Eo 771 mammary carcinoma. The difference in the tumour weight between the control group and the hormone-treated groups was found to be statistically significant (Student's t test $p < 0.05$).

Zusammenfassung. Verabreichung von bovinem Wachstumshormon oder Schafsprolactin fördert das Wachstum von Adenokarzinom der Brust (MMC_1A) transplantiert in eine weibliche Maus R III oder von Adenokarzinom der Brust Eo 771 transplantiert in eine weibliche Maus $C_{57}Bl$.

Z. SPEISER, S. GITTER, and Z. LARON

Departments of Pharmacology and Pediatrics, Tel Aviv University Medical School, and Rogoff Wellcome Medical Research Institute, Beilinson Hospital, Petah Tikva (Israel), March 15, 1966.

Action of β-Receptor Blocking Sympatholytics and of Catecholamine Depleting Agents on $CaCl_2$-Induced Arrhythmias in Rats

It has been established in earlier experiments[1,2] that the adrenergic β-receptor blocking dichloroisoproterenol derivative: I-06 [1-(3,4-dichlorphenyl)-2-isopropylaminopropanol] displays an antiarrhythmic action in cats, dogs and rabbits, and possesses only a slight initial β-receptor stimulating action. In contrast to the highly effective β-receptor blocking and antiarrhythmic agent propranolol (Inderal), I-06 proved to have also a catecholamine depleting effect on heart and brain when administered for several days[2]. The question arises as to what kind of difference in antiarrhythmic properties can be detected between the catecholamine depleting I-06 and the non-depleting propranolol. It has also been shown that the protecting action of reserpine, an agent with well-known catecholamine depleting effect in digitalis intoxication[3,4], is partly due to its antiarrhythmic action[5]. Thus there is indication of a possible interaction between the antiarrhythmic effect of drugs and their influence on the catecholamine content of the heart. To study these questions, the antiarrhythmic effect of propranolol and I-06, also that of known amine depleting agents such as reserpine[6], guanethidine[7], and prenylamine[8] as well as that of α-methyldopa[9] (an agent inducing partial depletion of the myocardial norepinephrine content by formation of α-methyl-norepinephrine), and that of bretylium[7] (which blocks the release of norepinephrine without altering myocardial catecholamine content), has been investigated.

Arrhythmia was produced by rapid i.v. injection of a 2.5% $CaCl_2$ solution (140 mg/kg dose) to Wistar rats of both sexes and 100–150 g body weight under urethane anaesthesia (1.5 g/kg i.p.). A direct-writing electrocardiograph enabled continuous recording of the cardiac activity. A few seconds after injection, 77% of the animals developed ventricular fibrillation leading to death within 60–90 sec. The remaining animals showed tachycardia of ventricular origin, sometimes transitory but not fatal ventricular fibrillation. In a few animals, $CaCl_2$ injection was followed by a lasting apnea with progressively developing bradycardia and cardiac arrest or fibrillation as a consequence of asphyxia. These experiments were excluded from further evaluation. For statistical analysis of the experimental data, the fourfold contingency test was used[10]. Myocardial norepinephrine content was determined by the spectrophotofluorometric method[11].

Results are summarized in the Table. As can be seen, the adrenergic β-receptor blocking agents I-06 and propranolol reduced significantly the incidence of $CaCl_2$-induced ventricular fibrillation if given immediately prior to the $CaCl_2$. Doses giving optimal protective action are shown in the Table. Prolonged administration for 5 days of these substances, in the highest doses tolerated, has shown propranolol to be ineffective against $CaCl_2$ fibrillation if the latter was administered 24 h after the last treatment, whereas I-06 exhibited under the same circumstances a highly significant protective action, just as in the acute experiments.

Parallel estimation of the myocardial norepinephrine content has indicated no significant change ($P > 0.2$) in the rats receiving prolonged propranolol treatment, whereas a 60% decrease was observed in the I-06 treated animals [NE content fell from 930 ng/g wet tissue ($n = 15$) to 379 ng/g wet tissue ($n = 15$), $P < 0.001$]. Prenylamine, known to possess similar catecholamine depleting action, provided, like I-06, significant protection 24 h after treatment even if given in the form of a sufficiently high single dose. Guanethidine displayed the strongest protective action 6 h after a single dose of the drug, but even after 24 h this effect was still present ($P = 0.02$). Reserpine – equally catecholamine depleting – had only a slight antiarrhythmic effect, in spite of the variation of dosage as well as of the time interval between treatment and $CaCl_2$ injection. Optimal effect was observed with a 5 mg/kg dose and a time interval of 24 h. α-methyldopa showed a very strong protective action if administered in a 500 mg/kg dose 30–60 min prior to $CaCl_2$ injection, a lower dose (320 mg/kg) had no effect. Bretylium tosylate in a dose of 40 mg/kg, given 30 min and 6 h respectively prior to $CaCl_2$, proved to be ineffective on the incidence of ventricular fibrillation.

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Effect of β-receptor blocking sympatholytics and of catecholamine depleting agents as well as of adrenergic neurone blocking agent on the severity of $CaCl_2$ induced arrhythmias in rats

Treatment	Dose mg/kg	Time interval between last treatment and $CaCl_2$ injection	n	Incidence of lethal ventricular fibrillation	Incidence of non-fatal arrhythmias	P value
Control						
$CaCl_2$	140 i.v.	–	26	77%	23%	–
Pretreatment with a single dose of β-receptor blocking sympatholytics						
Propranolol + $CaCl_2$	3.2 i.v.	30 sec	10	20%	80%	= 0.01
I-06[a] + $CaCl_2$	6.3 i.v.	30 sec	10	10%	90%	< 0.002
Prolonged pretreatment with β-receptor blocking sympatholytics						
Propranolol + $CaCl_2$	Day 1, 60; days 2–5, 40 i.p.	24 h	21	71%	29%	> 0.2
I-06[a] + $CaCl_2$	Day 1, 80; days 2–5, 50 i.p.	24 h	21	14%	86%	< 0.002
Pretreatment with catecholamine depleting agents						
Prenylamine + $CaCl_2$	100 s.c.	24 h	20	20%	80%	< 0.002
Guanethidine + $CaCl_2$	40 i.p.	6 h	21	10%	90%	< 0.002
	40 i.p.	24 h	23	39%	61%	= 0.02
Reserpine + $CaCl_2$	5 i.p.	6 h	19	47%	53%	= 0.1
	5 i.p.	24 h	22	41%	59%	= 0.02
	10 i.p.	24 h	18	44%	56%	= 0.1
	10 i.p.	48 h	20	50%	50%	= 0.1
α-Methyldopa + $CaCl_2$	320 i.p.	30–60 min	11	55%	45%	= 0.1
	500 i.p.	30–60 min	23	17%	83%	< 0.002
Pretreatment with adrenergic neurone blocking agent						
Bretylium + $CaCl_2$	40 i.p.	30 min	21	67%	33%	= 0.1
	40 i.p.	6 h	20	70%	30%	= 0.1

[a] Compound reducing the tissue catecholamine level too.

It is striking, in the data presented above, that a lasting antiarrhythmic effect could be observed if a reduced myocardial catecholamine level was present. Nevertheless, the correlation seems by no means to be a simple and direct one, as indicated by the relatively low efficacy of reserpine. In the absence of such reduction of the tissue catecholamine level, only the acute effect due either to the quinidine-like 'unspecific' antiarrhythmic action and/or to the blockade of the adrenergic β-receptors was found. These observations are supported by the findings of GRISK et al.[12], according to which elevation of the catecholamine content of the heart by MAO inhibitors reduced the effectiveness of different antiarrhythmic drugs, whereas a low myocardial catecholamine level considerably promoted antiarrhythmic action of the same drugs. From the favourable results with I-06 and prenylamine – having also an 'unspecific' antiarrhythmic action[13] – it may be inferred that the combination of a catecholamine depletion with a quinidine-like effect and a blockade of the adrenergic β-receptors seems to be a promising way to get not only acute but also prolonged antiarrhythmic action. Whether the site of action is the heart alone or also the central nervous system remains to be shown.

Zusammenfassung. Nach mehrtägiger Vorbehandlung zeigt das amindepletierende DCI-Derivat I-06 (noch 24 h nach letzter Verabreichung) einen starken antifibrillatorischen Effekt gegen $CaCl_2$-Ventrikelflimmern. Das nicht amindepletierende Propranolol ist zu diesem Zeitpunkt unwirksam. Eine Schutzwirkung verursachen auch Prenylamin, Guanethidin, α-Methyldopa und in geringerem Masse auch Reserpin. Bretylium bleibt ohne Einfluss. Die eventuelle Bedeutung der amindepletierenden Wirkung im Mechanismus der langdauernden antiarrhythmischen Wirkung wird diskutiert.

J. PAPP, W. FÖRSTER, L. SZEKERES, and V. RÖSLER

Department of Pharmacology of the University Medical Schools of Pécs (Hungary) and Magdeburg (DDR), February 5, 1966.

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