EFFECT OF INDOMETHACIN ON SENSITIVITY OF CARDIOVASCULAR ADRENORECEPTORS AND ACETYLCHOLINE RECEPTORS

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Indomethacin, an indoleacetic acid derivative, is a typical nonsteroid anti-inflammatory drug. The mechanism of the anti-inflammatory action of indomethacin is effected through direct inhibition of biosynthesis of prostaglandins, substances which increase permeability of the vascular wall, stimulate leukocyte migration, and so on [9, 10]. Many investigations have been devoted to the therapeutic effects and the study of the mechanisms of the anti-inflammatory action of indomethacin, whereas hardly any information is available on its effect on the cardiovascular system. Isolated data have recently been published on the adrenoprotective properties of indomethacin and its positive effect against experimental adrenal-induced myocardial damage [3, 4, 6].

Considering the extensive use of indomethacin in the combined treatment of rheumatic heart disease, it was decided to study its effect on sensitivity of cardiovascular adrenoreceptors and acetylcholine receptors.

EXPERIMENTAL METHOD

Experiments were carried out on 12 cats anesthetized with urethane (1 g/kg) and chloralose (50 mg/kg body weight). To determine the initial background sensitivity of cardiovascular chemoreceptors (as reflected in the response of the systemic arterial pressure) hypertensive and hypotensive effects were induced by injection of the corresponding mimetic agents by the method in [2, 7]. After a definite background of change of systemic pressure had been obtained by the choice of moderate doses of mimetics (the effect of which was taken as 100%), indomethacin was injected intraperitoneally in a dose of 30-40 mg/kg, and 30 min later the mimetics were again tested in the above-mentioned doses. The effect of indomethacin on muscarine-sensitive receptors was studied in 15 experiments on the isolated frog heart, whereas its effect on nicotine-sensitive acetylcholine receptors was studied by measuring changes in the acetylcholine contracture of the isolated frog rectus abdominis muscle by the usual method attributed to Scheiner.

EXPERIMENTAL RESULTS

General excitation of adrenergic structures of the cardiovascular system by adrenalin and noradrenalin in a dose of 5-10 μg/kg evoked a hypertensive effect of 22 ± 3.4% on average. Approximately the same elevation of the systemic pressure was observed after injection of subecholine (the dicholine ester of suberic acid) in a dose of 10-15 μg/kg, which excites nicotine-sensitive acetylcholine receptors.

A moderate hypotensive effect was produced on excitation of the β-adrenoreceptors by isoproterenol in a dose of 3-5 μg/kg and on excitation of muscarinesensitive acetylcholine receptors by acetylcholine in a dose of 10 μg/kg (Fig. 1). After intraperitoneal injection of indomethacin in a dose of 30-40 mg/kg, subsequent testing of the mimetics revealed the following relations between their sensitivity: in all experiments without exception, the sensitivity of the adrenoreceptors to adrenalin and noradrenalin was considerably and unequivocally reduced on average by 48.6 ± 12.1 and 31 ± 4.4 per cent respectively. The increase in sensitivity of the adrenoreceptors to exogenous isoproterenol, which averaged 34.4 ± 12.6%, was also stable and significant (Fig. 2).

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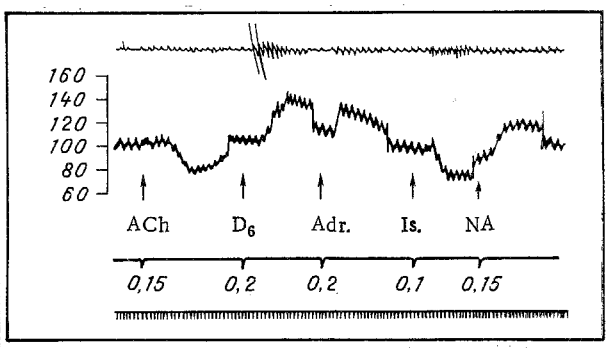

Fig. 1. Determination of sensitivity of cardiovascular acetylcholine receptors and adrenoreceptors of an anesthetized cat weighing 3.5 kg. From top to bottom: respiration, systemic pressure (in mm Hg), marker of injection of drugs, time marker (5 sec). ACh) acetylcholine (10^{-5} g/ml), D_6) subecholine (10^{-4} g/ml), Adr.) adrenalin (10^{-5} g/ml), Is.) isoproterenol (10^{-5} g/ml), NA) noradrenalin (10^{-5} g/ml). Numbers below indicate volume of drugs injected (in ml).

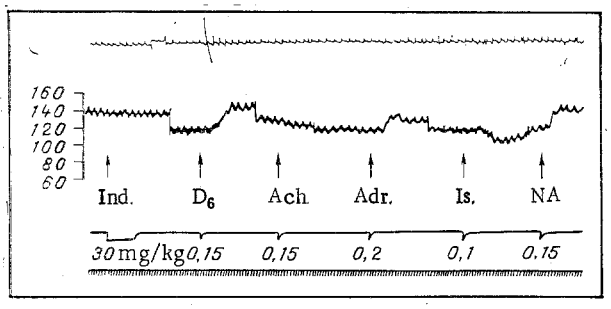

Fig. 2. Changes in sensitivity of cardiovascular acetylcholine receptors and adrenoreceptors of anesthetized cat weighing 3.5 kg after intraperitoneal injection of indomethacin in a dose of 30 mg/kg. Legend same as Fig. 1.

Nicotine-sensitive acetylcholine receptors were somewhat inhibited after injection of indomethacin (on average by 27.8 ± 13.6%), but this lytic effect was not significant. As regards muscarine-sensitive acetylcholine receptors, their reactivity showed changes of equal magnitude toward enhancement of the acetylcholine effect (by 51.6%) and toward a decrease: the lytic effect averaged 44%. The results of the change in chemoreceptor sensitivity under the influence of indomethacin, expressed in per cent, are given in Table 1. On the isolated frog heart, where mainly muscarine-sensitive acetylcholine receptors are represented, indomethacin gave a varied and inconstant effect in all concentrations studied (from 10^{-9} to 10^{-4} g/ml), just as in experiments on cats. In some experiments all the concentrations of indomethacin tested had a cholinomimetic action, intensifying the cardiodepressive effect of acetylcholine on average by 8 ± 3.2%. In other cases the action of acetylcholine was completely abolished, but in some experiments the response to acetylcholine was unchanged.

Cholinomimetic effects also were observed more frequently than cholinolytic on the frog rectus abdominis muscle in response to the use of concentrations from 10^{-6} to 10^{-4} g/ml, but their intensity hardly reached 6-18%. No changes in the acetylcholine effect were observed in 2-5% of cases.

In experiments on anesthetized cats indomethacin caused a stable and significant adrenonegative effect, blocking the possibility of manifestation of the mimetic effect of exogenous adrenalin. Differentiation of sensitivity of the adrenoreceptors showed that this blockade was produced selectively mainly on account of α-adrenergic structures, and

TABLE 1. Changes in Sensitivity of Cardiovascular Adrenoreceptors and Acetylcholine Receptors under the Influence of Indomethacin

Background of systemic pressure	Changes in sensitivity of receptors, percent relative to background	P
Adrenoreceptors		
Total adrenomimetic effect (adrenalin)	−51,4±12,7	<0,05
Excitation of α-adrenoreceptors (noradrenalin)	−69,0±4,4	<0,01
Acetylcholine receptors	+134,6±12,6	<0,05
Acetylcholine receptors		
Excitation of muscarinic acetylcholine receptors (acetylcholine)	−72,2±13,6	>0,05
Excitation of nicotinic acetylcholine receptors (subecholine)	+51,6 −44,0	—

Legend. +) mimetic effect, -) lytic effect.

it was manifested as a marked reduction of the effect of exogenous noradrenalin. Indomethacin had a significant positive effect on β-adrenoreceptors, increasing their reactivity to isoproterenol. At the same time, the effect of indomethacin on acetylcholine receptors was very variable: whereas in the case of nicotinic acetylcholine receptors a tendency toward their blocking was observed, it had a two-way action on muscarinic acetylcholine receptors. Experiments on isolated frog heart and on the frog rectus abdominis muscle confirmed these findings.

Indomethacin is thus an effective agent controlling reactivity mainly of the sympathetic components of the autonomic nervous system. The dominant role in the pathogenesis of ischemic heart disease and myocardial infarction is ascribed to an excess of catecholamines [1, 5, 8]. Their increased excretion during nervous stress leads to considerable changes in metabolism of the heart muscle and is accompanied by the development of micronecroses, of hypoxia, and of cardiac arrhythmias. For the prevention and treatment of such states and to reduce the effects of exposure to risk factors, one of which is hypercatecholaminemia, drugs blocking the harmful action of catecholamines on the myocardium and altering the reactivity of receptors of the sympathetic nervous system must be used. The fact that indomethacin has a component with β-adrenomimetic action evidently facilitates autoregulation and limitation of its powerful adrenoblocking effect. An increase in sensitivity of myocardial β-adrenoreceptors may also bring about an improvement in the conditions of its blood supply.

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