PRIMARY EFFECT OF GLUCAGON ON POSITIVE CHRONOTROPISM

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Abstract—Chronotropic and inotropic effects of glucagon were compared with those of norepinephrine using the excised SA node and the papillary muscle preparations cross-circulated with a donor dog. Glucagon was administered i.v. to the donor dog at doses of 1 to 30 μg/kg, which caused a marked chronotropic but less marked inotropic effect. Cardiohemodynamic response to glucagon of anesthetized dogs was simulated by an acceleration induced by atrial pacing. It was concluded that glucagon is more effective on chronotropism than on inotropism, and that its cardiohemodynamic effects are mainly ascribed to the increased heart rate.

Since glucagon-induced positive chronotropic and inotropic effects were demonstrated not only in the isolated heart preparation but also in the intact heart of different species of animals, many investigators have attempted to clarify the mode of action. It is generally accepted that the enhancement of cardiac performance induced by glucagon is not mediated by β-adrenoceptor stimulation (1, 2, 3, 4). Recent studies suggest that its effects are due to an increase in the intracellular concentration of cyclic 3', 5'-AMP resulting from activation of adenyl cyclase (5, 6, 7). Even at present, when glucagon has already been introduced for clinical use as a cardiotonic drug, the difference between glucagon and the adrenergic effects is not clear. In the present study, chronotropic and inotropic effects of glucagon were compared with those of norepinephrine in the excised SA node and the papillary muscle preparations cross-circulated with a donor dog, and its cardiohemodynamic effects were also investigated in the whole animal.

MATERIALS AND METHODS

Mongrel dogs of both sexes were anesthetized with 30 mg/kg of sodium pentobarbital, i.v. After 200 units/kg of sodium heparin, i.v., the heart was excised and immersed into Tyrode's solution at about 4°C, equilibrated with a gas mixture consisting of 95% O₂ and 5% CO₂. The excised SA node and the excised papillary muscle preparations were cross-circulated by a donor dog as illustrated in a diagram (Fig. 1). The SA node and the papillary muscle preparations have been previously described in detail by Kubota and Hashimoto (8) and Endoh and Hashimoto (9), respectively. Donor dogs were anesthetized with 30 mg/kg of sodium pentobarbital, i.v. Sodium heparin, 300 units/kg, was given at the beginning of the perfusion and maintenance dose of 100 units/kg was given every hour. Both preparations were perfused with the blood conducted from the left carotid
artery of the donor dog by the aid of a peristaltic pump (Harvard Apparatus Co., model 500-1200). The perfusion pressure was maintained at 100 mmHg by means of Starling pneumatic resistance draining an excess blood to the left jugular vein. Changes in systemic blood pressure and heart rate of the donor dog, sinus rate of the SA node preparation and contractile force of the papillary muscle preparation were simultaneously recorded on an ink-writing rectigraph (San-ei Sokki Instrument).

Cardiohemodynamic studies with anesthetized open-chest dogs were performed as follows. After ligating the azygos vein, non-cannulating electromagnetic flowmeters (Nihon Kohden, MF-5 and MF-25) were set at the pulmonary artery and the superior and inferior caval veins for measuring total cardiac output and venous return, respectively. Changes in pressure at the right atrium through the auricular appendix and at the left carotid artery were measured by pressure transducer (Nihon Kohden, MP-4T). Mean flow rates through these vessels and systemic blood pressure were recorded on an ink-writing rectigraph (San-ei Sokki Instrument). Bipolar electrodes for atrial pacing were sutured on the epicardial surface on the right atrial appendix. Rectangular pulses of 1-msec duration were delivered through the electrodes using an isolation unit (Grass, SIU4A) and an electronic stimulator (Nihon Kohden, MSE-3). Drugs used were glucagon (Novo Industri) and l-norepinephrine (Fluka AG).

RESULTS

Comparison of chronotropic and inotropic effects

Glucagon was administered to the donor dog at doses of 1 to 30 µg/kg i.v. A typical result is shown in Fig. 2. Glucagon caused a marked and long-lasting acceleration of heart rate which was accompanied by a slight decrease in systemic blood pressure in the donor dog. Sinus rate of the SA node preparation increased almost in parallel with the acceleration of heart rate of the donor dog. On the other hand, contractile force of the papillary muscle preparation hardly increased at doses of 1 to 3 µg/kg, and only slightly at doses of 10 to 30 µg/kg. The time-course of the response to glucagon at doses of 3 to 30 µg/kg is shown in Fig. 3. The duration of the acceleration of sinus rate both of the SA node preparation and of the donor dog was over 40 min at doses of 10 to 30 µg/kg. The increase in contractile force of the papillary muscle preparation disappeared within 25 min even at a dose of 30 µg/kg.

Unlike glucagon, norepinephrine induced a dose-dependent increase in contractile
FIG. 2. Effects of glucagon and norepinephrine (NE) on systemic blood pressure (SBP) and heart rate (HR) of the donor dog, sinus rate of the SA node preparation (SAR) and contractile force of the papillary muscle preparation (PMT). The papillary muscle was electrically driven at the frequency of 120 beats/min.

FIG. 3. Time-course of responses to glucagon on systemic blood pressure (SBP) and heart rate (HR) of the donor dogs, sinus rate of the SA node preparations (SAR) and contractile force of the papillary muscle preparations (PMT). Each point and vertical bars represent the mean value and S.E. Horizontal bars represent S.E. of the time to the peak response.

force simultaneously with an acceleration of sinus rate at doses of 0.1 to 3 µg/kg as shown in Fig. 2. The dose-response curves of glucagon and norepinephrine in sinus rate of the SA node preparation and in contractile force of the papillary muscle preparation are shown in Fig. 4. Glucagon and norepinephrine induced about a 40% increase in sinus rate at a dose of 3 µg/kg. The glucagon-induced increase in sinus rate then reached 76±12%
In contrast with this, glucagon induced a 41 ± 17% increase in contractile force even at a dose of 30 μg/kg, while, norepinephrine induced a 161 ± 19% increase at a dose of 3 μg/kg.

Cardiohemodynamic effects

A typical result obtained from cardiohemodynamic studies is shown in Fig. 5. Glucagon at doses of 1 to 10 μg/kg i.v. caused a dose-dependent acceleration of heart rate and an increase in the pulmonary arterial flow, i.e., the total cardiac output. It also caused an increase in venous return mainly from the lower part of the body as depicted in the increased flow in the inferior caval vein. The right atrial pressure decreased dose-dependently. Durations of responses to glucagon, i.e., the increased pulmonary arterial flow and the increased inferior caval flow and the decreased right atrial pressure, were almost the same as that of the increased heart rate. An acceleration of the heart rate produced by atrial pacing caused an increase both in the cardiac output and in the venous return and a decrease in the right atrial pressure, which corresponded closely to the effects of glucagon.

**DISCUSSION**

It has been recognized that glucagon possesses positive chronotropic and inotropic actions on the heart (1, 2, 10, 11). Glick (1) and Lucchesi (2) indicated that glucagon...
caused a dose-dependent increase in contractile force simultaneously with an acceleration of heart rate in open-chest dogs. The influence of the heart rate on the contractile force could not be eliminated under such an experimental condition, as the acceleration of heart rate secondarily induced an increase in contractile force through the mechanism of “frequency-force relationship” characterized in the myocardium (9, 12). In the preparation used in this study, contractile force was always measured at the fixed frequency of 120/min, and the influence of “frequency-force relationship” could be avoided.

Glucagon caused an acceleration of sinus rate both in the SA node preparation and in the donor dog at a threshold dose of 1 μg/kg. On the other hand, a threshold dose of glucagon causing an increase in contractile force was 3 μg/kg or more. Unlike glucagon, norepinephrine induced an increase both in sinus rate and in contractile force simultaneously at a threshold dose of 0.1 μg/kg. The degree of the acceleration of sinus rate induced by 3 μg/kg of glucagon was almost the same as that induced by the same dose of norepinephrine. Although norepinephrine induced about 160% increase in contractile force at a dose of 3 μg/kg, a glucagon-induced one was only about 40% even at a dose of 30 μg/kg. Comparing the effects of glucagon with those of norepinephrine, it can be concluded that glucagon is more effective on chronotropism than on inotropism.

Glucagon caused a simultaneous increase in both in cardiac output and venous return and a decrease in right atrial pressure. Since these cardiohemodynamic responses to glucagon could be simulated by atrial pacing, it is concluded that an acceleration of heart rate produced by glucagon plays an important role in its cardiohemodynamic effects through the mechanism of “frequency-force relationship” and that direct myocardial stimulation is only a subsidiary factor. These responses were resistant to β-adrenergic blocking agents in these experiments.

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