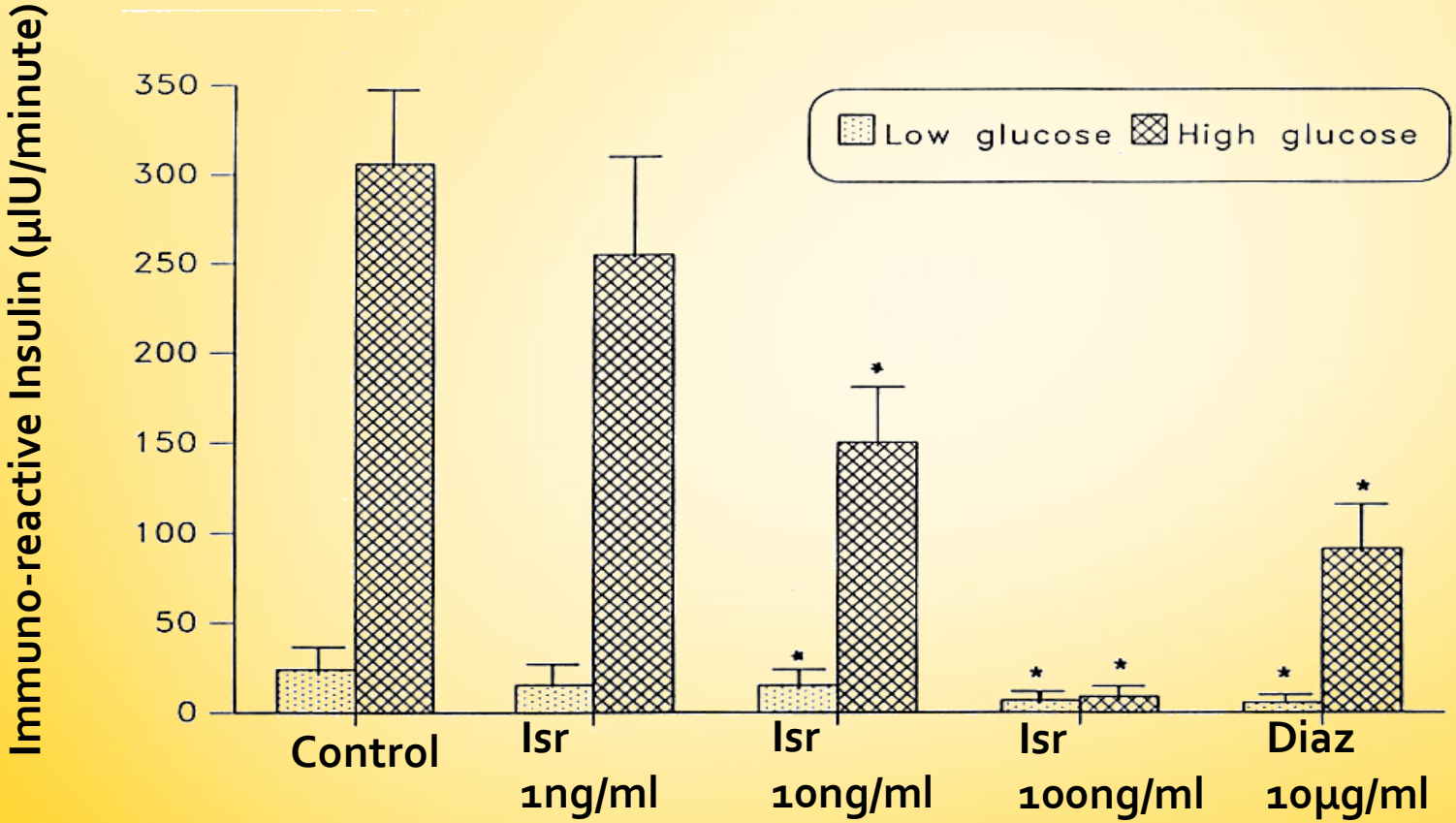
1. Effect of Glucose on Insulin Release is Biphasic Response.
2. Diazoxide a known insulin suppressant drug used as a positive control at a dose 10µg/ml shows inhibition of insulin release approximately by 50% (Howell et al. 1968, Henquin et al. 1982, Bergsten et al. 1988, Garrino et al. 1989 etc.)



Effect of Diazoxide (10µg/ml) on average insulin/min/pancreas (mean± sem) in low and high glucose perfusion in isolated rat pancreas (n=6) (*P<0.05).



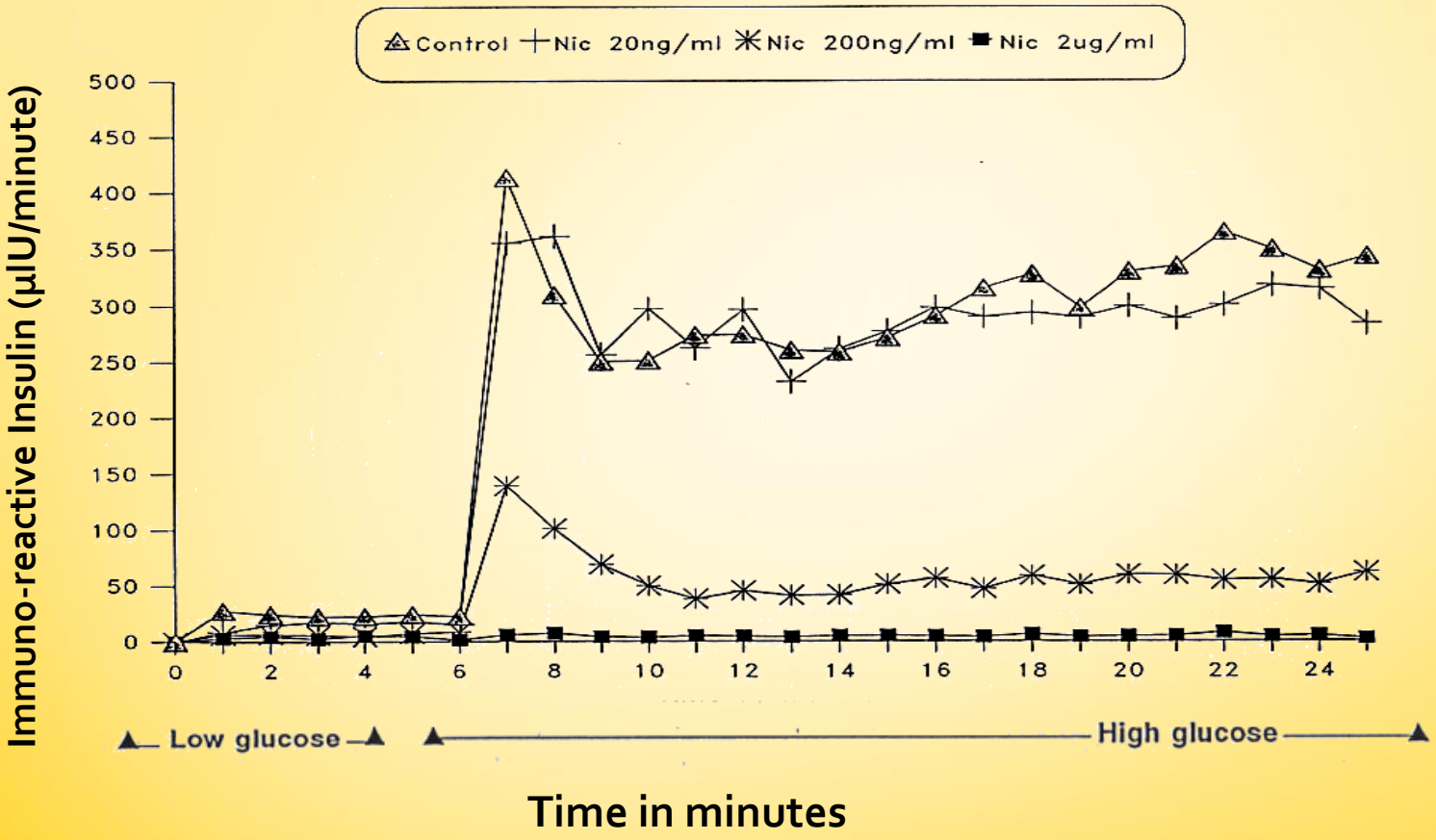
Effects of Isradipine (1ng/ml, 10ng/ml & 100ng/ml) on insulin release (µlU/min) in low and high glucose perfusion in isolated rat pancreas (n=6).



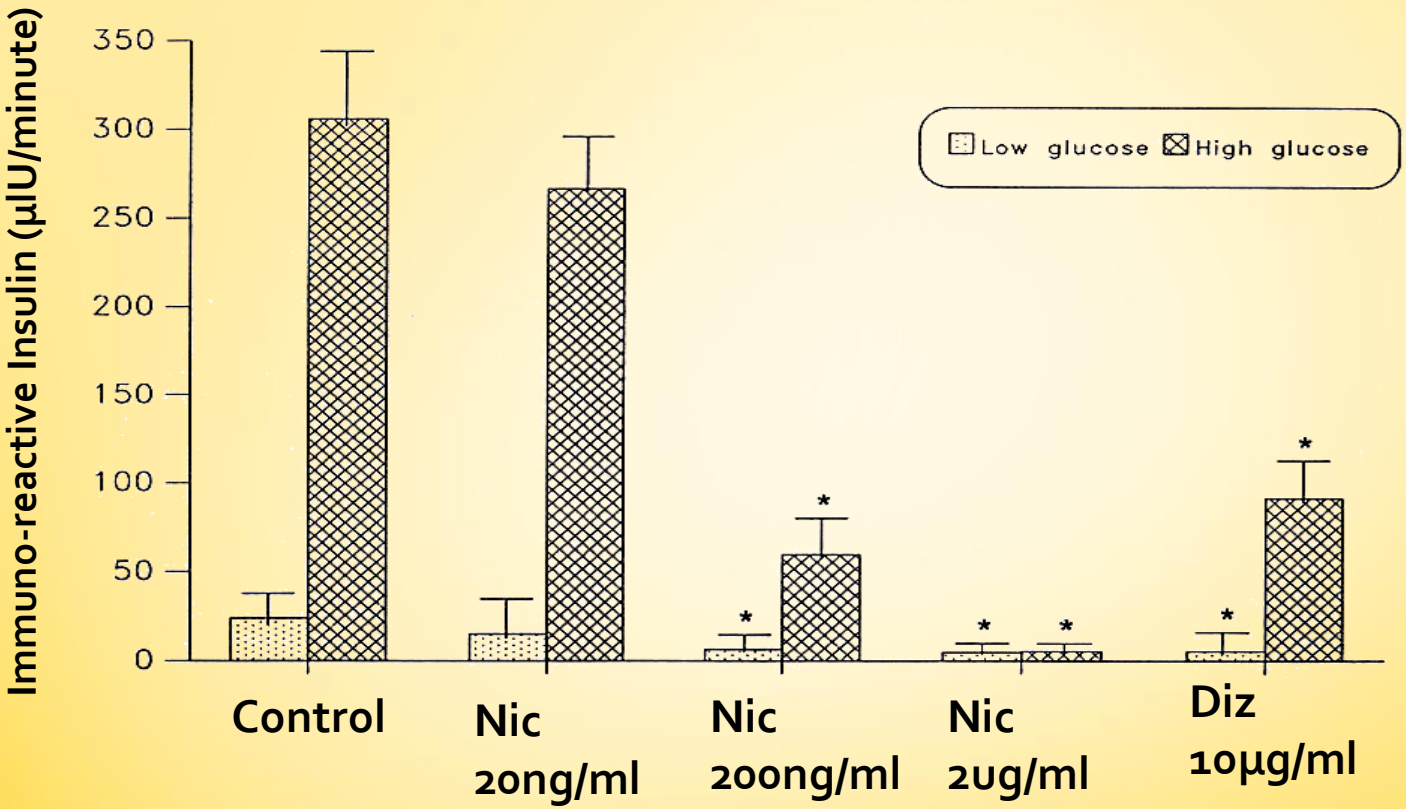
Effects of Isradipine (1ng/ml, 10ng/ml & 100ng/ml) on average insulin/min/pancreas (mean ± sem) in low and high perfusion in isolated rat pancreas (n=6). (*P<0.05)

Effects of Isradipine on Insulin Release

- At 1ng/ml there were no significant effect.
- At 10ng/ml and 100ng/ml there was significant inhibition of insulin release.
- Inhibition was dose dependent.



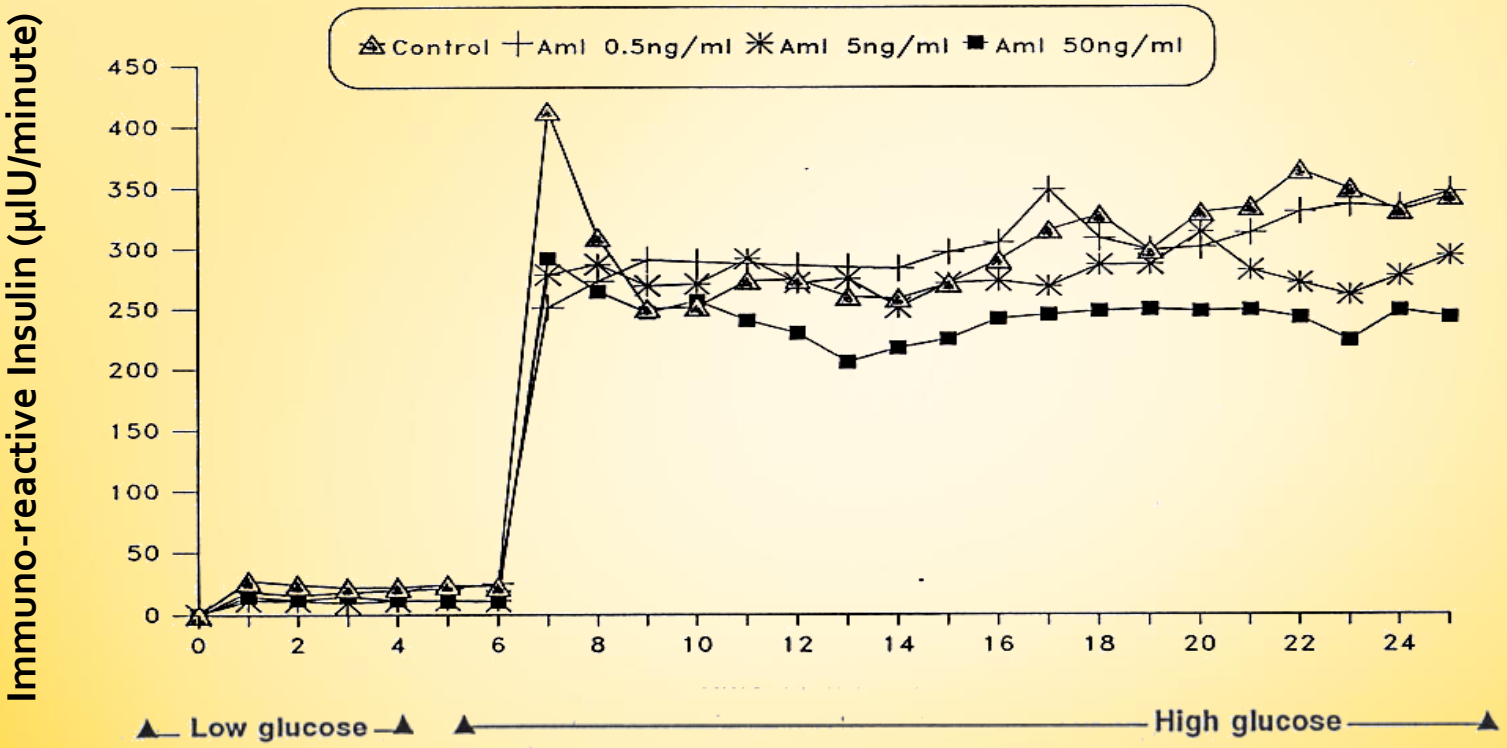
Effects of Nicardipine (20ng/ml, 200ng/ml, & 2µg/ml) on insulin release (µlU/min) in low and high glucose perfusion in isolated rat pancreas. (n=6)



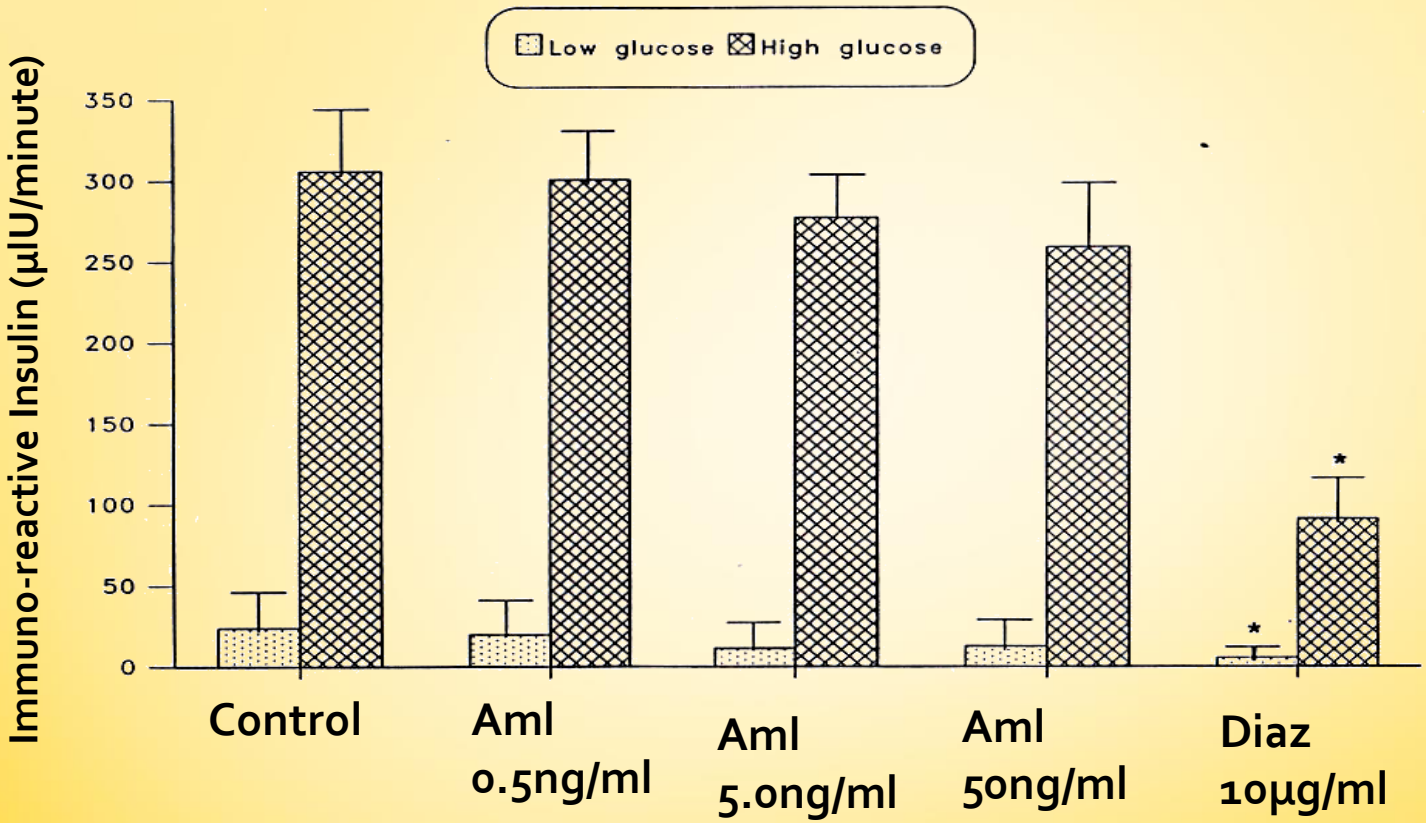
Effects of Nicardipine (20ng/ml, 200ng/ml, & 2ug/ml) on average insulin/min/pancreas (mean ± sem) in low and high glucose perfusion in isolated rat pancreas (n=6). (*P<0.05)

Effects of Nicardipine on Insulin Release

- At 20ng/ml there was no significant effect.
- At 200ng/ml and 2µg/ml there were significant inhibition of insulin release.
- Inhibition was dose dependent.



Effects of Amlodipine (0.5ng/ml, 5ng/ml & 50ng/ml) on insulin release (µlU/min) in low and high glucose perfusion in isolated pancreas (n=6).



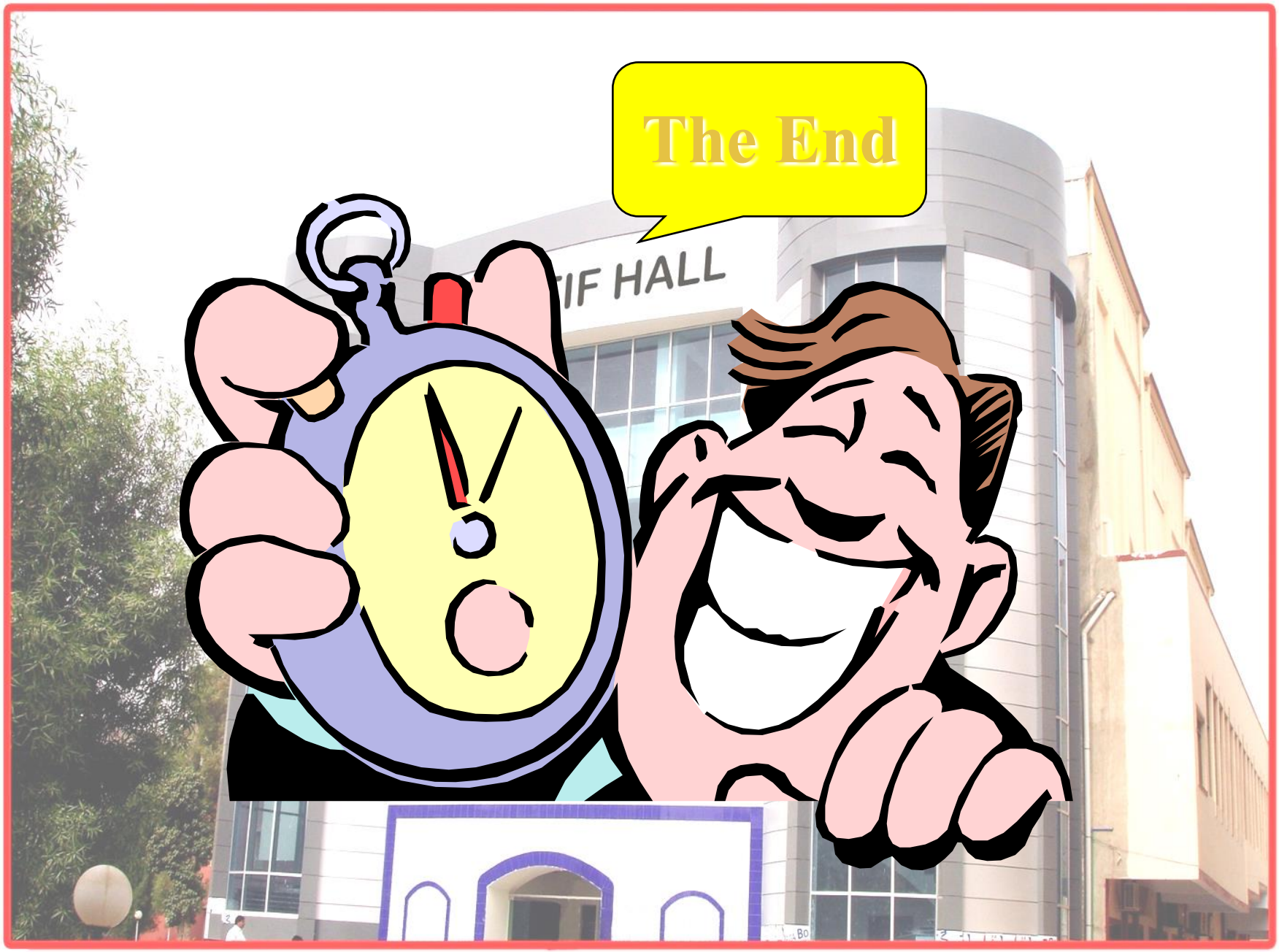
Effects of Amlodipine (0.5ng/ml, 5ng/ml & 50ng/ml) on average insulin/min/pancreas (mean ± sem) in low and high glucose perfusion in isolated rat pancreas (n=6). (*P<0.05)

Effects of Amlodipine on Insulin Release

- At 0.5ng/ml, 5ng/ml, and 50ng/ml, there were no significant inhibition on insulin release.

Conclusion

- Different Calcium antagonists have varying effects on insulin release at equivalent therapeutic doses.


The End
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