sin) would, at least in theory, result in marked hypotension, progressive hemoconcentration and marked RES phagocytic depression, all of which we see take place in Brattleboro rats subjected to only mild episodes of hemorrhage and intestinal ischemia.

A loss of RES phagocytic function, as seen in the present studies using Brattleboro rats subjected to mild blood and/or fluid loss, is known to result in a failure to inactivate pathogenic microorganisms, blood borne tissue mediators, endotoxins, metabolites and/or other noxious tissue products released in shock[6,7,9]. In addition, severe depression, or a loss of RES function is known to be associated with depressed microcirculatory blood flow, tissue ischemia and rupture of lysosomal membranes, thereby releasing hydrolytic enzymes into the circulation[6]. The fact that previous experiments have clearly demonstrated that vasopressins, when administered to normal animals subjected to severe forms of the same types of shock used here, can either restore or enhance RES phagocytic function[7] lends support to the concept that endogenous, released vasopressin probably aids in the maintenance of RES function after mild blood and/or fluid loss.

In conclusion, our current observations provide strong, direct evidence for a role for endogenous vasopressin in the compensatory phase of the shock syndrome and in homeostatic regulation of the RES after shock and trauma.

1 Supported in part by NIH Grant Nos HL-18002 and HL-18015 and NIDA Grant No. DA-02339. The author would like to acknowledge the excellent technical assistance provided by Y. Waldemar, J. Gargani and R.W. Burton.

2 M. Ginsburg and L.M. Brown, Br. J. Pharmac. Chemother. *11*, 236 (1956); R.A. Baratz and R.C. Ingraham, Am. J. Physiol. *198*, 565 (1960); D. Belesin, G.W. Bisset, J. Haldar and R.L. Polak, Proc. Roy. Soc. B. *166*, 443 (1967); M. Forsling, in: Anti-Diuretic Hormone. Eden Press, Montreal 1977. M. Rocha e Silva, Jr, W. Celso De Lima and E.M. Castro De Souza, Pflügers Arch. *376*, 185 (1978).

3 B.M. Altura, Am. J. Physiol. *219*, 222 (1970); B.M. Altura and B.T. Altura, Federation Proc. *36*, 1853 (1977).

4 B.M. Altura, Am. J. Physiol. *212*, 1447 (1967); Microvasc. Res. *3*, 361 (1971); Eur. J. Pharmac. *24*, 49 (1973); Proc. Soc. exp. Biol. Med. *142*, 1104 (1973); *146*, 1054 (1974).

5 A.D. Keller, Circulation Res. *11*, 214 (1954); M. Rocha e Silva, Jr, and M. Rosenberg, J. Physiol. *202*, 535 (1969); E. Szczepanska-Sadowska, Pflügers Arch. *335*, 139 (1972); *338*, 313 (1973); A.W. Cowley, Jr, E. Monos and A.C. Guyton, Circulation Res. *34*, 505 (1974).

6 B.M. Altura and S.G. Hershey, Adv. exp. Med. Biol. *33*, 545 (1973); T.M. Saba, Circulatory Shock *2*, 91 (1975); B. Schildt, Adv. exp. Med. Biol. *73A*, 375 (1976); B.M. Altura, Adv. Microcirculation *9*, 252 (1979).

7 B.M. Altura and S.G. Hershey, Bull. N.Y. Acad. Med. *43*, 259 (1967); Adv. exp. Med. Biol. *33*, 545 (1973); B.M. Altura, Eur. J. Pharmac. *37*, 155 (1976); Adv. Shock Res. *3*, 3 (1980).

8 B.M. Altura and B.T. Altura, J. Pharmac. exp. Ther. *191*, 300 (1974).

9 B.M. Altura and S.G. Hershey, Am. J. Physiol. *215*, 1414 (1968).

Effects of propafenone on TEA-induced action potentials in vascular smooth muscle of canine coronary arteries[1]

D.R. Harder and L. Belardinelli

Department of Physiology, East Tennessee State University, College of Medicine, Johnson City (Tennessee 37601, USA), and Department of Physiology, University of Virginia, School of Medicine, Charlottesville (Virginia 22903, USA), 27 November 1979

Summary. The Ca^{++}-dependent, TEA-induced action potential is blocked by propafenone in a dose-dependent manner. Such results suggests that in coronary arterial smooth muscle one mechanism of action of propafenone is to inhibit Ca^{++} inward current.

Propafenone has recently been demonstrated to possess antiarrhythmic properties in a significant number of individuals with ectopic beats and tachycardias of atrial or ventricular origin[2]. It also has been shown that propafenone has negative inotrophic actions in that it reduces systolic time intervals[3], transiently reduces cardiac function[2], and prolongs the refractory period[4]. Such negative inotrophic actions of this drug have been attributed, in part, to a decrease in Ca^{++} inward current[4].

Propafenone also induces a dose dependent increase in coronary blood flow in dogs and guinea-pigs, and relaxes strips of bovine coronary arteries[4,5]. Such findings suggest that propafenone may have similar action on coronary arteries and cardiac tissue in inhibiting Ca^{++} inward current necessary for excitation-contraction coupling.

Recently, Harder et al.[6] have demonstrated that in vascular smooth muscle (VSM) from canine coronary arteries tetraethylammonium ion (TEA) induces Ca^{++} dependent action potentials upon electrical stimulation. These TEA-induced action potentials are blocked by known Ca^{++} antagonists such as verapamil and Mn^{++}.

It is the purpose of the present study to determine the effect of propafenone on the Ca^{++} dependent action potential in the VSM of canine coronary arteries since it may serve as a useful tool in the study of Ca^{++} inward current in the cells.

Materials and methods. Mongrel dogs were anesthetized with sodium pentabarbital (30 mg/kg, i.v.) after which the hearts were rapidly removed. The left main coronary artery was cannulated and perfused with cold oxygenated Ringers' solution. Coronary arteries (1.0 mm outside diameters) were removed and slit down the longitudinal axis, allowing microelectrode penetration from the intimal sur-

Summary of membrane potential, action potential amplitude and maximal rate of rise measurements in canine coronary arterial smooth muscle in the presence of 10 mM TEA (±1 SEM)

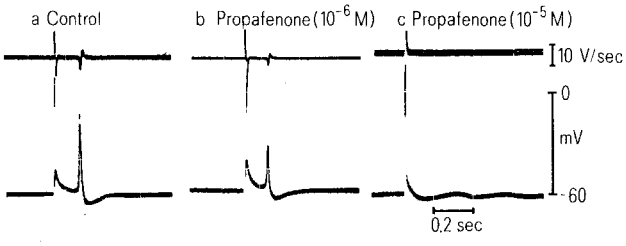
Condition	E_m (mV)	Amplitude (mV)	$+\dot{V}_{max}$ (V/sec)	N**
Control	48±1.0	54±1	6.8±0.7	9/5
Propafenone (10^{-6} M)	47±0.7	27±1.1*	2.9±1.4*	9/5
Propafenone (10^{-5} M)	45±1.0*	0	0	10/6

* Significantly less than control at $p<0.05$. ** Numerator refers to the number of cells impaled, denominator refers to the number of arteries.

face of the vessel. The arterial segments were placed in a non-recirculating organ bath and suffused with a physiological salt solution (PSS) containing (in mM): Na^+, 141; K^+, 4.7; Ca^{++}, 2.5; Mg^{++}, 0.76; Cl^-, 124; $H_2PO_4^-$, 1.7; HCO_3^-, 25; and glucose, 11. The solutions were aerated with 95% oxygen – 5% carbon dioxide (pH 7.3–7.4) and maintained at 37 °C. Tetraethylammonium chloride (10 mM) was added to induce excitability. Propafenone - HCl (Knoll AG, Ludwigshafen, Batch No. W33425) was added to the bathing solution at final concentrations of 10^{-6}–10^{-5} M. Transmembrane and action potentials were recorded with glass microelectrodes as previously described[6].

Results and discussion. The effect of propafenone on the resting membrane potential (E_m), amplitude and maximal rate of rise ($+\dot{V}_{max}$) of the TEA-induced action potential are summarized in the table. Addition of propafenone to the bathing solution caused a dose-dependent reduction in both amplitude and $+V_{max}$ of the action potential (figure). High doses (10^{-5} M) of propafenone also resulted in a small but significant reduction in E_m (table).

Since it has been shown that the TEA-induced action potential in canine coronary VSM is dependent upon extracellular Ca^{++} and are blocked by Ca^{++} antagonists, it is reasonable to conclude that the underlying inward current mediating these action potentials is carried by Ca^{++}[6,7]. The findings that propafenone markedly inhibits both the amplitude and rate of rise of the TEA-induced action potential suggests that one of its mechanisms of action is to inhibit Ca^{++} inward current in coronary VSM. Such a hypothesis is supported by the findings that propafenone reduces Ca^{++} inward current in cardiac muscle[8].



Effect of propafenone on the amplitude and maximal rate of rise ($+\dot{V}_{max}$) of the TEA-induced Ca^{++} dependent action potential in vascular smooth muscle of canine coronary arteries. *A* Control action potential induced by extracellular stimulation in the presence of 10 mM TEA. *B* Record from same cell showing a marked reduction in both the amplitude and $+\dot{V}_{max}$ of the TEA induced action potential by 10^{-6} M propafenone. *C* Complete inhibition of the action potential upon raising the concentration of propafenone to 10^{-5} M. Voltage, time and $+\dot{V}_{max}$ calibrations in C apply throughout.

1 This research was supported by a grant from the Tennessee Affiliate of the American Heart Association and VA grant No. 1A (74)111-430100). The authors wish to thank Dr Gerhard Pfennigsdorf for supplying us with propafenone. We also wish to thank Ms Penny Williams for her technical assistance.

2 D.A. Beck and H. Hochrein, Dt. med. Wschr. *103*, 1261 (1978).
3 G. Breithardt, E. Jochum, H. Kuhn, L. Seipel. Z. Kardiol. *67*, 6 (1978).
4 H.J. Hapke and E. Prigge, Arzneimittel-Forsch. *26*, 1549 (1976).
5 W.R. Kukovetz, G. Poech, S. Holzmann, A. Wurm and E. Paietta, ISS Fortschr. Pharmakother. Herzrhythmusstörungen *1*, 9 (1977).
6 D.R. Harder, L. Belardinelli, N. Sperelakis, R. Rubio and R.M. Berne, Circulation Res. *44*, 176 (1979).
7 L. Belardinelli, D.R. Harder, N. Sperelakis, R. Rubio and R.M. Berne, J. Pharm. exp. Ther. *203*, 62 (1979).
8 M. Kohlhardt, ISS Fortschn. Pharmakother. Herzrhythmusstörungen *1*, 35 (1977).

Diurnal variations in thermoregulatory responses to intrahypothalamic and intravenous injections of noradrenaline in the pigeon

H. Rintamäki and R. Hissa

Department of Zoology, Zoophysiological Laboratory, University of Oulu, SF-90230 Oulu 23 (Finland), 10 December 1979

Summary. The differences in responses of T_b, T_f and $\dot{V}O_2$ both to intrahypothalamic and i.v. administration of NA were measured both at noon and at midnight in the pigeon. Although the T_b and $\dot{V}O_2$ were at a higher level in the daytime, no differences in the magnitude of the fall in $\dot{V}O_2$ and T_b were obtained after either intrahypothalamic or i.v. injections of NA, whether it was measured during the day or at night. The only marked difference was the more prominent vasodilatation in the daytime after both routes of injection.

It is generally accepted that both the basal metabolic rate (BMR) and body temperature (T_b) show a diurnal variation in birds[1,2]. The pigeon, a typical day-active bird, displays its lowest T_b and $\dot{V}O_2$ at night[3]. It has been shown that both peripheral and intracerebral applications of noradrenaline (NA), in contrast to the results obtained in mammals, result in hypothermia[4,5]. This is at least partly associated with the impairment of shivering and increased heat loss resulting from the induced vasodilatation in the foot. Petrović et al.[6] have demonstrated a clear diurnal rhythm in the thermogenic response to NA in rats, which seems to be related to the accompanying changes in thyroid gland activity.

To test whether the degree of hypothermia after either peripheral or intrahypothalamic injections of NA is related to the endogenous diurnal changes in physiological activities in the pigeon, the injections were conducted both at 12.00 h and at 24.00 h.

Materials and methods. Experiments were performed with 11 adult Pigeons, weighing 290–370 g, at the environmental temperature of + 15 °C. Birds were divided into 2 groups. Group 1 was i.v. injected (tibial vein) with NA (1-arterenol bitartrate, Sigma, 0.4 mg/kg in 0.85% NaCl-solution). Group 2 was injected intrahypothalamically (PO/AH-area) with 10 µg NA per 1 µl. For intrahypothalamic injections a guide cannula was unilaterally implanted as described earlier[7,8]. The coordinates were 7.8–8.0 mm anterior from the intra-aural line and 1.0–1.5 mm lateral from the midline and 8.6–10.0 mm below the surface of calvarium. The details for measuring $\dot{V}O_2$ are given elsewhere[9]. In control experiments performed with the same animals an equal volume of NaCl-solution was given. The injections were made in the daytime at 12.00 h in a lighted environmental chamber and at night at 24.00 h in a darkened chamber.