Pharmacology Biochemistry & Behavior, Vol. 32, pp. 83–86. © Pergamon Press plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

Acute and Chronic Effects of a Nutmeg Extract on the Toad Heart

M. SALEH,*[1] Z. NABIL,† H. MEKKAWY‡
AND G. ABD ALLAH‡

**Department of Zoology, Faculty of Science, Al Azhar University*
Nasr City, Cairo, Egypt
†Department of Zoology, Faculty of Science, Suez Canal University
Ismailia, Egypt
‡Biological Laboratory, The National Center for Sociological and Criminological Research
Cairo, Egypt

Received 26 June 1986

SALEH, M., Z. NABIL, H. MEKKAWY AND G. ABD ALLAH. *Acute and chronic effects of a nutmeg extract on the toad heart.* PHARMACOL BIOCHEM BEHAV 32(1) 83–86, 1989.—Electrocardiographic and flexible suction electrode techniques were used to investigate the effects of a nutmeg extract on the toad heart. Acute treatment with the extract resulted in a dose-related sinus tachycardia, faster atrioventricular conduction speed and an increased amplitude of ventricular action potential. Chronic treatment resulted in sinus bradycardia and decreased amplitude and increased duration of ventricular action potential.

Myristica fragrans Nutmeg Ventricular action potential EKG Heart rate *Bufo regularis*

THE seeds of nutmeg (*Myristica fragrans* Houtt.) are widely used as a food condiment in folk medicine and more recently as a hallucinogenic agent (23,25). Several pharmacological effects of nutmeg are described in the literature (11, 16, 17) and have been attributed to a number of phenylallyl derivatives, particularly myristicin and elemicin (6, 11, 16, 17). The biological transformation of some of these compounds into amphetamine derivatives, or their action as monoamine oxidase inhibitors, have been suggested as possible mechanisms for many of the pharmacological effects of nutmeg (1, 14, 18).

Cardiovascular symptoms, particularly those related to heart rate and blood pressure, have been frequently reported in human subjects following the ingestion of nutmeg (17,24). However, the action of nutmeg or its active components on the heart have never been described in any detail. The present report provides information on both acute and chronic effects of a nutmeg extract on the electrophysiology of the toad heart.

METHOD

Extraction and Doses

Normal hexane extract of dried nutmeg seeds was prepared according to the method of El Darawy *et al.* (3). This extract has an LD_{50} of 810 mg/kg body weight in the toad *Bufo regularis* (Saleh *et al.*, in preparation), and is known to contain the compounds myristicin, elemicin, safrol, eugenol and others (3).

For the acute treatment, three extract doses of 190, 375 and 750 mg/kg body weight were used. In the chronic experiments, the animal received an extract dose of 75 mg/kg body weight daily for a total of 15 days. The extract was suspended in a 1:1 mixture of Tween 80 and amphibian Ringer's solution immediately before injection. Each dose was administered in a volume of 10 ml/kg body weight and injected into the lymph sac of the toad. Control animals received only Tween 80 and amphibian Ringer's solution mixture.

Animals and Surgical Preparations

Adult toads (*Bufo regularis*), 35–40 g in body weight, were used. For the acute experiments, 40 animals, divided into four equal groups, were used. Three groups were treated with the extract, each receiving one of the three doses used, and one group served as a control. For the chronic experiments, 45 animals, divided into 30 treated and 15 control animals, were used. They were kept in glass aquaria containing a thin layer of moist soil and fed on insect larvae throughout the duration of the experiment. Ten treated and five control animals were randomly selected and used for recording at each of the three test intervals of 5, 10 and 15 days. All the experimental work was carried out during the spring and summer, the normal activity season of this toad, at an ambient temperature of 24±4°C.

[1]Requests for reprints should be addressed to M. Saleh at his present address: Department of Biology, University of Bahrain, P.O. Box 1082, Bahrain, Arabian Gulf.

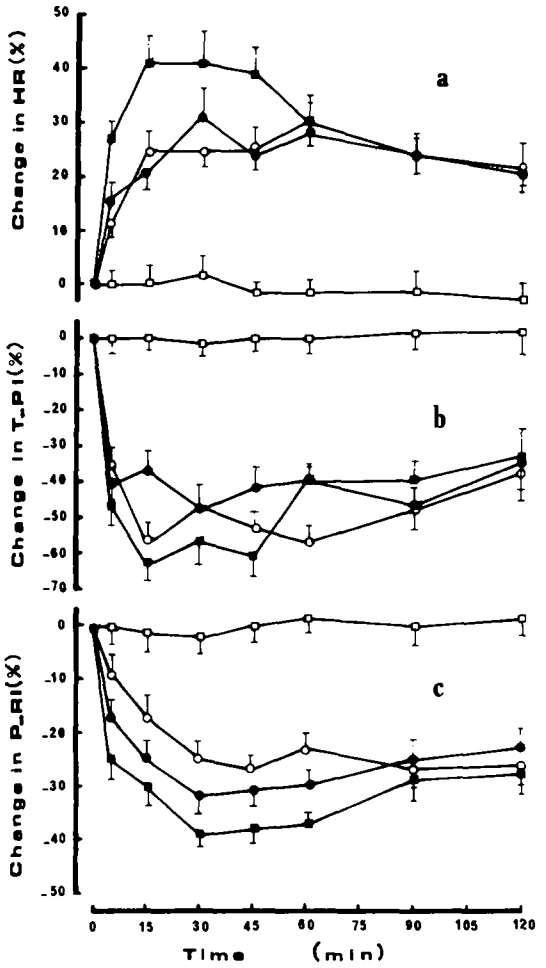

FIG. 1. Effects of three doses of nutmeg extract of 190 (●), 375 (○) and 750 (■) mg/kg body weight and control injection (□) on (a) heart rate (HR), (b) T-P interval, (c) P-R interval. Vertical bars = ½ SD.

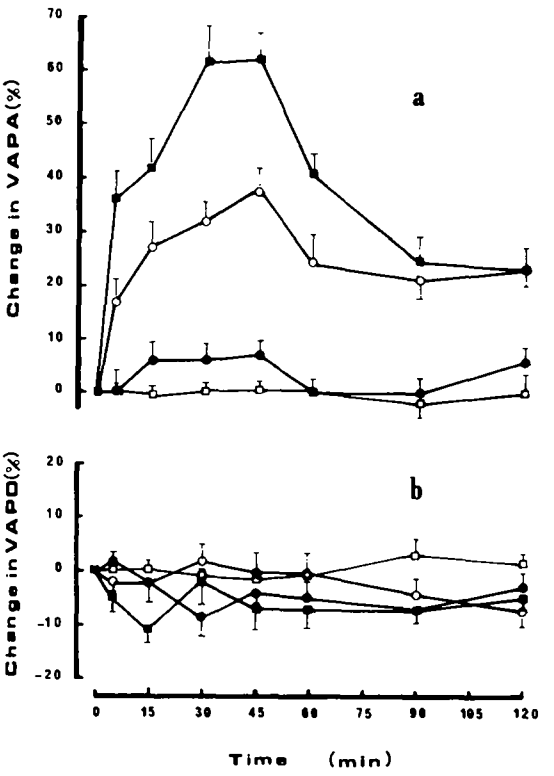

FIG. 2. Effects of three doses of nutmeg extract of 190 (●), 375 (○) and 750 (■) mg/kg body weight and control injection (□) on (a) Amplitude of ventricular action potential (VAPA), (b) Duration of ventricular action potential (VAPD) of the toad. Vertical bars = ½ SD.

Recording

Ventricular action potential was recorded using a flexible suction electrode according to the method described by Hoffman *et al.* (4) and Nabil *et al.* (9). This technique allows continuous recording of action potential from myocardiac fibers while the heart is beating. The tip of the electrode (40 μm in diameter) was placed on the ventral surface of the ventricle approximately at the midpoint of its long axis. The electrode was applied to the myocardium only during the brief recording period, which lasted less than thirty seconds, then released until the next recording.

Electrocardiograms (EKGs) were recorded using two pieces of cotton thread saturated with amphibian Ringer's solution and placed directly on the myocardium. The end of one thread was placed on the right atrium and that of the other on the apex of the ventricle. Action potential and EKG signals were amplified, monitored on an oscilloscope and recorded on a chart recorder.

In acute experiments, ventricular action potential and EKG were first recorded, then the animal was injected with the extract or control solution and recording was carried out at 5, 15, 30, 45, 60, 90 and 120 minutes following the injection. In the chronic experiments, the animal was injected and action potential and EKG were recorded 30 minutes after the injection.

Responses to the treatments are expressed as percent change from pretreatments values. Differences among animal groups were assessed by analysis of variance. Statistical significance was reached when $p<0.05$.

RESULTS

A significant increase in heart rate occurred following the administration of each on the three extract doses (Fig. 1a). EKGs of all nutmeg-treated animals showed a significant reduction in the T-P (Fig. 1b) and P-R intervals (Fig. 1c). Maximum effects were generally reached within two hours of the extract injection but gradually declined towards normal levels thereafter. No significant change in EKG was observed in control animals (Fig. 1 a, b and c).

A significant increase in the amplitude of ventricular action potential occurred following the injection of each of the two larger extract doses. With the smallest dose, a slight, statistically insignificant, increase in amplitude occurred (Fig. 2a). No significant change in the duration of the ventricular action potential was detected following the injection of any of the three extract doses (Fig. 2b). Control animals showed no significant change in ventricular action potential (Fig. 2 a and b).

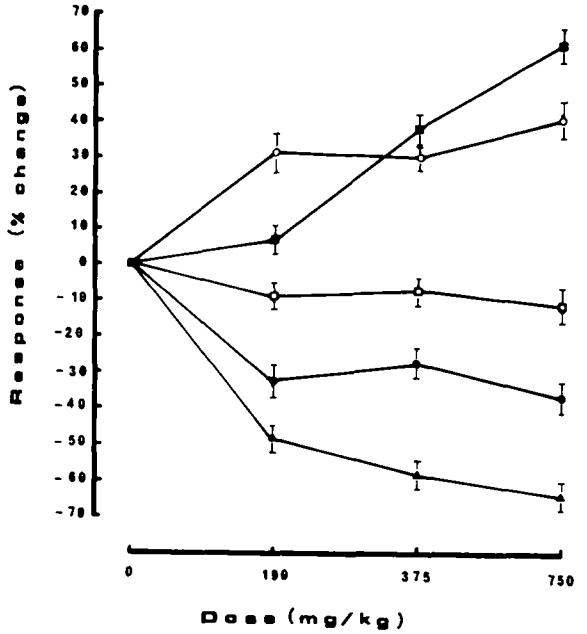

FIG. 3. Maximum changes in heart rate (○), T-P interval (▲), P-R interval (●) and ventricular action potential amplitude (■) and duration (□) in response to injection of control solution and three doses of nutmeg extract. Vertical bars=SD.

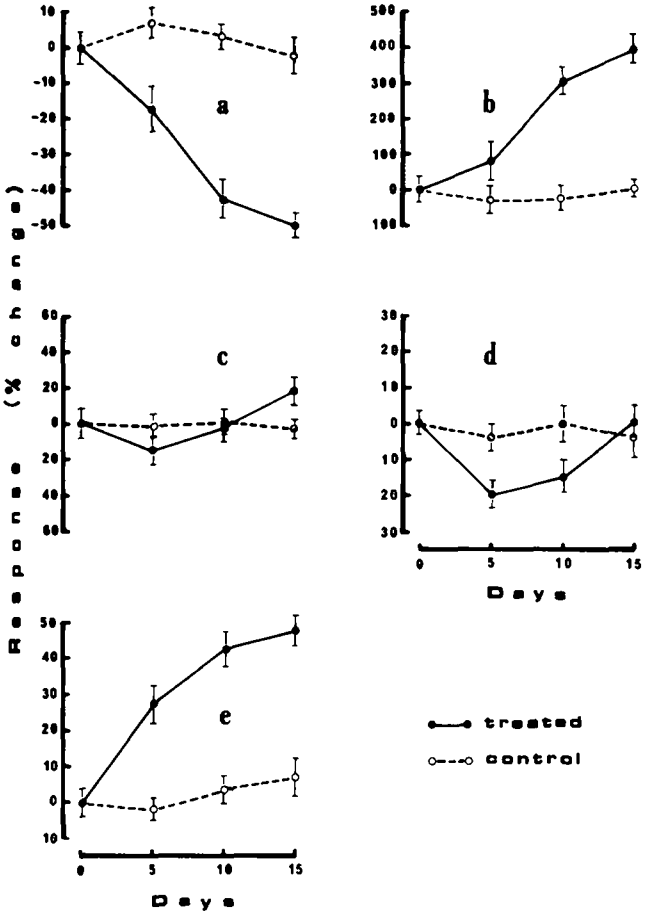

FIG. 4. Effects of chronic administration of nutmeg extract and control solution on heart rate (a), T-P interval (b), P-R interval (c) and ventricular action potential amplitude (d) and duration (e). Vertical bars=SD.

Figure 3 compares maximum changes in heart rate, T-P and P-R intervals of EKG and amplitude and duration of ventricular action potential, occurring in response to the three acute doses of nutmeg extract. The figure shows that, in the case of heart rate, T-P and P-R intervals and amplitude of ventricular action potential, the response was maximum with the largest extract dose. The effect of the extract on the duration of ventricular action potential was not significantly dose-related.

The daily injection of nutmeg extract resulted in a gradual drop in heart rate, reaching close to 50% of its original value after 15 days of the treatment (Fig. 4a). The duration of the T-P interval showed a gradual, highly significant increase, reaching a maximum value after 15 days of the treatment. P-R interval, on the other hand, showed an initial significant drop after five days of treatment, then a gradual rise to a value significantly higher than that of the control at the end of the 15 days of treatment (Fig. 4b and c).

Chronic treatment with nutmeg extract resulted in a significant reduction in the amplitude of ventricular action potential after five and ten days of the treatment. After 15 days of the treatment, however, it returned to a level not significantly different from that of control animals (Fig. 4d). The duration of action potential showed a gradual increase becoming significantly higher than the control after five, ten and fifteen days of the treatment (Fig. 4e).

DISCUSSION

The heart of the toad responded to administration of nutmeg extract in a fashion suggesting a sympathomimetic nature of active components of that extract. The positive chronotropic effect of the acute treatment with the extract appears to be the result of a stimulatory effect of the extract on the sinus pacemaker as is clear from the reduction in the T-P interval of the EKG. It is also clear that the administration of the extract significantly increased the atrioventricular conduction speed as evident in the shorter P-R interval of the EKG in treated animals. These effects are similar to those of sympathetic stimulation or treatment with epinephrine (5, 19, 21, 22) or amphetamine (15). Tachycardia has been observed in human subjects following the ingestion of whole nutmeg seeds (17,24).

The profound increase in the amplitude of ventricular action potential in response to acute treatment with the extract is similar to the effects of adrenergic transmitters and amphetamine on a variety of vertebrate hearts (4, 7, 10, 13, 20).

The effects of the extract on heart rate, T-P and P-R intervals and amplitude of ventricular action potential are dose-dependent. Similar dose-response relationships have been reported for the effects of oil of nutmeg on fertility and meiotic chromosome rearrangement in mice (12) and of a number of nutmeg compounds on rope climbing performance in rats (2).

The results also show that, contrary to the stimulatory effect of acute treatment, chronic administration of the

extract results in a progressive depression of the heart. It appears that the drop in the heart rate is caused mostly by the inhibition of the sinus pacemaker leading to the considerable lengthening of the T-P interval. The increase observed in the duration of ventricular action potential also contributes to the slower heart rate. Reduction in atrioventricular conduction speed, as reflected in the shorter P-R interval, appears to contribute to the slower heart rate only after 15 days of the treatment. This depressive effect of the chronic nutmeg treatment is possibly the result of the depletion of intracellular catecholamine stores in the sinus pacemaker and AV node by amphetamine derivatives formed as a result of the biotransformation of active nutmeg components (1,14). Similarly, chronic abuse of phenylisopropylamines is known to have an inhibitory effect on the heart (8,20). It has been suggested that the inhibitory effect of chronic treatment with metamphetamine on the heart of bullfrog is produced through the blocking of postsynaptic beta receptors (20).

In chronically-treated animals, a significant decline in the initial response to the treatment was observed in case of the P-R interval and amplitude of the ventricular action potential, possibly indicating the development of tolerance to active compounds in the extract. Development of tolerance to the nutmeg compounds myristicin and elemicin in rats, as measured in rope climbing performance, is reported by De Mello *et al.* (2).

ACKNOWLEDGEMENT

We would like to thank Dr. Philip Basson for kindly reviewing the manuscript and providing valuable comments.

REFERENCES

1. Braun, U.; Kalbhen, D. A. Evidence for the biogenic formation of amphetamine derivatives from components of nutmeg. Pharmacology 9:312–316; 1973.
2. De Mello, A. C.; Carlini, E. A.; Dressler, K.; Green, J. P.; Kang, S.; Margolis, S. Behavioral observations on compounds found in nutmeg. Psychopharmacologia 31:349–363; 1973.
3. El-Darawy, Z. I.; Mobarak, Z. M.; Zaky, N. G.; Aly, M. I.; Abdel-Rahman, M. O. Chemical studies on psychotomimetic drugs (hallucinogens). J. Pharmacol. U.A.R. 9:147–157; 1967.
4. Hoffman, B. F.; Carnefield, P. F.; Lepeschkin, E.; Surawicz, B.; Herrlich, H. C. Comparison of cardiac monophasic potentials recorded by intracellular and suction electrodes. Am. J. Physiol. 196:1297–1301; 1959.
5. Hutterof, T. W. Vagal and sympathetic effects of the pacemaker fibers in the sinus venosus of the heart. J. Gen. Physiol. 39:715–733; 1956.
6. Kalbhen, D. A. Nutmeg as a narcotic: a contribution to the chemistry and pharmacology of nutmeg (*Myristica fragrans*). Angew. Chem. Int. Ed. 10:370–374; 1971.
7. Levy, M. N.; Zieske, H. Autonomic control of cardiac pacemaker activity and atrioventricular transmission. J. Appl. Physiol. 27(4):465–470; 1969.
8. Machii, S. Pharmacological studies on the optical isomers of ephedrine and methylephedrine. Folia Pharmacol. (Japon) 53:638–659; 1957.
9. Nabil, Z.; Saleh, M.; Mekkawy, H.; Abd Allah, G. Effects of an extract of khat (*Catha edulis*) on the toad heart. J. Ethnopharmacol. 18:245–256; 1986.
10. Nathan, D.; Beeler, D. Electrophysiologic correlates of inotropic effects of isproternol in canine myocardium. J. Mol. Cell. Cardiol. 7:1–15; 1975.
11. Payne, R. B. Nutmeg intoxication. N. Engl. J. Med. 269:36–38; 1963.
12. Pecevski, J.; Savkovic, N.; Radivojevic, D.; Vuksanovic, L. Effect of oil of nutmeg on the fertility and induction of meiotic chromosome rearrangements in mice and their first generation. Toxicol. Lett. 7:239–243; 1981.
13. Randall, W. C. Sympathetic control of the heart. In: Randall, W. C., ed. Neural regulation of the heart. New York: Oxford University Press; 1976:43–94.
14. Shulgin, A. T. Possible implication of myristicin as a psychotropic substance. Nature 210:380–384; 1966.
15. Simpson, L. L. Blood pressure and heart rate responses evoked by d- and l-amphetamine in the pithed rat preparation. J. Pharmacol. Exp. Ther. 193(1):149–159; 1974.
16. Truitt, E. B., Jr. The pharmacology of myristicin and nutmeg. In: Efron, D. H.; Holmstedt, B.; Kline, N. S., eds. Ethnopharmacologic search for psychoactive drugs. Washington, DC: U.S. Government Printing Office; 1967:215–222.
17. Truitt, E. B.; Callaway, E.; Braude, M. C.; Krantz, J. C. The pharmacology of myristicin; a contribution to the psychopharmacology of nutmeg. J. Neuropsychiatry 2:205–210; 1961.
18. Truitt, E. B.; Duritz, G.; Ebersberger, E. M. Evidence of monoamine oxidase inhibition by myristicin and nutmeg. Proc. Soc. Exp. Biol. Med. 112:647; 1963.
19. Ueda, H.; Yanai, Y.; Marao, S.; Harumi, K.; Mashima, S.; Kuriowa, A.; Sugimoto, T.; Shimomura, K. Electrocardiographic and vectrocardiographic changes produced by electrical stimulation of the cardiac nerves. Jpn. Heart J. 5:359–372; 1964.
20. Urabe, M. Inhibitory mechanisms of methamphetamine in the isolated myocardium of bullfrog. Arch. Int. Pharmacodyn. 257:239–254; 1982.
21. Urthaler, F.; James, T. N. Effect of tetrodotoxin on AV conduction and AV junctional rhythm. Am. J. Physiol. 224:1155–1161; 1973.
22. Urthaler, F.; James, T. N. Cholenergic and adrenergic control of the sinus node and AV junction. In: Randall, W. C., ed. Neural regulation of the heart. New York: Oxford University Press; 1973:247–263.
23. Weil, A. T. Nutmeg as a narcotic. Econ. Bot. 19:194–217; 1965.
24. Weil, A. T. Nutmeg as a psychoactive drug. In: Efron, D. H.; Holmstedt, B.; Kline, N. S., eds. Washington, DC: U.S. Government Printing Office; 1967:188–201.
25. Weiss, G. Hallucinogenic and narcotic-like effects of powdered myristica (nutmeg). Psychiatr. Q. 34:346–356; 1960.