crease in the enzyme activity, mostly below 50% of that found in the same organs of equally old untreated control females. In certain cases phosphatase activity of the treated 3-day-old females averaged only about 30% of the control values. These results clearly show that the dietary supply of sublethal doses of (S)-DHPA interferes with physiological functions of the digestive and excretory phosphatase enzymes. We believe, therefore, that the previously reported massive excretion of the phosphorylated metabolites of unnatural nucleosides supplied in the diet[7,8] was most probably due to the inhibition of phosphatase activity in the intestine and in the Malpighian tubules.

Females of *Pyrrhocoris* which were sterilized by oral administration of 1 mg · ml^{-1} of (S)-DHPA also showed considerable suppression of the activity of SAH-hydrolase in the ovaries[7]. We concluded that the inhibition of SAH-hydrolase and consequently a decrease in the methylation index might be responsible for the induction of sterility in this system. Now, with these results, we can see that an inhibition of phosphatase activity in the visceral organs can be involved in female sterility as well. Phosphatase is a common hydrolytic enzyme that functions in all living organisms, including viruses. Inhibition of this enzyme is obviously an important factor which must be considered in calculations concerning the pharmacobiological action of any chemical compound. We still cannot decide whether inhibition of phosphatase would also be involved in causing the adverse effects of these drugs in biological systems other than insects. The general concept explaining the action of nucleoside analogues on the basis of inhibition of SAH-hydrolase[5-7,11] has some weak points. Thus, for example, recent studies have shown that certain open-chain nucleoside analogues (3'-O-phosphonyl-9-(S)-(2,3-dihydroxypropyl) adenine) can exhibit strong ovicidal and sterilization effects, although they do not inhibit SAH-hydrolase from rat liver[12]. Moreover, in the case of the aspermatogenic effect in mice[4], phosphatase inhibition would certainly be a more vulnerable biological target than inhibition of the SAH-hydrolase, because testicular tissues and accessory sexual glands of vertebrates are always linked with enormously large phosphatase activities. Correlations between biological activity and phosphatase functions can be found in various other target systems of the nucleoside analogues. They exist in insect reproduction[3,13] or in the effects of these drugs on the development of the seedling root system in plants[2]. Characteristically, in all these processes the phosphatase mediated extra-or intracellular transport of molecules plays a vital role.

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Dopamine-induced relaxation in human pulmonary arteries

M. Yamauchi*, Y. Kobayashi, K. Hattori**, K. Yamada* and A. Nakase*

*Departments of Pharmacology and * 1st Surgery, Shimane Medical University, Izumo, Shimane 693 (Japan)*
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Summary. Dose-dependent relaxations were induced by dopamine in human pulmonary arteries that had been contracted with prostaglandin $F_{2\alpha}$ without α-adrenergic blocking agents. The dopamine-induced relaxation was inhibited by haloperidol and fluphenazine, but not by domperidone, suggesting that this relaxation was mediated via DA_1 receptors.
Key words. Dopamine; vasorelaxation; human; pulmonary arteries; DA_1 receptors.

It is well known that in some species dopamine has a specific vasodilator effect on several vascular beds, particularly in the renal and gastro-intestinal circulation. This vasodilator effect is generally ascribed to the stimulation of specific vascular dopamine receptors[1-4].

The subtype of dopamine receptors in vascular beds such as the dog renal arteries[2] and rabbit mesenteric[3] and splenic arteries[4] appears to be DA_1 receptors. In human vascular beds, dopamine-induced relaxation occurs in the renal[5] and cerebral arteries[6,7], but the basilar artery is the only one known to have DA_1 receptors. Recently, Hoshino et al. reported the relaxant effect of dopamine via DA_1 receptors in isolated rabbit pulmonary arteries[8]. However, there have been no reports on the relaxant effects of dopamine in the isolated human pulmonary artery, though the disorders in pulmonary circulation are clinically important[9-11].

The present study was undertaken to examine the effects of dopamine on human pulmonary arteries, and the subtype of receptors in the arteries was investigated.

Methods. Five pulmonary arteries (artery segments, 3 to 5 mm in diameter) were obtained from pneumonectomized or lobectomized specimens of lung tumors. The 5 patients (two men, 58 and 75 years old; and 3 women, 53, 57 and 59 years old) did not suffer from pulmonary or systemic hypertension and were not treated with drugs acting on adrenoceptors or dopamine receptors. The arteries were cut into helical strips, approximately 10 mm long. The strips were fixed vertically under a resting tension of 1.5 g in a cuvette containing 3 ml of Krebs-Henseleit buffer solution maintained at 37 ± 0.5 °C and aerated with a gas mixture of 95% O_2 and 5% CO_2. Preparations were allowed to equilibrate for 90 to 120 min before the start of experiments. Isometric

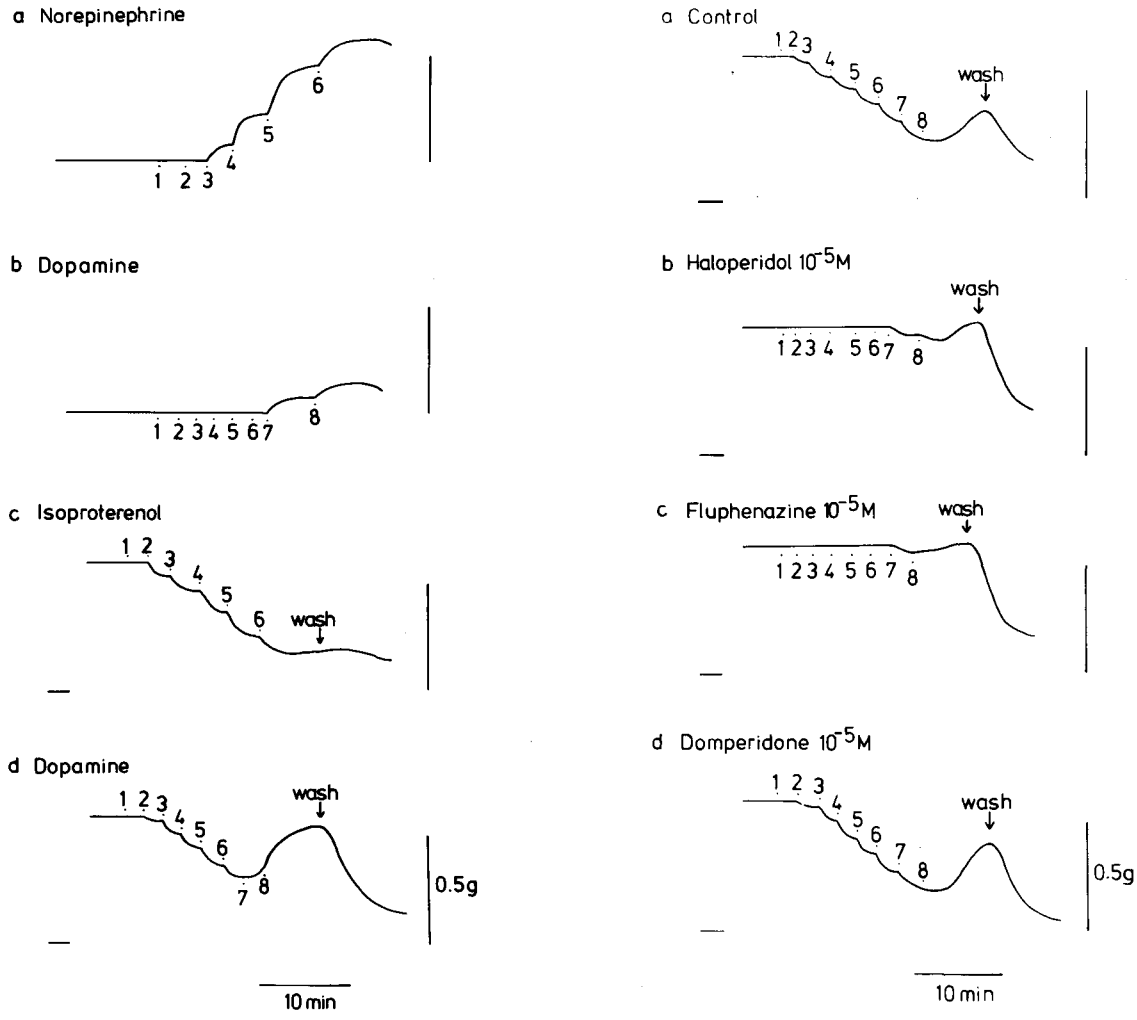

Figure 1. Responses of human pulmonary arteries to norepinephrine (*a*), dopamine (*b* and *d*) and isoproterenol (*c*). In the lower tracing (*c* and *d*), the preparations had been contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 5×10^{-6}M). The horizontal lines just left of the lower tracings (*c* and *d*) represent the level prior to the addition of $PGF_{2\alpha}$. Concentrations of norepinephrine and isoproterenol from 1 to 6 were 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} and 10^{-4}M, respectively. Concentrations of dopamine from 1 to 8 were 10^{-7}, 3×10^{-7}, 10^{-6}, 3×10^{-6}, 10^{-5}, 3×10^{-5}, 10^{-4} and 3×10^{-4}M, respectively.

Figure 2. The effects of dopamine (*a*) and the modifications with haloperiodol (*b*), fluphenazine (*c*) and domperidone (*d*) with α- and β-blockers. The concentrations of dopamine are the same as those in figure 1.

contractions and relaxations were recorded. To prepare for the measurement of relaxation, the strips were contracted with prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 5×10^{-6}M). Prazosin (gift from Pfizer-Taito Co. Ltd., 10^{-6} M), DG5128 (Daiichi Pharmaceutical Co. Ltd., 10^{-6}M) and propranolol (10^{-6}M) were used as α_1, α_2[12], and β-blockers. As dopaminergic blockers, haloperidol (10^{-5}M), fluphenazine (10^{-5}M) and domperidone (10^{-5}M) were used.

Results and discussion. A dose-dependent contraction for norepinephrine (10^{-9}–10^{-4}M) in the human pulmonary artery is shown in figure 1 a. Dopamine produced a small contraction at high doses in the same preparation (fig. 1 b). Isoproterenol produced a dose-dependent relaxation (fig. 1 c). Dopamine produced a relaxation at low doses and a contraction at high doses (fig. 1 d). Such a dopamine-induced relaxation without blockers is in accord with the results with human renal[5] and basilar arteries[6]. In arterial preparations from experimental animals, dopamine did not produce relaxation but showed dose-dependent contractions[1–4] without blockers. In human vascular beds, the contractile effects of dopamine were less and dopamine may have a more important role as a vasorelaxant.

Relaxations induced by low doses of dopamine were potentiated and contractions induced by high doses were reversed to relaxations when the preparation was treated with prazosin, DG5128 and propranolol for 20 min before the addition of $PGF_{2\alpha}$ (fig. 2 a). Norepinephrine-induced contraction or isoproterenol-induced relaxation was attenuated by these blockers. So contractions produced by high doses of dopamine (fig. 1 d) apparently were mediated through α-receptors. Relaxation produced by dopamine did not appear to be mediated through β-receptors. The vasodilator responses reached a maximum in a relatively short time compared with those in the human basilar arteries[6,7] and dog renal[1] and coronary arteries[12]. Relaxations induced by dopamine in concentrations of 3×10^{-7}, 3×10^{-6}, 3×10^{-5} and 3×10^{-4}M averaged 4.0 ± 1.6, 12.0 ± 2.3, 21.0 ± 3.3 and 42.2 ± 9.4%, respectively, with the maximum contraction induced by $PGF_{2\alpha}$ taken as 100%. The maximum relaxation induced by dopamine in the human pulmonary arteries was similar to that in the human renal arteries[4] (ca 40%), but relatively small compared with that in the human basilar arteries[5,6] (60–80%).

Both dopamine antagonists, haloperidol (fig. 2 b) and fluphenazine (fig. 2 c), markedly attenuated the relaxations

induced by dopamine. Domperidone did not influence the relaxations induced by dopamine (fig. 2d). These findings indicate that the relaxations induced by dopamine in the human pulmonary arteries are associated with activation of dopamine receptors and the subtype of dopamine receptors appears to be DA_1 receptors. This conclusion regarding the subtype of dopamine receptors agrees with the results with other human [7] and animal [2-4] arteries.

This is the first study demonstrating dopamine-induced relaxation in the human pulmonary arteries. Dopamine and its analogues may be useful therapeutic drugs for certain disorders in pulmonary circulations such as increased pulmonary vascular resistance or right heart failure [9-11].

** To whom reprints requests should be addressed.

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Single injections of triazolam, a short-acting benzodiazepine, lengthen the period of the circadian activity rhythm in golden hamsters

J. E. Joy, S. Losee-Olson and F. W. Turek

Department of Neurobiology and Physiology, Northwestern University, Evanston (Illinois 60208, USA)
Received 29 August 1988; accepted 26 October 1988

Summary. Single injections of the benzodiazepine, triazolam, induce phase shifts and cause a lengthening of the circadian activity rhythm in the golden hamster. The effect of triazolam on period depends on the phase of injection, but is not dependent on the direction of the phase shifts. Triazolam injections caused increases in period that were associated with phase advances as well as phase delays in the activity rhythm. This relationship between triazolam-induced phase shifts and changes in period is different from the relationship between light-induced phase shifts and period changes.
Key words. Circadian rhythms; benzodiazepines; golden hamsters.

Since the components of circadian oscillators remain unknown, the only two parameters of biological rhythms that provide meaningful information about underlying pacemakers are phase and period [1]. Many different agents are known that can change either phase or period of circadian rhythms, but very little is known about how changes in phase can alter period and vice versa. Light is the only agent for which changes in both phase and period have been described following a single, discrete stimulus. One-hour light pulses that cause phase advances in the circadian activity rhythms of golden hamsters and mice, also cause a shortening of the free-running activity period [2, 3]. In mice, a 1-h light pulse that causes a phase delay also causes a lengthening of the free-running period [2].

It is not known if this relationship between changes in phase and changes in period is a fundamental property of circadian organization or is, instead, a specific property of light-induced phase shifts. Therefore, we decided to explore the interaction between changes in phase and changes in period using an agent other than light. The benzodiazepine, triazolam, is an ideal agent to contrast with the effects of light on different parameters of circadian rhythms. Triazolam is a short-acting benzodiazepine with a half-life in the golden hamster of about 30 min [4]. Like light, triazolam causes both phase advances and phase delays, depending on when it is given to the animal [5]. However, the relationship between the time of the triazolam treatment and the direction of the phase shifts is quite different from the relationship for light pulses. For example, injections of triazolam given to hamsters 6 h before the onset of activity cause maximum phase advances of 90 min, whereas light pulses given at this time cause no phase shifts. Light pulses given 6–8 h after the onset of activity cause phase advances of about 2 h [6, 7], whereas triazolam given at this time causes phase delays of about 30 min [5].

We have previously suggested that triazolam may act on circadian rhythms through a pathway other than the light input pathway [5]. It is also possible that light and triazolam may act on the circadian system in fundamentally different ways. This study shows that the relationships between phase shifts and period changes differ, depending on whether light or triazolam is used to probe the circadian system.

Materials and methods. Adult male golden (Syrian) hamsters, *Mesocricetus auratus* [LAK:LVG(SYR)] were initially group housed under a 14:10-h light/dark cycle before being transferred to constant darkness. Upon transfer to constant darkness, the animals were placed in individual cages equipped with a running wheel connected to an event recorder to allow for continuous monitoring of running wheel activity.

Beginning after two weeks in constant darkness, 92 animals received an intraperitoneal injection of either 2.5 mg of triazolam dissolved in 0.1 ml dimethyl sulfoxide (DMSO) or DMSO alone. This dose of triazolam causes maximum phase advances when injected at the appropriate phase of the activity cycle [8]. All injections were made in the dark with the aid of an infrared viewer (FJW Industries). Some animals received more than one injection. In these cases, consecutive