A study of the cardio-depressant actions of harman alkaloids isolated from the seeds of *Peganum harmala*

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ABSTRACT

Introduction: The plant *Peganum harmala* is a shrub native to the arid parts of the world including India. It's therapeutic value is attributed to the presence of alkaloids harmala and harmine in the dried ripe seeds. In traditional medicine these seeds are considered to have anti-spasmodic, hypnotic, anodyne, emetic, emmenogogue, stimulant, aphrodisiac, lactogogue and antihelminthic actions.

Objectives: The present study was undertaken to find out the effects of the active principle extracted from the seeds of *Peganum harmala* on isolated cardiac muscle and skeletal muscle preparations and the probable mechanism of action

Materials & Methods: The harman alkaloid isolated from *Peganum harmala* seeds was used for experiments on isolated preparations of frog heart and frog rectus abdominis muscles and the responses were recorded on a rotating smoked drum on a kymograph.

Results: The Harman alkaloids were shown to inhibit the normal contractions and also the inotropic actions of Adrenaline, 5HT and calcium on isolated frog heart. These have not shown any effect on the frog rectus abdominus muscle either on their own or on the contractions induced by Acetyl-choline.

Conclusion: Harman alkaloids have cardio-depressant activity, it is unlikely that these alkaloids have a specific receptor antagonistic activity. Also these have found to inhibit the cardiac muscle contractions but not the skeletal muscle contractions. The cardio-depressant action may be due to calcium channel blockade.

Keywords: Cardiac muscle, Harman alkaloid, depressant.

INTRODUCTION

Peganum harmala is a perennial succulent shrub native to the arid parts of North Africa, the Mediterranean, the Middle East, Pakistan and India.The dried seeds of the plant constitute the active principle Harmal, used in India for various medicinal purposes. The seeds are of a dull, earthy-brown color with a reticulated seed coat and have a bitter taste. The therapeutic value of the plant is attributed to the presence of alkaloids which occur in varying amounts in seeds, roots, leaves, flowers, stem, bark and wood. The dried ripe seeds contain 3.8-5.8% alkaloids concentrated mainly in the coat, roots contain over 3%, bark 2.2% and wood 1.06%. Seeds contain Harmaline, Harmine, Harmalol and Vasicine with the first two predominating. The first three known as harman alkaloids are closely related and contain an indole nucleus, while Vasicine is a quinazoline derivative. In the traditional medicine the seeds of the plant are considered to have anti-spasmodic, hypnotic, anodyne, emetic, emmenogogue, stimulant, aphrodisiac, lactogogue and antihelminthic actions[1,2,3].

OBJECTIVES

A perusal of literature shows that the few studies were done mostly on the smooth muscle using aqueous extract of the seeds of *Peganum harmala,* very few studies have been done using the pure compound isolated from the plant.

The present study was undertaken to find out the effects of the active principle extracted from the seeds of *Peganum harmala* on isolated frog heart muscle and frog rectus abdominus muscle preparations and the probable mechanism of action [4,5,6].

MATERIALS & METHODS

Peganum harmala seeds were crushed and treated with dilute 3% acetic acid and pressed after 48 hours. To this liquid, sodium chloride was added and kept in the refrigerator for a day, to isolate the harman alkaloids, which are precipitated as yellow material. This is dried in air to get yellow powder, which is used in experiments on isolated frog heart and frog rectus abdominus muscle.

1) Using the isolated frog heart, normal heart rate and cardiac output are noted and the responses are recorded on a rotating smoked drum on a kymograph.

2) Using the isolated frog rectus abdominus muscle, the responses to Harman alkaloids and their effect on frog rectus

abdominus muscle contractions induced by Acetyl-choline is also recorded.

RESULTS

Experiment No.1:- Effect of Harman alkaloids on isolated frog heart.

With small doses of 1,3 and 10 micrograms of Harman alkaloids, no significant effect was observed. Arrhythmia was induced at the dose of 30 micrograms, together with reduction of heart rate and cardiac output, there was reduction in amplitude of heart contractions with doses of 1 and 3 milligrams and with a dose of 10 milligrams there was cardiac arrest.[Table 1]

The contractions of the heart resumed after washing off the drug with frog ringer solution indicating that the cardio-depressant action of Harman alkaloids is reversible.

Table 01:Effect of Harman alkaloids on isolated frog heart

S. No.	DOSE	Heart Rate per Minute	Cardiac output per Minute	Amplitude of Heart Contraction
1	0 (Normal)	38	10 ml	1.5 cm
2	1,3,10 µg	38	10 ml	1.5 cm
3	30, 100, 300 µg	36	8 ml	1.5 cm
4	1 mg	36	8 ml	1.0 cm
5	3 mg	24	8 ml	1.0 cm
6	10 mg	Cardiac arrest	-	-

Experiment No.2:- Effect of Harman alkaloids on the action of Adrenaline on isolated frog heart

With 1 milligram of Harman alkaloids, there was decrease in the amplitude of heart contractions and with 3 milligrams, the response to 100 nanograms of Adrenaline was not only completely blocked but there was cardiac arrest.

The contractions of the heart resumed after washing off the drug with frog ringer solution indicating that the cardiac arrest was reversible.[Table 2]

Table 02:Effect of Harman alkaloids on the action of Adrenaline on isolated frog heart

S. No.	DOSE	Heart Rate per Minute	Cardiac output per Minute	Amplitude of Heart Contraction
1	0 (Normal)	50	15 ml	3.8 cm
2	100 nanogram of Adrenaline	54	15 ml	7.1 cm
3	100 nanogram of Adrenaline + 300 µg Harman alkaloids	46	15 ml	5.5 cm
4	100 nanogram of Adrenaline + 1 mg Harman alkaloids	46	15 ml	5.5 cm
5	100 nanogram of Adrenaline + 3 mg Harman alkaloids	Cardiac arrest	-	-

Experiment No.3:- Effect of Harman alkaloids on the action of 5-Hydroxytryptamine on isolated frog heart

With 1 milligram of Harman alkaloids, there was decrease in the amplitude of heart contractions and with 3 milligrams the response to 10 micrograms of 5-Hydroxytryptamine was not only completely blocked but there was cardiac arrest. The contractions of the heart resumed after washing off the drug with frog ringer solution indicating that the cardiac arrest was reversible.[Table 3]

Table 03: Effect of Harman alkaloids on the action of 5-Hydroxytryptamine on isolated frog heart

S. No.	DOSE	Heart Rate per Minute	Cardiac output per Minute	Amplitude of Heart Contraction
1	0 (Normal)	44	14 ml	3.0 cm
2	10µg 5-HT	48	15 ml	7.0 cm
3	10µg 5-HT + 300 µg Harman alkaloids	44	14 ml	6.8 cm
4	10µg 5-HT + 1 mg Harman alkaloids	42	14 ml	6.2 cm
5	10µg 5-HT + 3 mg Harman alkaloids	Cardiac arrest	-	-

Experiment No.4:- Effect of Harman alkaloids on the action of calcium chloride on isolated frog heart.

With 300 micrograms of Harman alkaloids, there was decrease in the amplitude of heart contractions and with 1 milligram the response to 1 milligrams of calcium chloride was not only completely blocked but there was cardiac arrest.

The contractions of the heart resumed after washing off the drug with frog ringer solution indicating that the cardiac arrest was reversible.[Table 4]

Table 04: Effect of Harman alkaloids on the action of calcium chloride on isolated frog heart

S. No.	DOSE	Heart Rate per Minute	Cardiac output per Minute	Amplitude of Heart Contraction
1	0 (Normal)	44	14 ml	3.8 cm
2	1mg calcium chloride	40	14 ml	4.6 cm
3	1mg calcium chloride + 300 µg Harman alkaloids	40	13 ml	1.0 cm
4	1mg calcium chloride + 1 mg Harman alkaloids	Cardiac arrest	-	-

Experiment No.5:- Effect of Harman alkaloids on frog rectus abdominus muscle:

Harman alkaloids did not produce any effect on frog rectus abdominus muscle [Table 5]

Table 05: Effect of Harman alkaloids on frog rectus abdominus muscle

S. No.	DOSE	Amplitude of Contraction
1	Harman alkaloid 1µg	NIL
2	Harman alkaloid 3µg	NIL
3	Harman alkaloid 10µg	NIL
4	Harman alkaloid 30µg	NIL
5	Harman alkaloid 100µg	NIL
6	Harman alkaloid 300µg	NIL
7	Harman alkaloid 1mg	NIL
8	Harman alkaloid 3mg	NIL
9	Harman alkaloid 10mg	NIL

Experiment No. 6:- Effect of Harman alkaloids on the action of Acetyl-choline on frog rectus abdominus muscle [Table 6]

There was no change in response to Acetyl-choline 100 micrograms in the presence of Haarman alkaloids in doses of 100 micrograms, 300 micrograms, 1 milligram and 3 milligrams.

Table 06: Effect of Harman alkaloids on the action of Acetyl-choline on frog rectus abdominus muscle

S. No.	DOSE	Amplitude of Contraction
1	Ach - 30µg	0.7 cm
2	Ach - 100µg	0.9 cm
3	Ach - 300µg	0.9 cm
4	Ach - 100µg + Harman alkaloid 100µg	0.9 cm
5	Ach - 100µg + Harman alkaloid 300µg	0.9 cm
6	Ach - 100µg + Harman alkaloid 1mg	0.9 cm
7	Ach - 100µg + Harman alkaloid 3mg	0.9 cm

DISCUSSION

In this study, Harman alkaloids isolated from *Peganum harmala* seeds were shown to inhibit the normal contractions of isolated frog heart and the inotropic actions of Adrenaline, 5-Hydroxytryptamine and calcium. These inhibitions were concentration dependent and reversible. Harman alkaloids have not shown any effects on frog rectus abdominus muscle on their own and they have also not shown any effect on the contractions of frog rectus abdominus muscle induced by Acetyl-choline.

The data suggests that Harman alkaloids isolated from *Peganum harmala* seeds have cardio-depressant activity [7].

Contractions of the skeletal, cardiac and smooth muscles are dependent on an increase in the concetration of cytoplasmic free calcium which activates the contractile element. The source of activator calcium may be intracelluar or extracellular. The relative contribution of calcium from these two sources however depends largely upon the type of muscle tissue, the intracellular calcium from sarcoplasmic reticulum having a main role in case of skeletal muscle contraction and the extracellular calcium having a predominant role in case of cardiac and smooth muscle contractions.

The contractile response of the cardiac muscle is regulated by cycles of depolarisation and repolarisation. Action potentials appear at the height of depolarisation and constitute a rapid influx of calcium through voltage dependent calcium channels. Since, Harman alkaloids isolated from *Peganum harmala* seeds inhibit the heart contractions, they may be interfering with calcium influx via voltage dependent calcium channels or with membrane depolarisation which opens these channels [8].

It is unlikely that Harman alkaloids have a specific receptor antagonistic effect because they antagonise the effects of many agonists like Adrenaline, 5-Hydroxytryptamine and calcium. As the Harman alkaloids were found to inhibit the cardiac muscle contractions and not the skeletal muscle contractions, they may be inhibiting calcium influx via receptor operated calcium channels or voltage dependent calcium channels [9,10].

CONCLUSION

It seems that the Harman alkaloids isolated from *Peganum harmala* seeds affect the cardiac muscle contractions by blocking the calcium influx into the cell via voltage dependent calcium channels and receptor operated calcium channels. They do not affect the skeletal muscle contractions as it is dependent on sodium and potassium channels and calcium is released from sarcoplasmic reticulum inside the cells in response to depolarisation.

Hence, the cardio-depressant actions of Harman alkaloids may be due to calcium channel blockade.

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How to cite this article : Rajkumar T, Devde R. A study of the cardio-depressant actions of harman alkaloids isolated from the seeds of *Peganum harmala.* Perspectives in Medical Research 2018;6(2):21-24.

Sources of Support: Nil,Conflict of interest:None declared