# Pharmacological Properties of Blood Pressure and Heart Rate Control in Suncus

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*Received January 21, 1993 Accepted February 18, 1993*

ABSTRACT—Blood pressure and heart rate and responses to various physiological substances in suncus were characterized and compared with those in mice. The blood pressures of the two species were similar, but the heart rate of suncus (about 400 beat/min) was significantly lower than that of mice. Norepinephrine increased the blood pressure but decreased the heart rate in suncus. The latter was blocked by cervical vagotomy. Sensitivities to acetylcholine and isoproterenol were lower in suncus. These results suggest that regulation of blood pressure and heart rate in suncus is very unique and different from the well-defined system of the rodents.

*Keywords*: Blood pressure control, Species-dependent difference, Vagus reflex, Suncus

Many lines of evidence showing the usefulness of *Suncus murinus* as an experimental animal model, e.g., nerve growth factor (1, 2), emesis (3, 4), motion sickness (5, 6), fatty liver degeneration and lipid metabolism (7, 8), have been accumulated. The suncus belongs to the order of insectivore, which is considered as the most primitive mammal and direct ancestor of other placental mammals (9). Therefore, the suncus probably possesses the fundamental characteristics of mammals. However, its cardiovascular properties have not been reported, and even normal blood pressure data are not available.

In the present study, we measured the blood pressure of *Suncus murinus* and investigated effects of physiological substances. Mice were used for comparison.

## MATERIALS AND METHODS

Animals: Male adult *Suncus murinus* (50–80 g body weight, 3- to 5-month-old, Clea Japan, Tokyo) or male ddy mice (30–45 g body weight, 2- to 4-month-old, Nihon SLC, Hamamatsu) were used.

To measure blood pressure directly, animals were anesthetized with 25 mg/kg $\alpha$-chloralose and 1 g/kg urethane, and a polyethylene catheter filled with saline containing 200 U/ml heparin was inserted into a carotid artery. Blood pressure was monitored on an ink-writing oscillograph (WI-621G, Nihon Kohden, Tokyo) via a transducer (TMI MPU-0.5-290-0-III, Gould, Inc., Valley View, OH, USA) and a preamplifier (RP-5, Nihon Kohden). Drug solution was injected via a catheter inserted into a femoral vein. Animals were kept under a light to maintain their body temperature.

In some experiments blood pressure was monitored in unanesthetized animals indirectly. Animals were put in a cage maintained at 37℃ for 10 min and then placed in a plastic holder to partly restrain their movement, and a tail-cuff plethysmograph (MK-1000, Muromachi Kikai, Tokyo) was used to measure systolic and mean blood pressure. Diastolic pressure was calculated from these two values. The apparatus was also warmed to 37℃ during the measurement.

Drugs used were *l*-norepinephrine bitartrate (NE, Wako, Osaka), *dl*-isoproterenol hydrochloride (ISO, Sigma, St. Louis, MO, USA), acetylcholine hydrochloride (ACh, Daiichi, Tokyo) and histamine dihydrochloride (Wako). Statistical significance was evaluated by Student's *t*-test.

## RESULTS

Table 1 shows blood pressure and heart rate of suncus and mice recorded either directly or indirectly. There was no significant difference in blood pressure between suncus and mice. However, the heart rate of suncus was about 400 beats/min, which is significantly lower than that of mice.

**Table 1.** Comparison of the blood pressure and heart rate between suncus and mice

| | N | Blood pressure (mmHg) systolic | mean | diastolic | Heart rate (beats/min) |
|---|---|---|---|---|---|
| Direct measurement | | | | | |
| Suncus | 17 | 110±4.0 | 90±3.2 | 82±2.9 | 435±16.8** |
| Mice | 21 | 101±4.0 | 81±3.5 | 70±3.5 | 636±15.6 |
| Indirect measurement | | | | | |
| Suncus | 5 | 110±5.3 | 87±4.6 | 75±4.6 | 382±32.1** |
| Mice | 5 | 118±6.5 | 91±3.8 | 78±4.0 | 637±15.6 |

Values are mean±S.E.M. N: The number of animals. **: Statistically significant difference from mice ($P<0.01$).

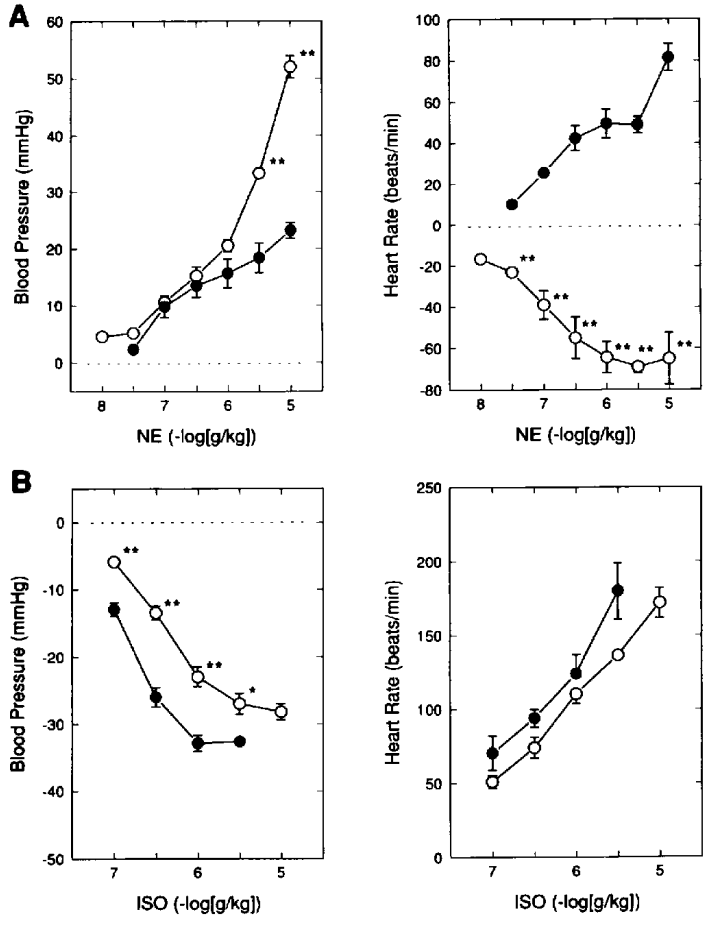


**Fig. 1.** Dose-response curves of changes in blood pressure (left) and heart rate (right) for NE (A) and ISO (B) in suncus (open circles) and mice (filled circles). Maximum changes from the baseline values induced by the drugs are plotted. Drugs were injected after complete recovery from the effects of the previously injected drug. Symbols and vertical bars represent mean±S.E.M. from five animals. Asterisks indicate a statistically significant difference from the corresponding values in mice (*: $P<0.05$, **: $P<0.01$).

Figure 1 indicates effects of NE (A) and ISO (B) on mean blood pressure and heart rate. NE increased both the blood pressure and heart rate dose-dependently in mice. However, NE decreased the heart rate in suncus, whereas the increase in blood pressure was greater in suncus. ISO decreased the mean blood pressure and in-

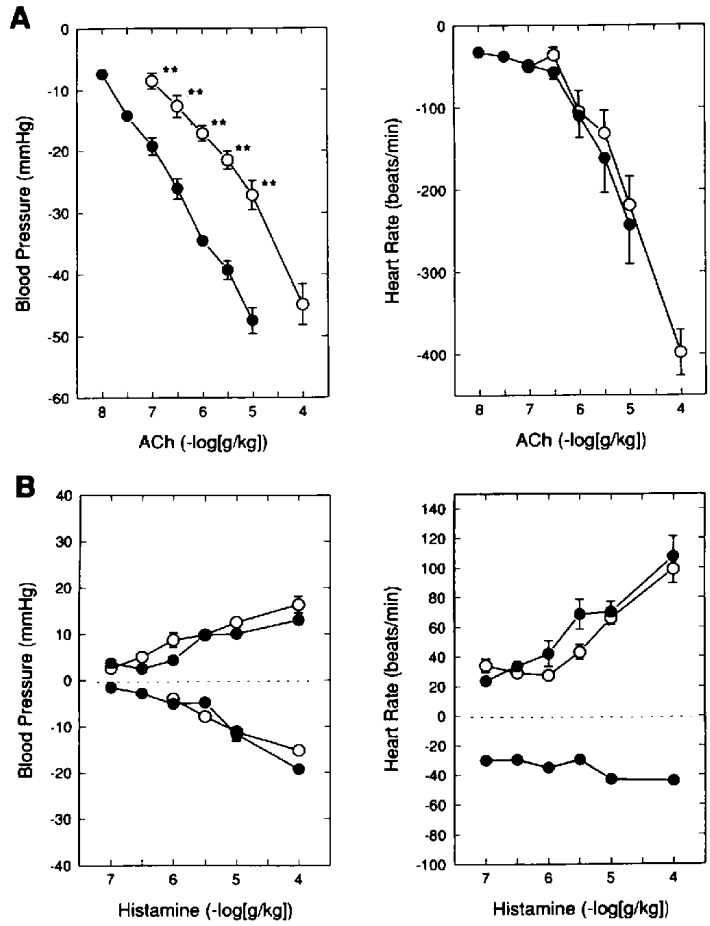


**Fig. 2.** Dose-response curves for ACh (A) and histamine (B). Symbols and axes are the same as in Fig. 1. Since histamine caused biphasic responses (initial decrease in blood pressure and heart rate followed by the increase of both parameters), both the maximum decrease and increase were plotted. The initial decrease of heart rate in suncus was not significant. The number of animals was five.

creased the heart rate both in suncus and mice. The sensitivity of decrease in blood pressure was greater in mice. The decrease in blood pressure by ACh was also greater in mice (Fig. 2A) whereas the sensitivities of heart rate were not significantly different. Histamine caused biphasic, initial decline followed by an increase, changes of blood pressure both in suncus and mice (Fig. 2B). The two dose-response curves of blood pressure were very similar. However, in mice, the drug caused a biphasic change in the heart rate.

Effects of bilateral cervical vagotomy on NE-induced decrease in heart rate were studied. As shown in Fig. 3, surgical vagotomy strongly attenuated the decrease (23.4±8.1% of pre-vagotomy value, n=3), and the increase in blood pressure became greater. However, the heart rate also did not increase under this condition.

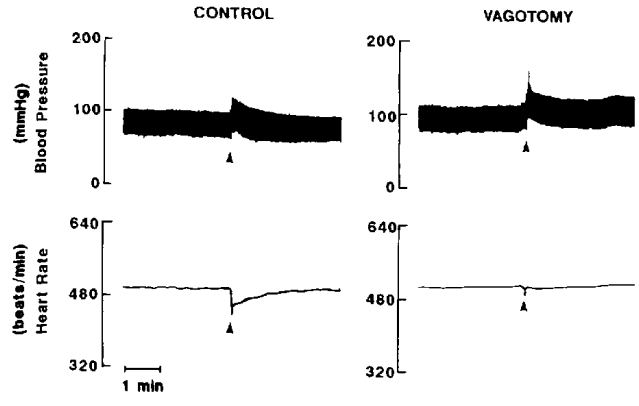


**Fig. 3.** Typical responses to 1 μg/kg NE before (left) and after (right) the vagotomy. The decrease of heart rate was strongly reduced in bilaterally vagotomized animals. NE was injected at the arrow head.

## DISCUSSION

The heart rate of mouse was about 600 beats/min, which is comparable to previously reported data (see 10). It is generally believed that the smaller the animal the higher the heart rate (10, 11). However, the heart rate of suncus was about 400 beats/min both in conscious and anesthetized conditions. The heart rate of suncus is comparable to the level of rats, and it seems to be exceptionally low for their body weight. The recording was very stable, and no arrhythmic irregular pattern was observed. The duration of cardiac action potential, which is important to reduce the risk of arrhythmia, is very short in suncus (12). Therefore, it will be interesting to investigate how suncus can keep a low heart rate but avoid the occurrence of arrhythmia. Effects of stimulus frequency on the contraction of suncus cardiac muscle also have not been reported.

We have shown previously that $\beta$-adrenoceptor-mediated responses in the heart and trachea are very small in suncus (13, 14) and suggested the deficient coupling between $\beta$-adrenoceptors and the adenylate cyclase system. The present study showed that the decrease in blood pressure by ISO is also small in suncus. Therefore, the $\beta$-adrenoceptor-mediated responses may be relatively small in this animal. Furthermore, the response to ACh was also small. ACh relaxes the artery by releasing the endothelium-derived relaxing factor (EDRF), or nitric oxide (15, 16). It is possible that either EDRF-mediated relaxation or the number of ACh receptors, or both, is small in suncus. There was no significant difference in histamine-induced decrease in the blood pressure between suncus and mice. The effect of histamine is also considered to be mediated by EDRF (17).

In contrast to these results, the NE-induced increase in blood pressure was greater in suncus, and NE decreased the heart rate. The decrease was strongly attenuated by bilateral vagotomy, indicating that the reflex through the vagus is very strong in this animal. However, even in the vagotomized animals NE failed to increase the heart rate. The actual transmitter of the sympathetic nervous system in suncus has not been reported. If it is NE, it will be difficult to increase the heart rate in suncus. The content of epinephrine in suncus heart is greater than mouse heart (18). Therefore, suncus may use epinephrine rather than NE as a sympathetic neurotransmitter. Generally, an increase in heart rate is important for the increase in blood circulation. Therefore, it is interesting to investigate the physiological factor(s) which increases the heart rate in suncus.

There are only a few reports concerning the species-dependent difference in cardiovascular response to drugs. Mescaline decreases blood pressure in dogs and cats, whereas the same drug produces pressor responses in rats (19). Nicotinic acid increases the blood pressure of rabbits, but decreases those of dogs and cats (20). To our knowledge, suncus is the only species whose heart rate is not increased by NE. Currently, we do not have any explanation for why ISO increased heart rate but NE did not. NE may release ACh. Further experiments are necessary to clarify the cardiovascular properties of suncus.

It is not known whether the unique characteristics of suncus shown in the present study are common to other insectivores. If so, other species of mammals must have obtained various regulatory systems during their evolution. The present results suggest that regulation of cardiovascular function in suncus is very unique and different from the well-characterized regulatory system of the rodent.

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