Khat Chewing
&
Physical Health

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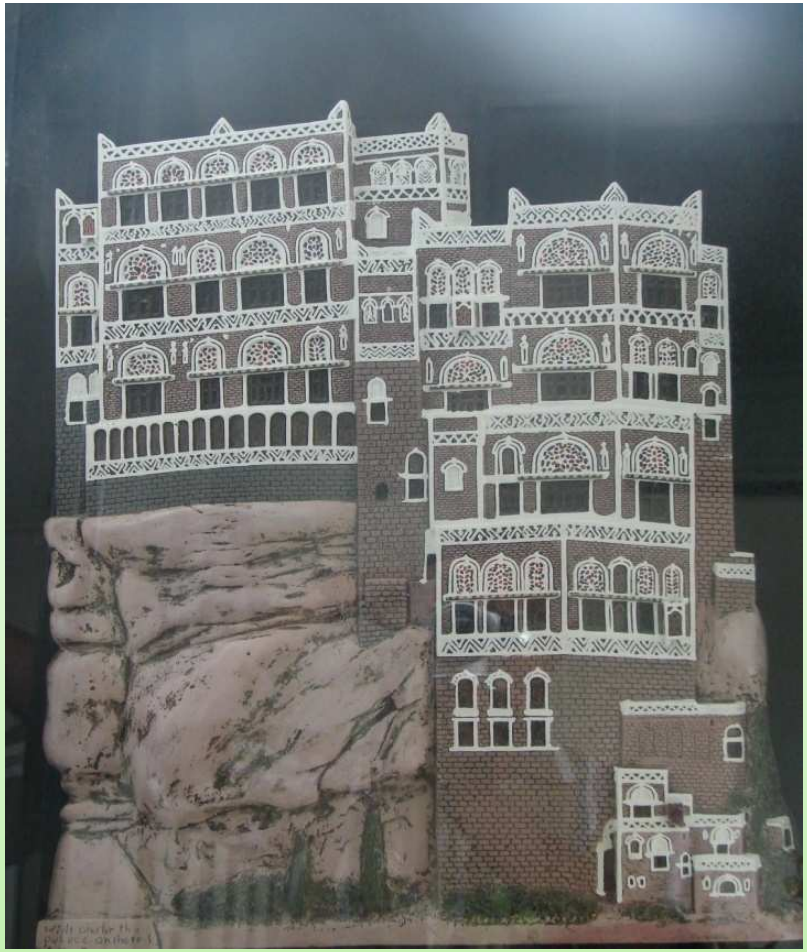
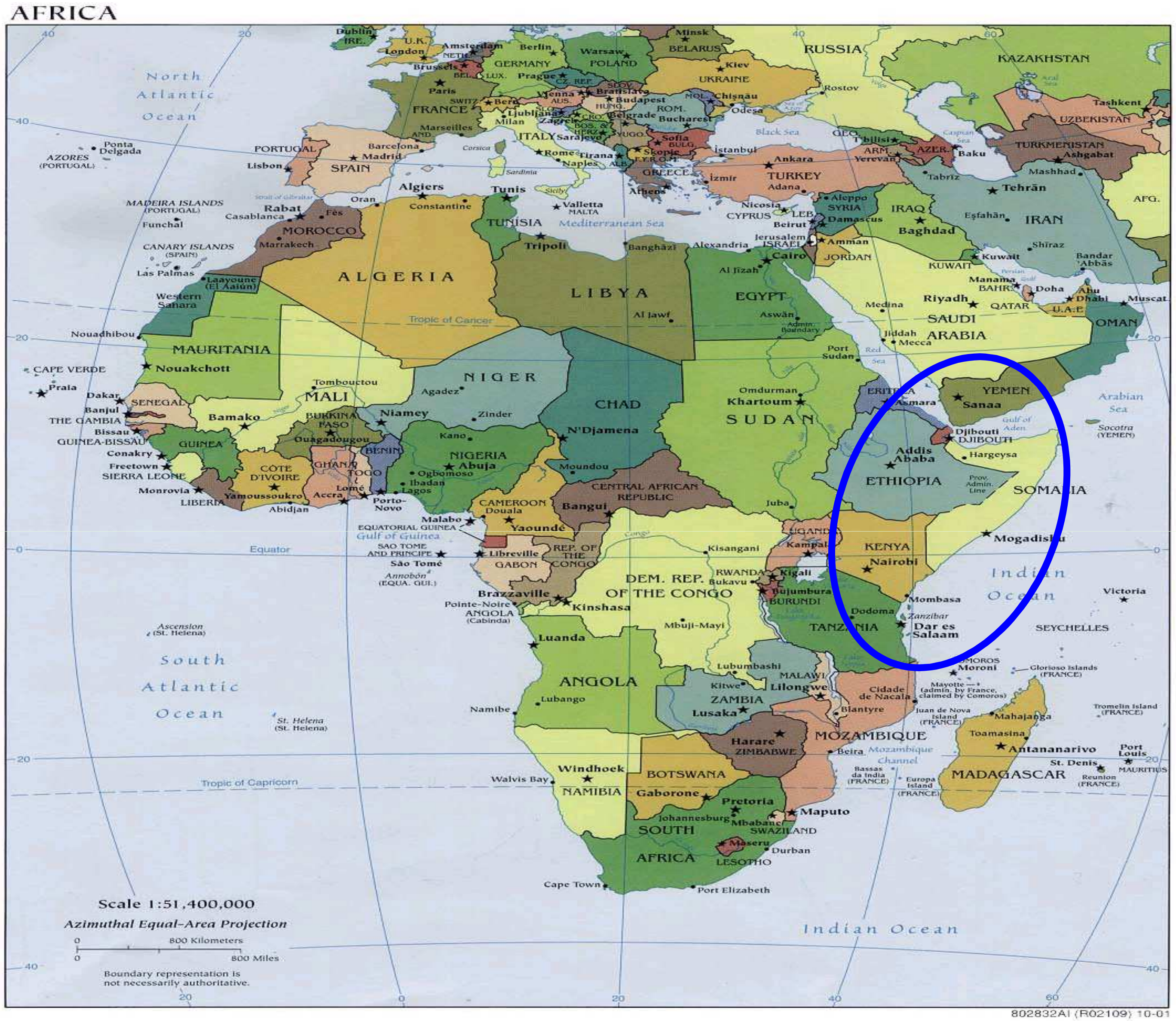


Population:

July 2007 census = 22,230,531

2009 estimation = 23,580,000

Location of Yemen


AFRICA
North Atlantic Ocean
South Atlantic Ocean
Indian Ocean
Mediterranean Sea
Black Sea
Red Sea
Arabian Sea
Gulf of Aden
Gulf of Guinea
Mozambique Channel
Equator
Tropic of Cancer
Tropic of Capricorn
MOROCCO
ALGERIA
TUNISIA
LIBYA
EGYPT
Western Sahara
MAURITANIA
MALI
NIGER
CHAD
SUDAN
ERITREA
DJIBOUTI
ETHIOPIA
SOMALIA
KENYA
UGANDA
RWANDA
BURUNDI
TANZANIA
SENEGAL
THE GAMBIA
GUINEA-BISSAU
GUINEA
SIERRA LEONE
LIBERIA
CÔTE D'IVOIRE
BURKINA FASO
GHANA
TOGO
BENIN
NIGERIA
CAMEROON
CENTRAL AFRICAN REPUBLIC
EQUATORIAL GUINEA
GABON
REP. OF THE CONGO
DEM. REP. OF THE CONGO
ANGOLA
ZAMBIA
MALAWI
MOZAMBIQUE
ZIMBABWE
NAMIBIA
BOTSWANA
SOUTH AFRICA
LESOTHO
SWAZILAND
MADAGASCAR
COMOROS
SEYCHELLES
MAURITIUS
CAPE VERDE
SAUDI ARABIA
YEMEN
OMAN
IRAQ
IRAN
TURKEY
SYRIA
JORDAN
KUWAIT
QATAR
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UZBEKISTAN
TURKMENISTAN
UKRAINE
POLAND
GERMANY
FRANCE
SPAIN
PORTUGAL
ITALY
GREECE
Rabat
Algiers
Tunis
Tripoli
Cairo
Khartoum
Asmara
Addis Ababa
Djibouti
Mogadishu
Nairobi
Kampala
Kigali
Dodoma
Dar es Salaam
Mombasa
Nouakchott
Dakar
Bamako
Niamey
N'Djamena
Abuja
Lagos
Accra
Yaoundé
Bangui
Libreville
Brazzaville
Kinshasa
Luanda
Lusaka
Lilongwe
Harare
Maputo
Windhoek
Gaborone
Pretoria
Johannesburg
Maseru
Mbabane
Cape Town
Port Elizabeth
Durban
Antananarivo
Moroni
Sanaa
Riyadh
Scale 1:51,400,000
Azimuthal Equal-Area Projection
800 Kilometers
800 Miles
Boundary representation is not necessarily authoritative.
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Khat tree & Leaves

Khat tree & leaves

Yemeni Khat bundle

Khat Leaves

Row of khat tree

Single khat branch

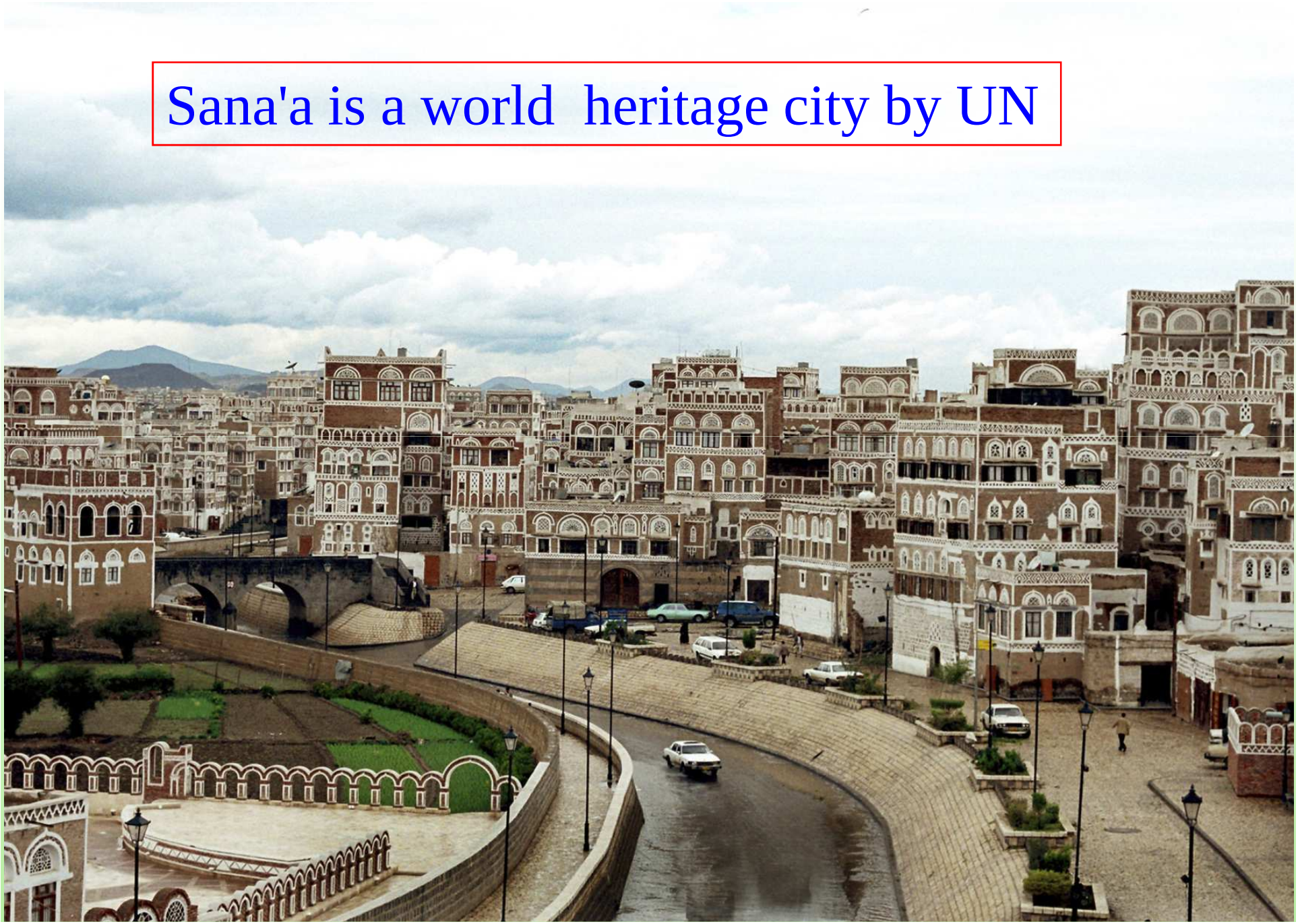
Khat habit

- Khat chewing is a social habit in Yemen and east African countries
- It is deeply –rooted in the Yemeni society
- Millions of people are chewing khat leaves every day
- Yemenis are chewing khat in large scale than before
- Morning working hours are continues in the afternoon and night time during khat sessions
- Lawyers, businessmen ,shops, taxi drivers and all other manual work using khat as a common energetic factors for their work

KHAT Habit & People life

- Mohammed Al-Zubairi, a national figure has said that khat is the only ruler in Yemen society.
- It controls the heart and mind of Yemenis.
- It controls their activities and dictate their way of life.
- Women & children are chewing khat too
- Even the house design ,khat place has a big role and best place in the house.

Sana'a is a world heritage city by UN

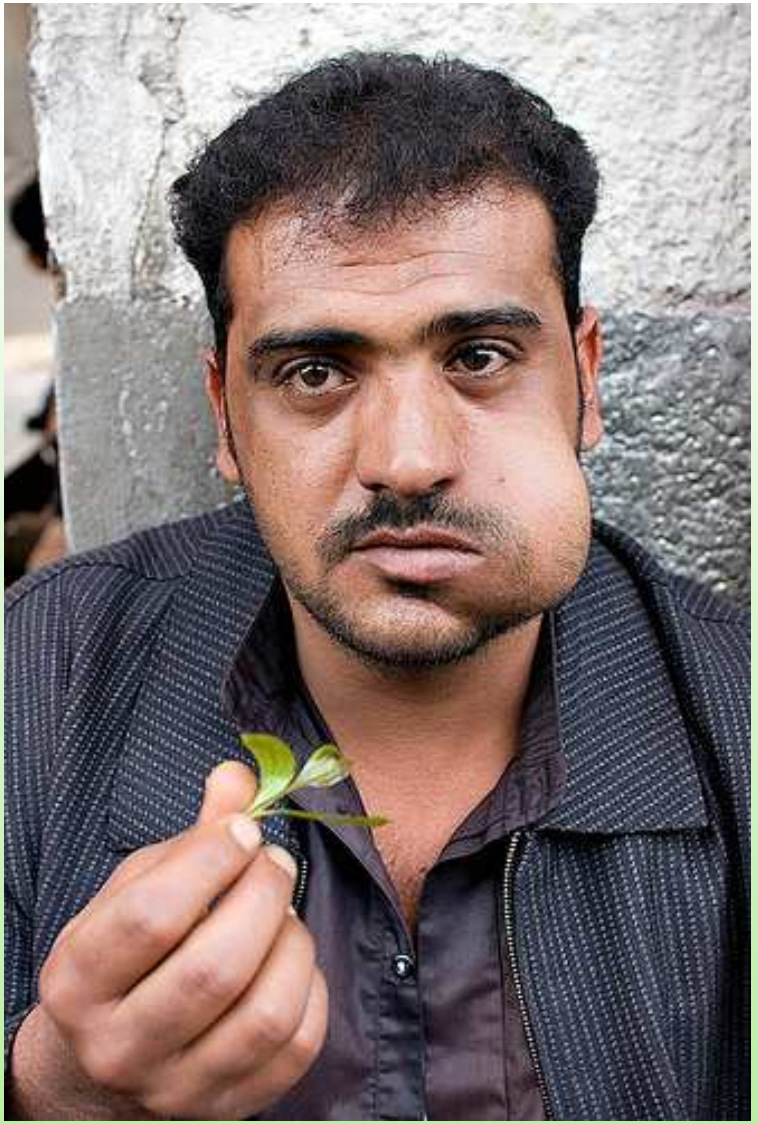


Big halls designed for khat chewing during social activities

Wedding parties, Condolences gathering and Election campaigns


A Khat chewer

A Khat Chewer



Khat Chewing has increased sharply among Ladies

Khat and women

- 34 % of the Yemeni women are chewing khat [1]
- 50.5% of the Yemeni women whom recruited in the Gulf RACE in 2006 where regular khat chewer
- Women ACS cases represent 21% of the whole cases in 2006 ,while in 1997 the percentage was 10%
- This was due to changes in the life style of Yemeni women in particular khat chewing habit

Najat Sayem 1998

Khat among Children

- In a recent khat survey among children aged 7-15 years old;
- 87% were boys and 13% were girls
- 53.3% of the whole age were chewing khat in the social occasions only
- 38.3% were regular khat chewers on daily bases

Najat Saym 2006 , faculty of art journal

Khat impact on the physical health

- When the majority of the society is chewing khat
- When the habit is growing with larger scale than before
- And the attitude of khat chewing is changing toward the bad habit behavior and people are not restricted to the khat sessions traditional
- we can expect a larger damaging health impact among the people

Khat effect on Blood Vessels

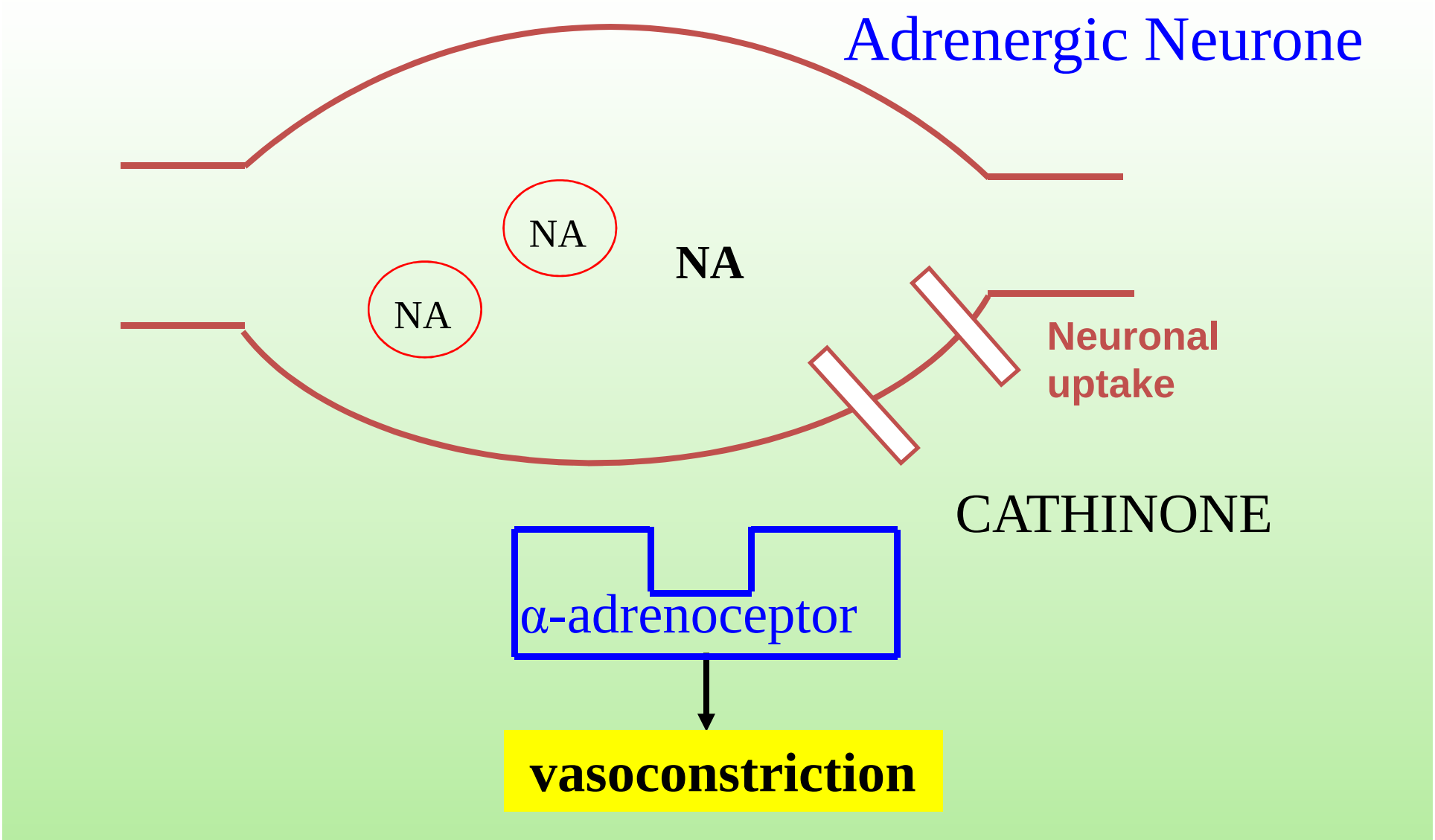
- khat chewer experiences an increase in heart rate presented clinically by palpitation , body temperature and sweating
- This is associated with cold extremities which indicate the clinical picture of peripheral vasoconstriction caused by khat chewing

Cardiovascular effects of amphetamines

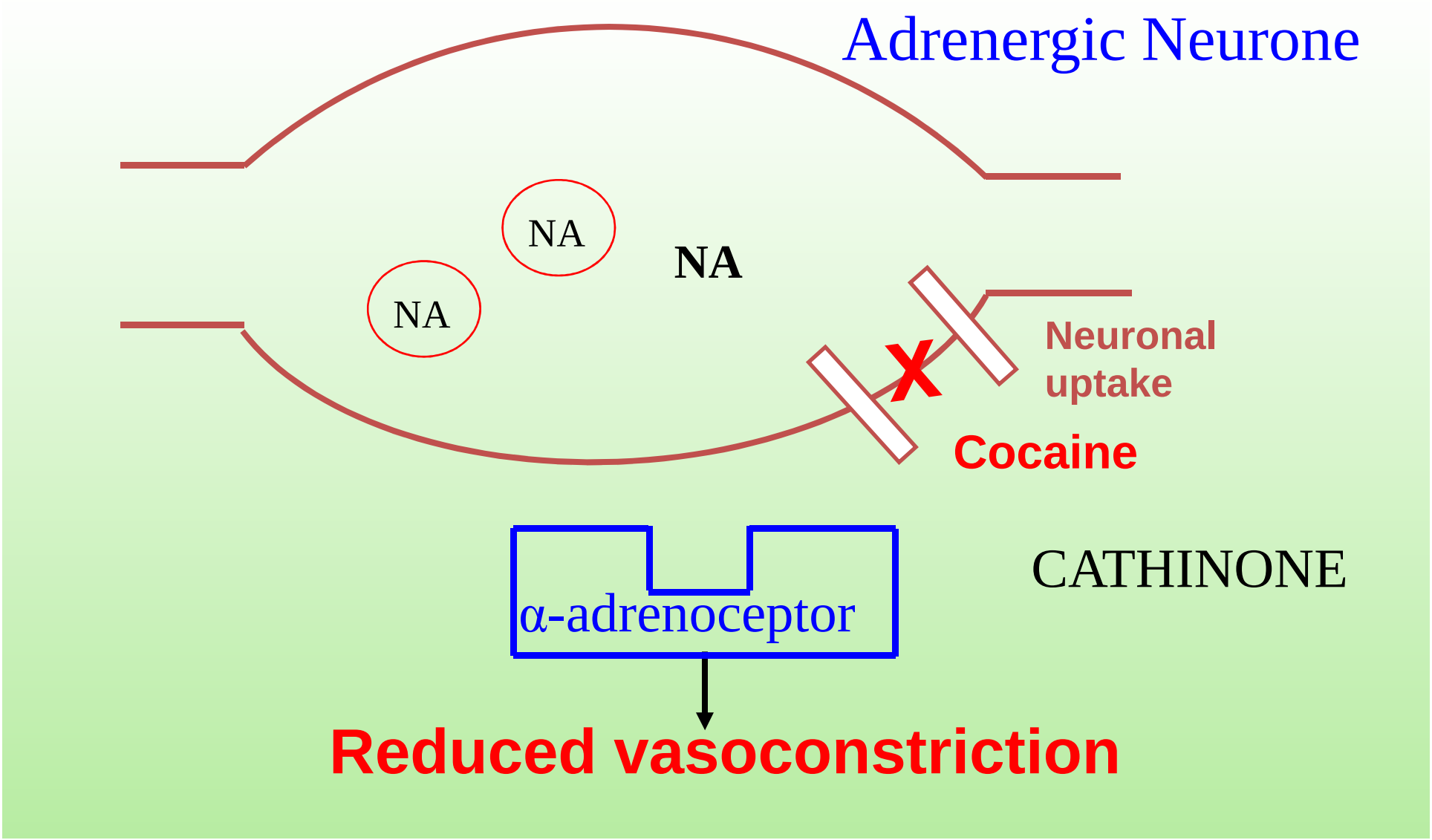
- Amphetamines such as cathinone and ecstasy cause increases in blood pressure and heart rate and vasoconstriction

- This is widely regarded as being due to indirect sympathomimetic actions

Indirect Sympathomimetic Activity



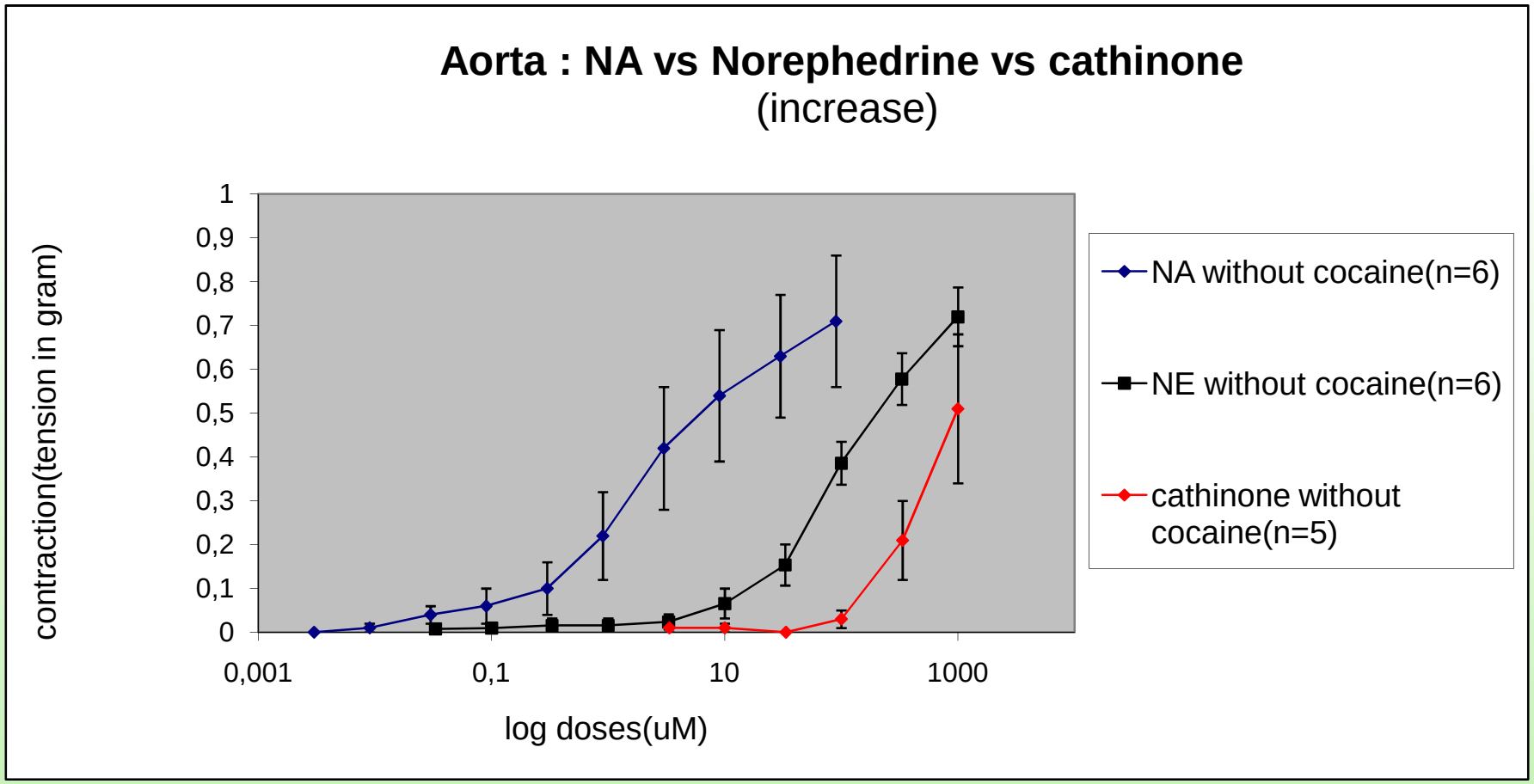
Indirect Sympathomimetic Activity



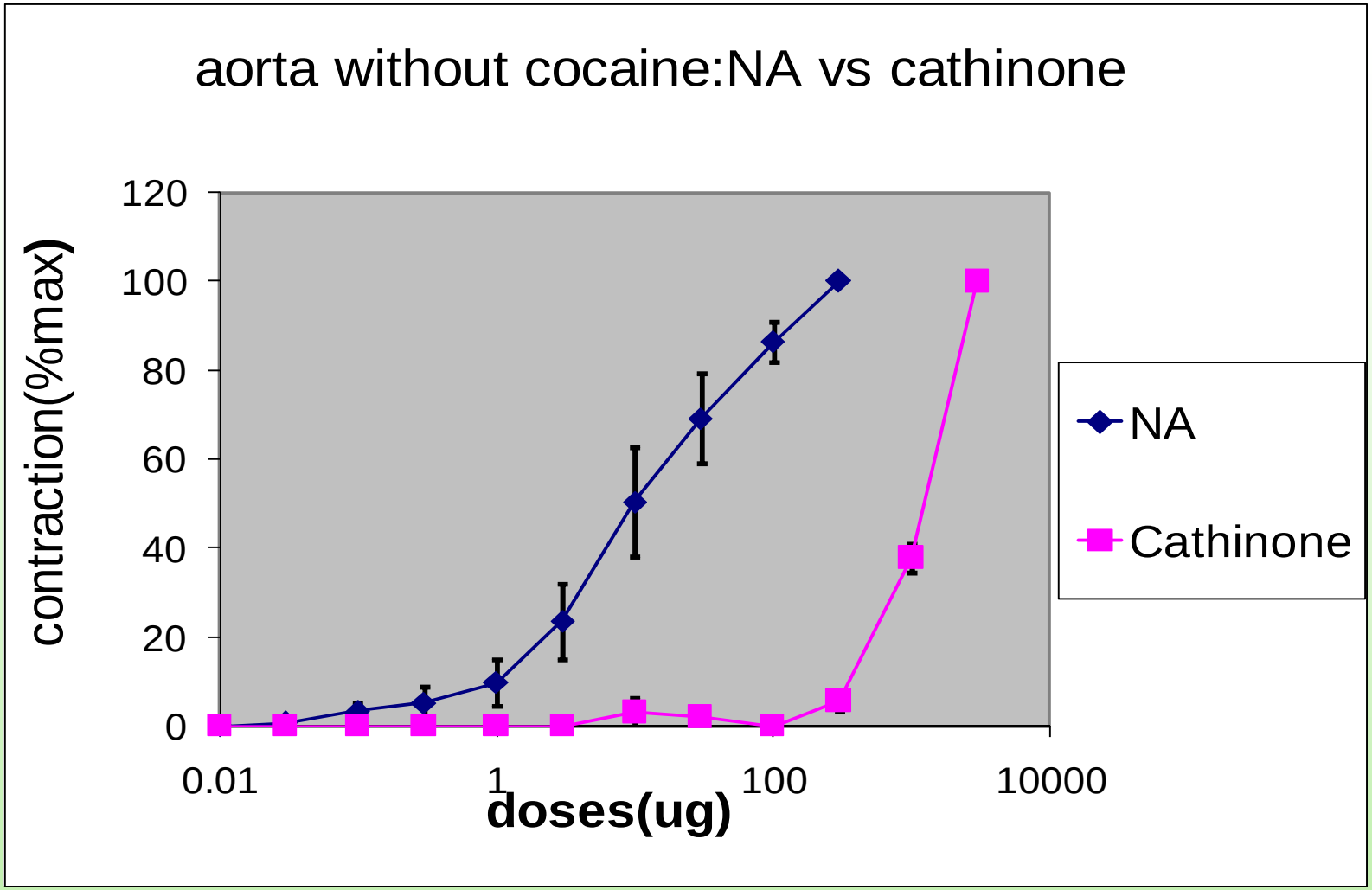
Cardiovascular effects of cathinone

- In guinea pigs aortic ring preparation , cathinone and its major metabolites, norephedrine , both caused aortic ring vasoconstriction

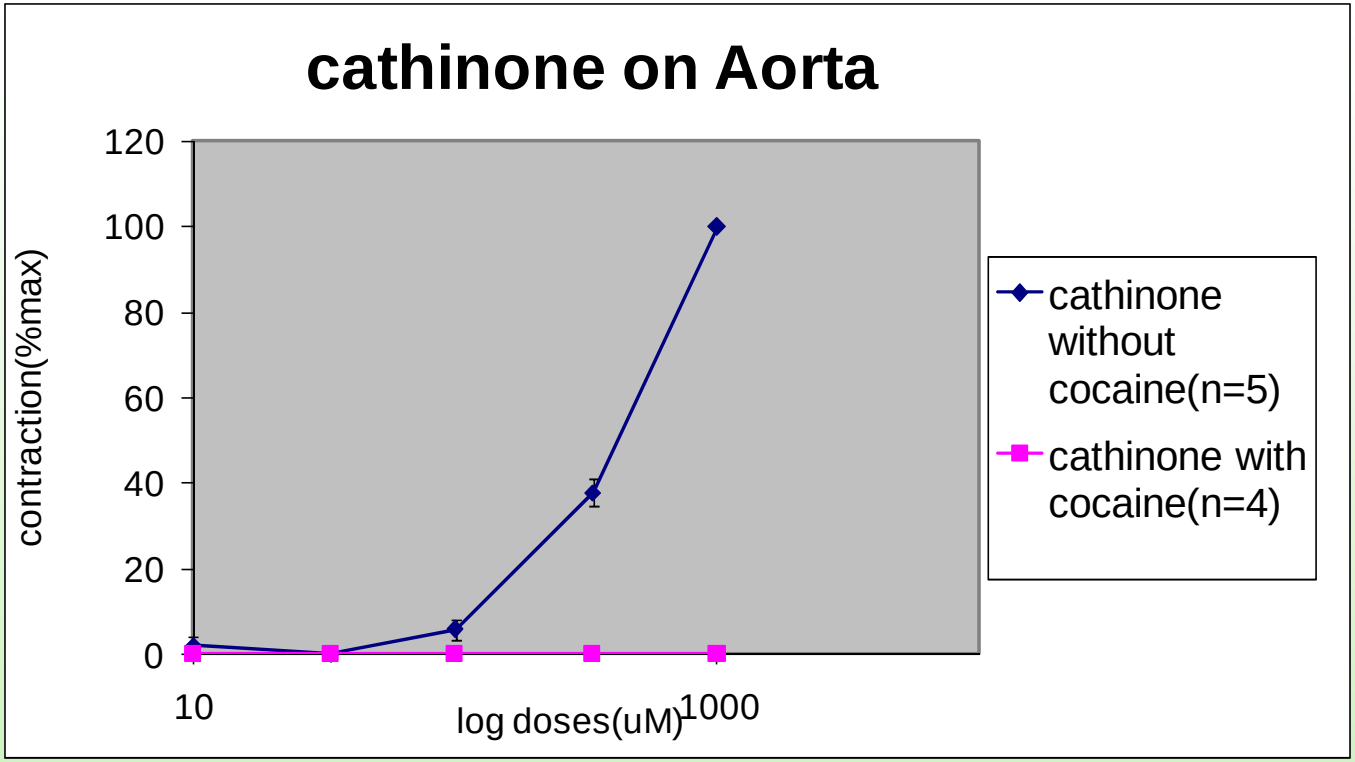
A L Al-Motarreb & KJ Broadley 2004. Autonomic & Autocoid pharmacology.23:319-326



NA was more potent than either of NE & cathinone in absence of cocaine.

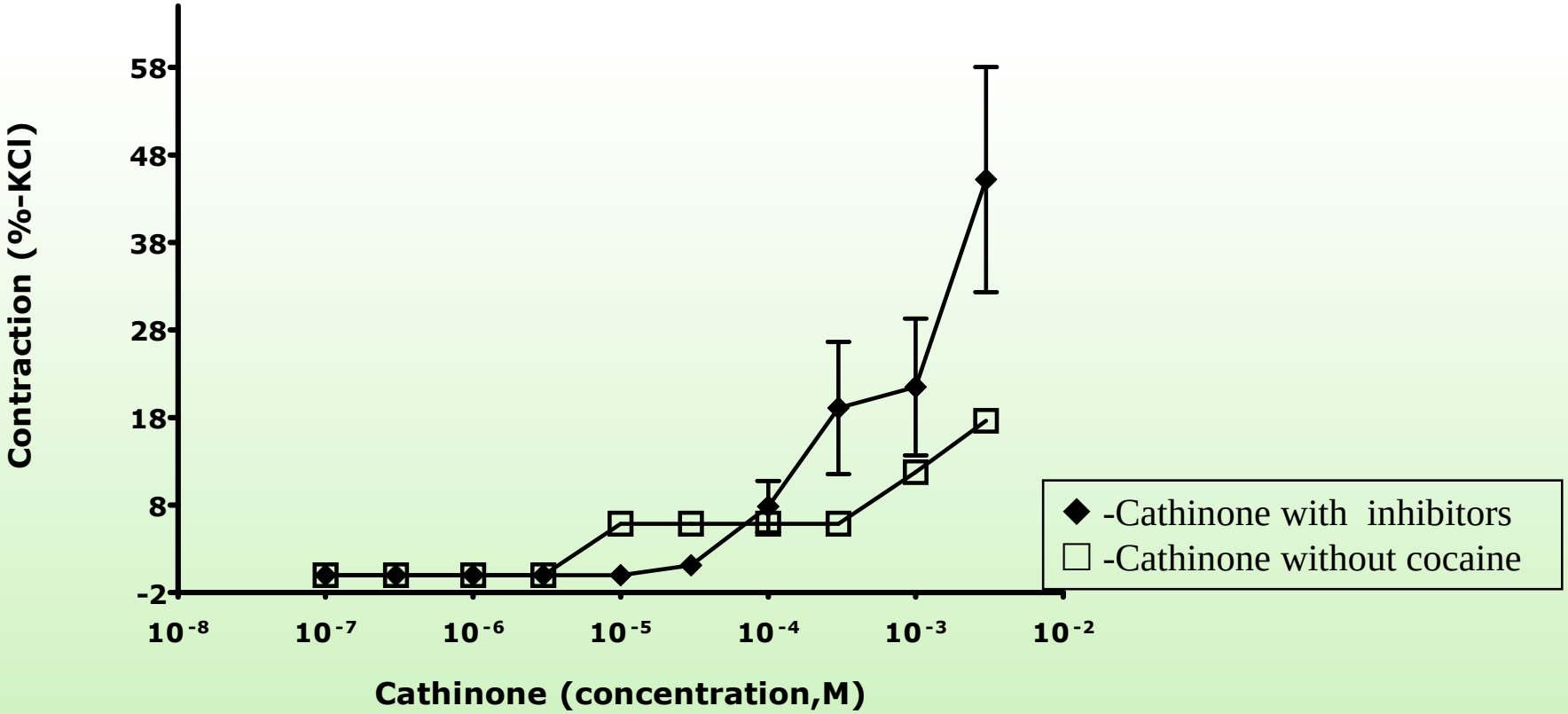


Cathinone is more potent in larger doses



Cathinone produced dose-related contraction of the aortic ring
This effect was abolished by cocaine
(indirect sympathomimetic effect)

Cathinone effect on aortic rings in presence of cocaine



Inhibitors are: cocaine (10μM), MAO inhibitor, pargyline (10μM),
β2-adrenoceptor antagonist ICI118551 (1μM)
and α1-adrenoceptor antagonist prazosin (1μM).

Cocaine does not block the effect of cathinone .
It is not indirect sympathomimetic effect

Two mechanism of cathinone vasoconstriction

- Release of catecholamine through its indirect sympathomimetic actions

- A local effect on blood vessels that is independent of noradrenaline release and stimulation of α-adrenoceptors – this is probably via the recently identified trace amine-associated receptors (TAARs)[1]

1-Baker, Herbert & Broadley *Vascular Pharmacol* 2007, 47, 10-17

Mechanism of Elevated BP among khat chewers

- *Cathinone causes a dose-related blood vessels vaso-constriction (VC)*

- Cathinone releases catecholamine from presynaptic nerve endings ⇨ blood vessel VC and subsequently contribute to the observed elevated blood pressure caused by khat chewing.[1]

- *Therefore the effect of cathinone & its major metabolite NE is the main mechanism of elevated blood pressure among the khat chewers [2].*

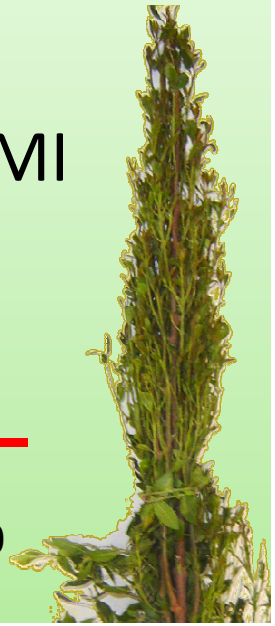
1- Hassan 2000.Trop Doct. **30**: 107-108 , Brenneisen 1990 Br J Clin Pharmacol **30**:825-828

2-A L Al-Motarreb & KJ Broadley 2004. Autonomic & Autocoid pharmacology.23:319-326

Khat Effect on the Coronary arteries

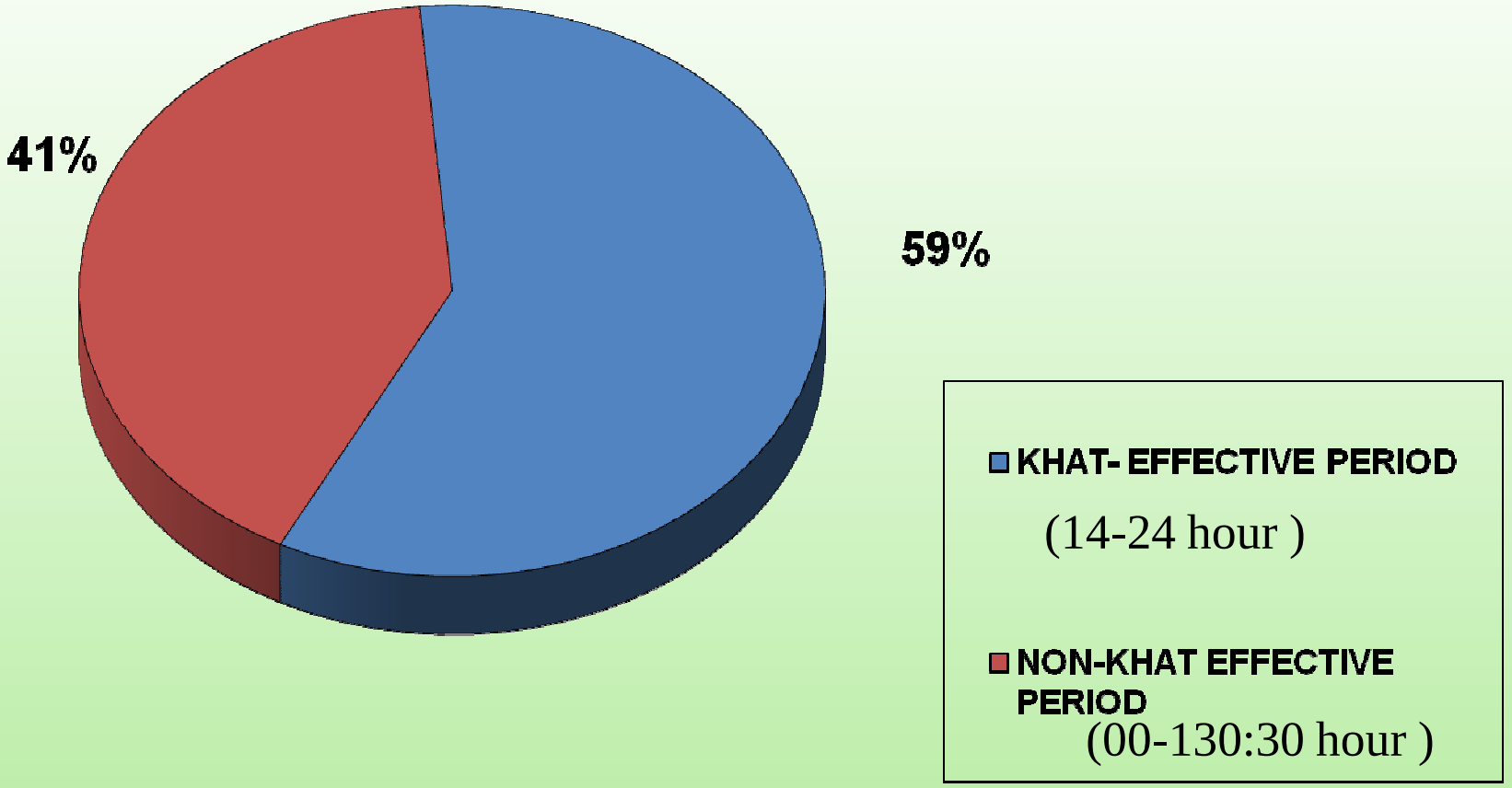
Khat chewing changes the circadian rhythm of AMI presentation

- Usual first peak of AMI presentation occurs in the early morning [1]
- Khat chewers first peak of presentation of AMI was in afternoon and evening time (khat effective period) 14-24 hours
- Khat chewing changes the circadian rhythm of AMI presentation.[2]

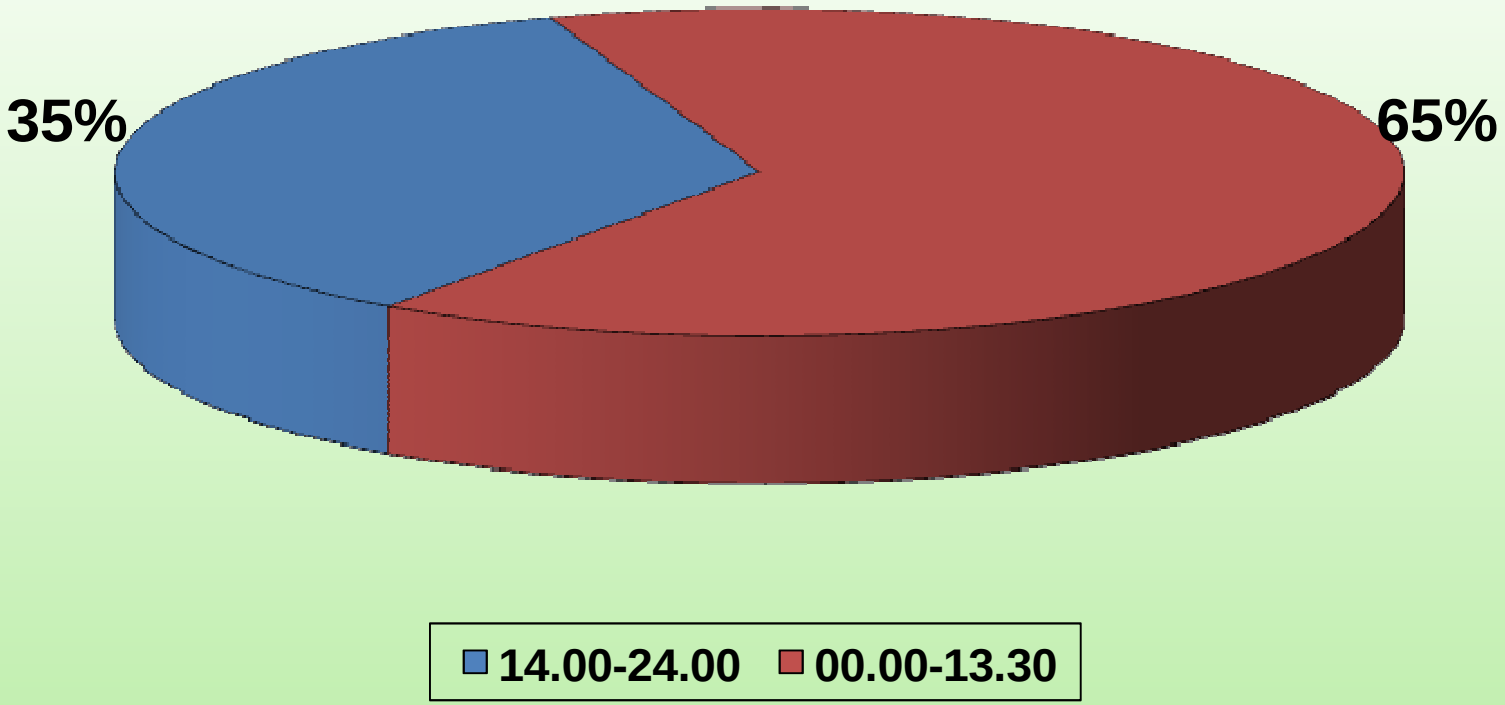


1-ISIS-2. 1988.the Lancet 332:349-360,
2-A Al-Motarreb et al 2002.Heart.87:279-280

Time of onset of AMI



TIME OF SYMPTOM'S ONSET IN NON-KHAT CHEWERS



65% of the patients presented in the non-Khat effective period

Potential Mechanism

- Coronary Vasospasm
- Catecholamine can trigger coronary thrombus formation through rupture of asymptomatic atherosclerotic plaque [1]
- Excessive catecholamine discharge: [2]
  *Ischemic Myocardial necrosis
  *Catecholamine-Mediated Platelets Aggregation

1-Ragland S. et al 1993 Am Heart J.;125:247–9.

2-Bashour et al 1994Heart J.;128:1237–9

Khat chewing as major risk factors for AMI

1. Khat chewing is leading to:

- Increase of BP & Heart rate
- Increase Oxygen demand
- Nervous tensions (catecholamine release)
- Increase desire to smoking
- Leading to passive smoking
- Inactive lifestyle

Khat chewing as major risk factors for AMI

- Khat chewing was significantly more frequent among AMI cases than control (OR=5)
- An evidence of significant dose-related response was found.
- Mild khat chewers were not at risk, while moderate khat chewer were at high risk and heavy khat chewer were at higher risk (OR=7.6 and 22.28 respectively)
- A dose–response relationship was observed, the heavy khat chewers having a 39-fold increased risk of AMI.

Al-Motarreb et al 2005.Br J Clin Pharmacol.; 59(5): 574–581.

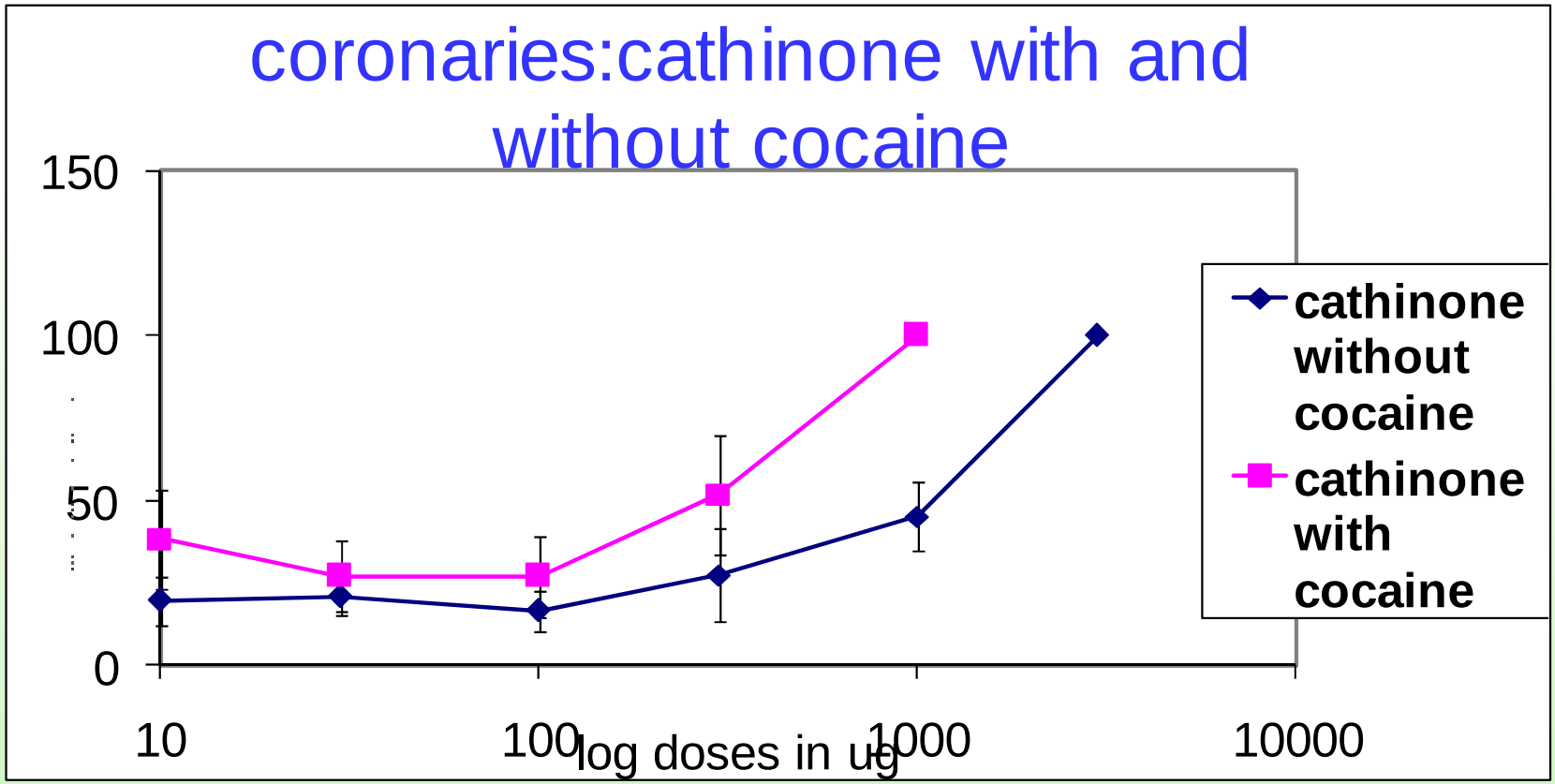
Khat Produces Heart Attack (AMI)

- Khat chewing is not only a major risk to AMI

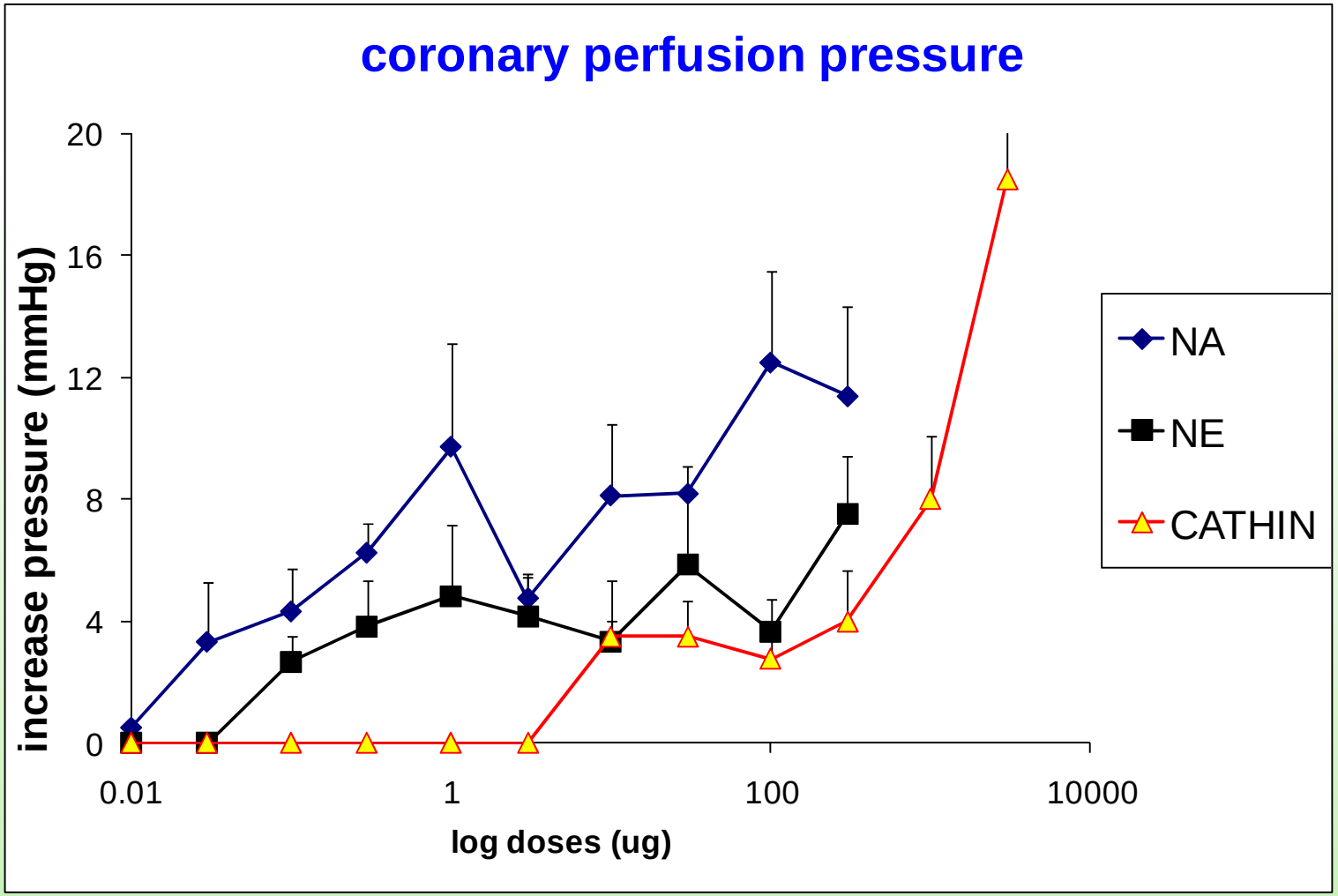
- Khat chewing has been linked to produce AMI [1]
- AMI among khat chewers occurs mainly in Khat –effective period [2]
- Khat chewers had AMI at earlier age than non-khat chewers [2]

1-AL-Kadhi 2002; Saudi Med J. 23:1195-8

2-Al-Motarreb et al 2002;.Heart.87: 279-

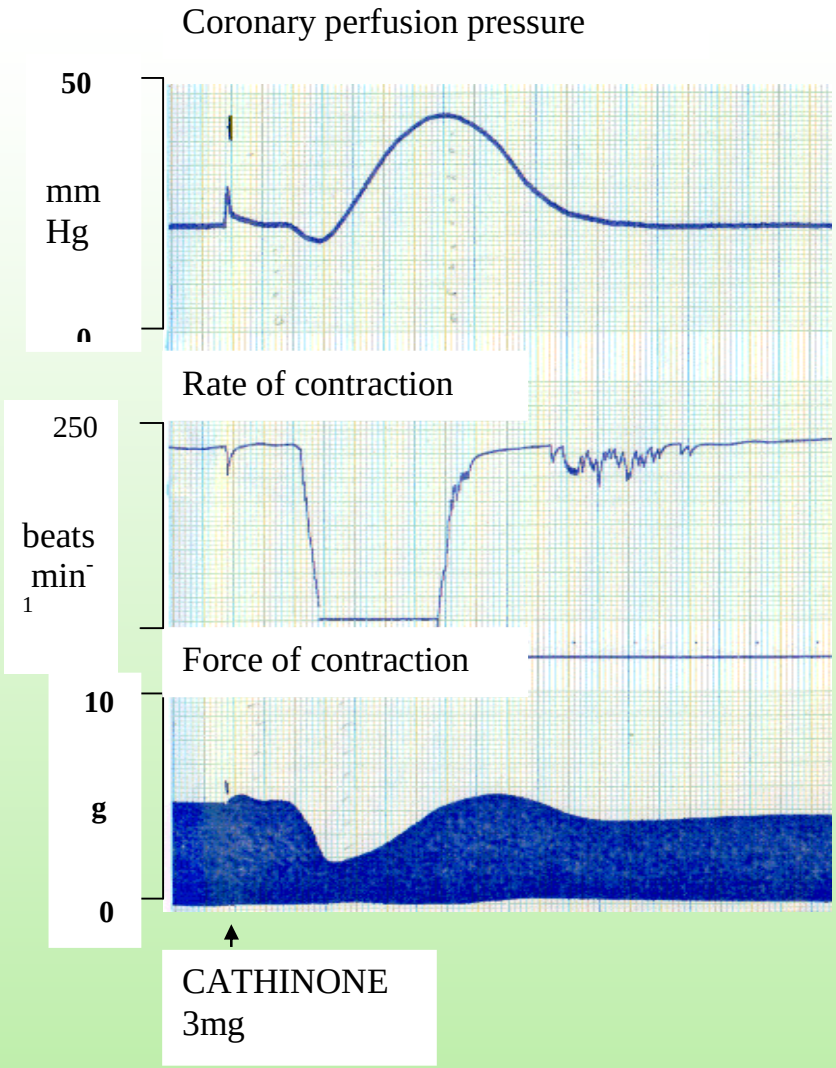


Cathinone produce coronary VC in the absence & presence of cocaine



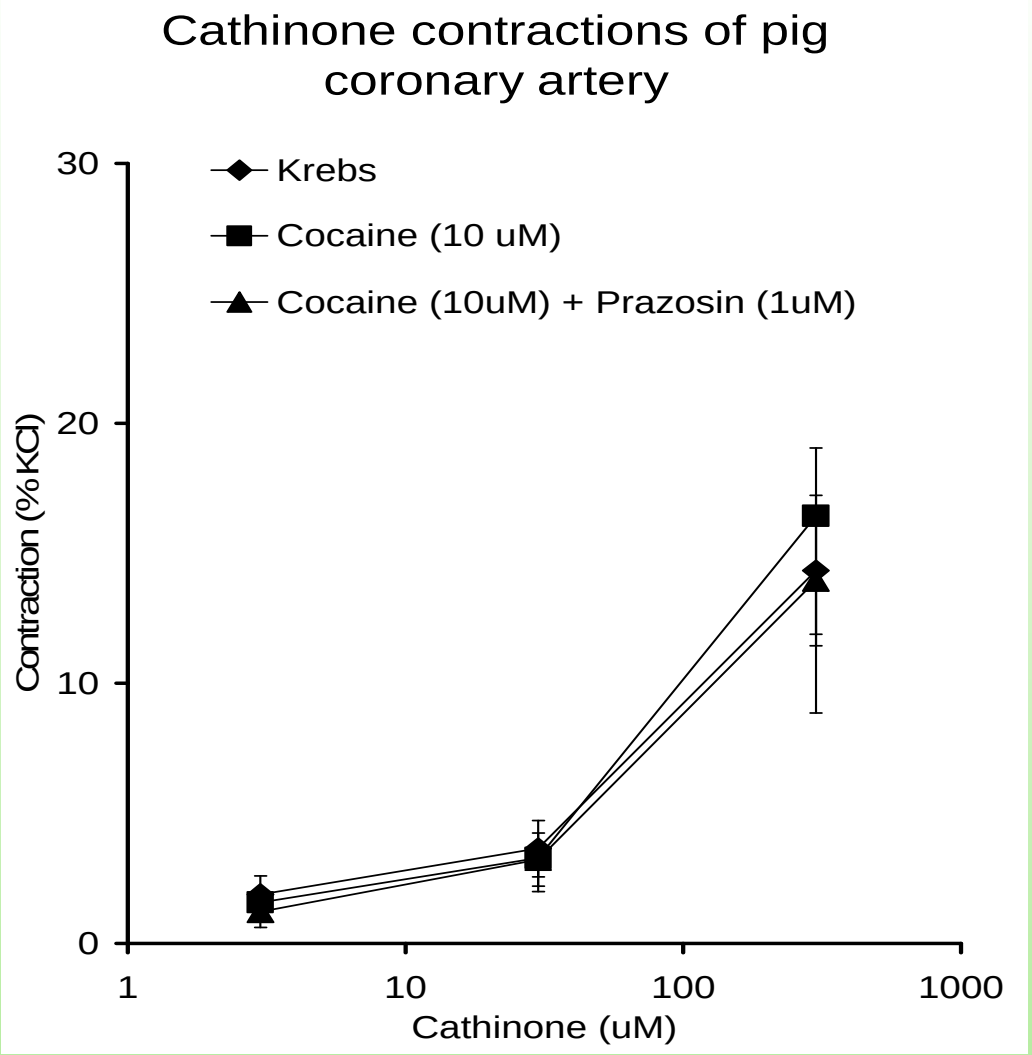
NA, NE & Cathinone Produce coronary VC with larger constriction to cathinone in larger doses

Coronary vascular pharmacology of cathinone



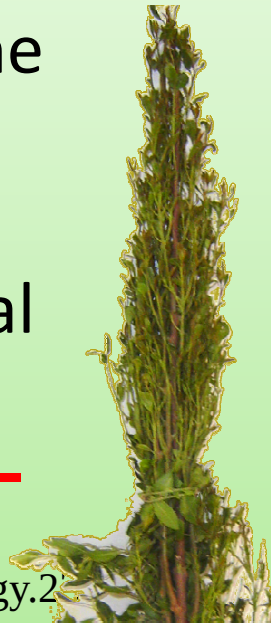
- Guinea-pig isolated Langendorff heart preparation
- Cathinone causes coronary vasoconstriction and negative inotropy

Effects of cocaine and prazosin on coronary vasoconstriction by cathinone



Mechanism of producing AMI by Cathinone

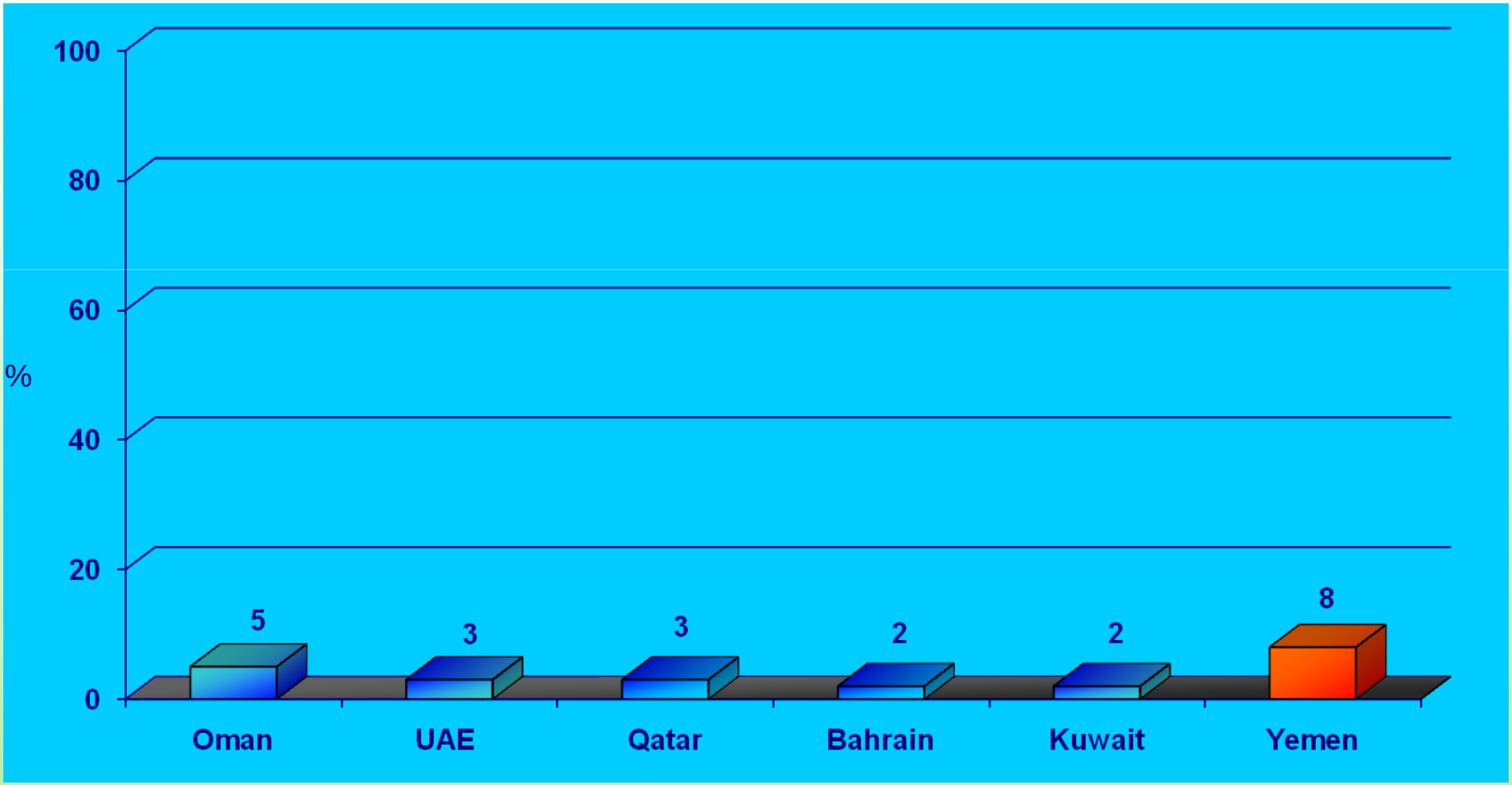
- The vasoconstriction to Cathinone, is substantially greater than either Noradrenalin or Norephedrine at higher doses.
- This vasoconstriction is not indirect sympathomimetic action as it is not blocked by cocaine or prazosin
- Therefore , Cathinone" the main ingredient of Khat leaves produces DIRECT vasoconstriction on the coronary arteries.1,2
- This findings are strong evidence to support our clinical work in that KHAT can produce myocardial infarction.



1-K Baker et al 2007.Vascular Pharmacology.47:10-17

2-A L Al-Motarreb et al 2004. Autonomic & Autocoid pharmacology.2

Gulf RACE Mortality



Is there a Khat effect

?

Khat chewing Induces Dilated Cardiomyopathy

- Amphetamine Abuse has been linked to dilated cardiomyopathy[1]
- Cathinone may have same effect on heart muscle as it has same properties as amphetamine [2]
- Cathinone has negative inotropic effect in an isolated guinea pigs hearts [3]
- Catecholamine discharges may cause ischemic myocardial necrosis [4]
- All of these may contribute to induce dilated cardiomyopathy in the susceptible patients

1-Thomas et al 1982.Ann.Int.Med.97:559-560
2-Kalix 1992 Pharmacol Toxicol **70**:77-86
3-A L Al-Motarreb et al 2004. Autonomic & Autocoid pharmacology.23:319-326
4-Bashour et al 1994Heart J.;128:1237–9

Khat chewing Induces Dilated Cardiomyopathy

- A study involve 50 Yemeni patients with dilated cardiomyopathy who were regular khat chewers
- Patients with secondary dilated cardiomyopathy were excluded.
- The histopathological of the heart muscle showed a myocyte hypertrophy and interstitial fibrosis
- Khat chewing contribute to the occurrence of dilated cardiomyopathy in young patients (20-50 years) with inherited predisposition

M Al-Saadi & M Grigorov 2004. Bulgarian Medical Review;40:61-64

Khat chewing Induces Dilated Cardiomyopathy

- This published study was continued till 100 patients with follow up for 5 years (1997-2001)
- A Significant clinical improvement has been obsererved in patients who have stopped khat chewing
- The conclusion was that, khat chewing contribute to the occurrence of dilated cardiomyopathy and worsening its clinical picture .

Khat chewing and Stroke

Amphetamine and the Stroke

- Amphetamine is a potent sympathomimetic that may lead to vascular events including myocardial Infarction and stroke [1]
- Intracerebral hemorrhage secondary to methamphetamine abuse have been reported [1,2,&3]

1-Perez JA Jr et al 1999.Jemerg Med;17:469-71

2-Mc Gee et al 2004. AM J of Forensic Medicine and Pathology ;25:334-337

3-Tomoko Miyashita et al 2007.

Amphetamine and the Stroke

- An association between a sympathomimetic drugs and cerebral infarction have been reported [1]
- A possible mechanism for cerebral infarction is focal arterial vasoconstriction
- Association between sympathomimetic drugs and intracranial hemorrhage have been reported too

  and the possible mechanism is acute arterial hypertension

Bruno A. 2003. Curr Neurol Neurosci Rep.;3:40-5

Khat chewing causes stroke

- As most of Yemenis seek medical advice at very advanced stage including hypertensive patients
- Because of the resemblance between central and cardiovascular complications of khat and amphetamine , there is a high risk of cerebrovascular events in khat chewers [1]
- Several case-reports suggesting that khat induced ischemic stroke [1 , 2 &3]

1-I.Vanwalleghem et al 2006. Cerebrovasc Dis.; 22:198-200

2-de Ridder S et al 2007. Nethrland Heart Journal;15:269-27

3-Bruno A. 2003. Curr Neurol Neurosci Rep.;3:40-5

Khat & CVA

- In a case-control study in Yemen where 358 patients with acute cerebral infarction (ACI) were enrolled and compared to a control group;
- Khat chewing was common habit among cases than the control group (p=<0.01)
- Khat increases blood pressure in patients with acute cerebral infarction and it was a risk factor for the occurrence of ACI
- Therefore

  khat chewing increases the incidence of ACI

Hadi M Mujalli et al 2005. Neurosciences;10:219-222

Khat & Type II Diabetes

- In contrast to the general believe that khat reduces blood glucose in the diabetes patients
- A study in 2003 showed that chronic khat chewing does not effect serum glucose in healthy individuals while it increase glucoses levels during khat session in diabetics individuals [1]

Saif-Ali et al 2003.J Ethnopharmacol; 86: 45-49

Effect of khat chewing on serum glucose (mg/dl) of normal and type 2 diabetic individuals

Parameters	Normal		Type 2 diabetics	
	Non-khat chewers (*n* = 16)	Khat chewers (*n* = 20)	Non-khat chewers (*n* = 15)	Khat chewers (*n* = 21)
2 h glucose	94.8 ± 3.7	101.8 ± 1.9	302.6 ± 37.3	329.3 ± 31.9
3 h glucose	97.6 ± 3.2	97.8 ± 3 2	268.9 ± 34.6*	**344.0 ± 29.8**
4 h glucose	100.5 ± 3.1	101.3 ± 3.4	269.2 ± 32.2*	**328.3 ± 25.8**

Saif-Ali et al 2003.J Ethnopharmacol; 86: 45-49

Khat and Type II Diabetes

- This is further confirmed by a case control study for diabetes mellitus type II with khat and non-khat chewer;
- Four blood samples for glucose level in both group were obtained; fasting, post prandial, pre-khat chewing and post-khat chewing .
- The study conclusion was that there was no significant differences between two groups and khat chewing has no effect on glucose metabolism and has no role in controlling diabetes.

Zayed Atef et al 2009 . Unpublished data

Khat and Respiratory Tract

- A recent single study on the effect of cathinone in respiratory system had shown that;

- Cathinone may have beneficial effect in relieving respiratory symptoms

Freund-Michel et al 2008.Eur Respir J ;32:579-584

Khat Chewing and Liver

- Hepatotoxicity of khat was evident from raised plasma concentration of alkaline phosphatase, alanine aminotransferase and total bilirubin.
- Histopathological changes to the liver was found after three months of khat ingestion to the rabbit [1]
- 6 months later, the histopathological analysis showed evidence of acute hepatocellular degeneration and regeneration activities with porto-portal fibrosis [2]

1-Al-Mamary et al 2002.phytother Res ;16:127-132

2-Al-Habori et al 2002. J ethnopharmacology; 83:209-217

Khat & Liver (clinical)

- Several cases of cryptogenic liver disease in young khat chewer Somalian men living in Bristol in England were reported
- All 7 men presented with jaundice and predominantly hepatocellular derangement in liver function.
- Most of the men were successfully treated with resolution of jaundice and liver function abnormalities following withdrawal of khat

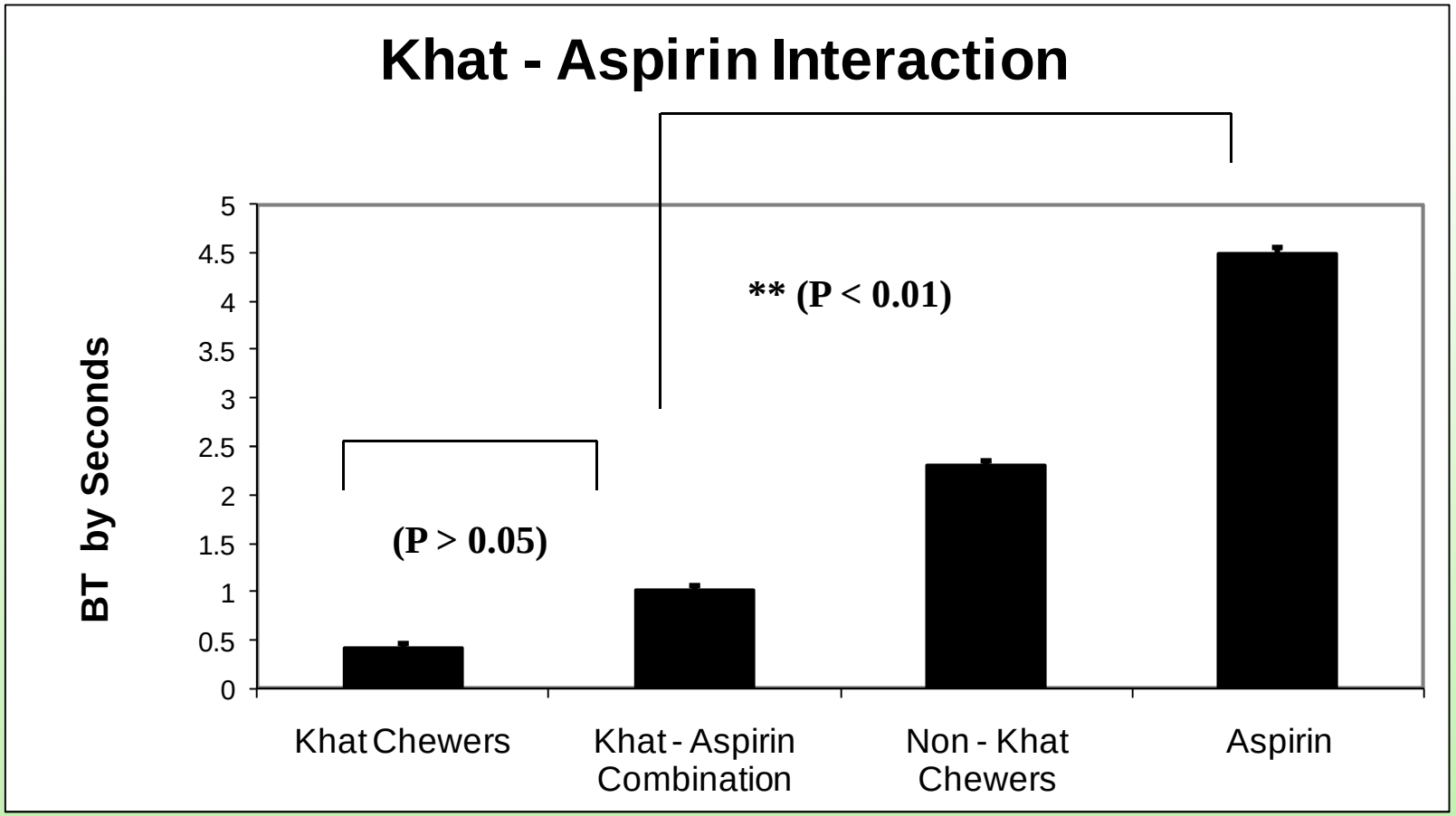
C.A.Mc Cune et al 2007.Journal of Hepatology;46(1):s276

Khat chewing and Auto-Immune Hepatitis

- In a case control study;
- Khat chewing was significantly more frequent among cases than control group
- More damaging effect was found among heavy khat chewers
- Khat chewing has been shown to be associated with Auto-immune hepatitis in Yemen.
- Men (74.1%) were more affected than women

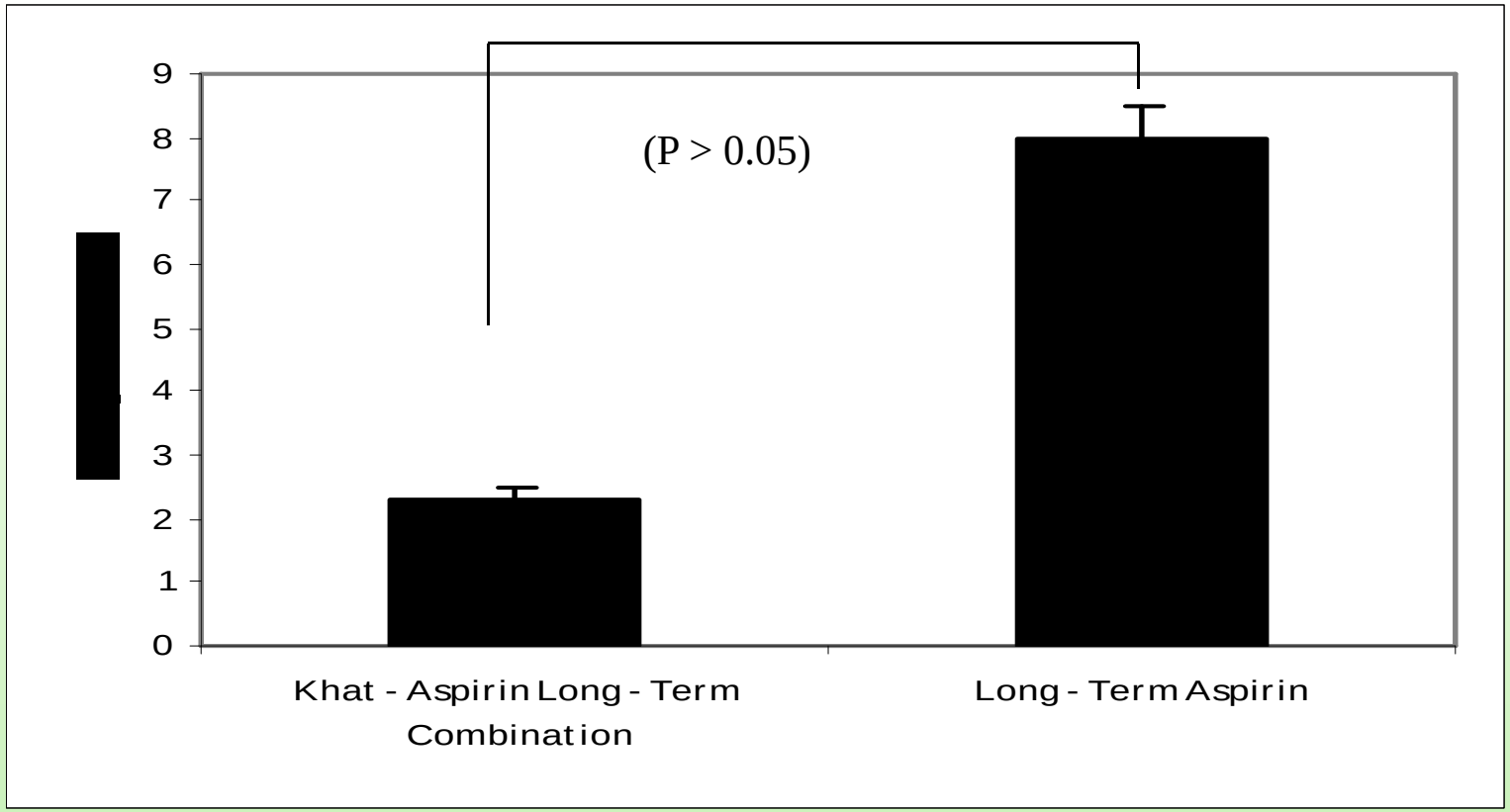
Al-Droish et al 2009. MSc Theses, Unpublished data

Khat Chewing & Aspirin Intake



Significant reduction was observed in BT in khat-aspirin combination (n=30) in comparison with aspirin group (n=30) 100 mg Aspirin was given for 10 days

Long-term Aspirin intake in AMI patients



A significant difference between both two groups where observed

the mean of BT in khat chewing associated long-term aspirin (n=7) was 2.3 minutes while the mean of BT in long-term aspirin group (n=7) was 8 minutes.

Khat chewing and Aspirin intake

- Aspirin as a preventive therapy against cardiovascular events is given to prevent heart attack

- Khat stimulate platelet aggregation
- This interfere with the anti platelet effect of Aspirin
- Catecholamine release will lead to platelet aggregation too
- Therefore the preventive therapy of the aspirin will not be the same among khat chewer

Al-Kamarani et al 2005.Yemeni J Phramaceutical & Biological science

Khat Chewing and GIT

- Tannin causes stomatitis, oesophagitis and gastritis [1]
- Delayed gastric emptying [2]
- delayed intestinal absorption
- Contribute to constipation and antispasmodic action [3]
- Decrease appetite and body weight by increasing plasma level of the anorectic hormones (leptin) [4]

1-WHO 1980 BULLNETEN Narcotic 32:83-93

2-Heymann et al 1995 Alimentary pharmacology and therapy. 9:81-83

3-Makannon 2000 phytomedicine.74:309-312

4-Al-Dobai et al 2006 .Nutritional research 26:632-636

Running studies

- Biochemical markers in ACS in khat chewers
- Coronary arteries morphology in khat chewers
- Khat chewing and anticoagulation (warfarin)
- Hypertension , kidney and khat chewing
- Khat chewing in ACS, morbidity and mortality
- Nationwide prevalence of khat will be conducted next year

Future Studies

- Many lab and clinical ideas are available and strongly needed to be studied.
- We prefer to collaborate with other people in khat researches [Khat Team]
- Multicentre studies in different countries are preferred
- **Budget still the main obstacle for researches**

Conclusion

- Khat chewing is a serious medical health problem

- Doctors should be aware about the effect of khat chewing on health

- Society must be aware about the khat medical side effects

- Medical research and scientific facts are the main gate to persuade people to avoid khat chewing

- Khat chewing must be regulated and controlled

Conclusion

We would like to protect our next Generation from Khat Chewing