Circulatory effects of coronary occlusion ($n = 10$)

	Myocardinal blood flow (%)	Vascular conductance (%)	Mean blood pressure (mmHg)	Pulse pressure (mmHg)	Heart rate (min^{-1})
Initial value	100 ± 0	100 ± 0	112.3 ± 8.7	27.1 ± 3.6	171.0 ± 12.1
Change after occlusion	− 52.9 ± 8.6	− 50.4 ± 10.2	− 2.2 ± 6.7	+ 0.9 ± 1.8	+ 4.6 ± 6.7
p	< 0.001	< 0.001	> 0.5	> 0.5	> 0.5

Mean values ± S.E.M.

of the ishaemia. By contrast, isoproterenol was shown to increase calculated conductance values during both periods, although the slopes of regression lines characterizing the two dilatory responses differed significantly from each other. LAD occlusion potentiated the systemic hypotension elicited by large doses of isoproterenol and reduced the pulse pressure augmenting effect of the drug. The latter modifications are probably associated with a reduced sensitivity of the damaged heart to inotropic stimuli. Moreover, after LAD occlusion somewhat higher concentrations were required to elicit chronotrophic responses than were needed for a similar response in the normal state.

Conclusions. The results indicate that, after coronary occlusion, β-adrenergic activation induces dilatory vascular responses in the ischaemic myocardium. In order to characterize the collateral (ischaemic) vascular response the effects of isoproterenol infusions were measured in the same tissue locus before and after LAD occlusion. It seems that collateral dilatation corresponds to some 50% of the normal response. Since a large amount of vasodilator metabolites are released by the ischaemic myocardium, it may rightly be assumed that collateral channels are delivering blood into a maximally dilated microvasculature, which is insensitive to β-adrenergic stimuli. Thus, β-dilator effects are presumably exerted on the netlike arrangement of small collateral arteries surrounding the ischaemic focus. β-adrenergic excitation, however, is not necessarily beneficial to the ischaemic myocardium, since, during isoproterenol administration, the local oxygen requirement may be expected to increase as well. Indeed, isoproterenol has been reported to augment both active contractile force[1] and the severity of ischaemic damage[2] within a hypoxic myocardial area after experimental coronary occlusion.

Zusammenfassung. Am ischämischen Myokard löst Isoproterenol eine vasodilatatorische Reaktion aus, die qualitativ ähnliche, quantitativ jedoch geringere Werte zeigt als diejenigen, die vor dem Koronar-Verschluss in derselben Myokardzone gemessen wurden.

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A Novel Spasmolytic and CNS Active Agent: 3-(2-benzylmethylamino ethyl) Benzoic Acid Methyl Ester Hydrochloride

In the course of investigations on the influence of structural modifications of related *m*-(aminoalkyl) benzoic acid derivatives[1,2] the title compound (II) was synthesized. Hydrolysis of *N*-benzyl-*N*-methyl-3-trifluoromethyl-phenethyl-amine with conc. sulfuric acid followed by esterification with methyl alcohol yielded (II). The hydrochloride of (II) has a mp 150–151 °C. Analysis for $C_{18}H_{21}NO_2 \cdot HCl$: Calcd: C, 67.60; H, 6.93; found: C, 67.75; H, 6.95. The IR-spectrum recorded on a Beckman IR 8 spectrophotometer is consistent with the assigned structure.

Compound (II) is a potent spasmolytic agent exhibiting approximately three times the activity of papaverine in the rabbit ileum preparation. The spasmogenic effect of 20 mg of $BaCl_2$ is overcome by 0.075–0.1 mg of II.

In the normotensive dog no blood pressure effects are observed following i.v. administration of 1 and 2 mg/kg. Additional doses of 4 and 8 mg/kg cause brief depressor responses. No changes in the heart rate are observed at these levels. In doses up to 16 mg/kg pressor responses to epinephrine and depressor responses to acetylcholine and bradykinin are unaffected. The acute toxicity LD_{50} (p.o.) of II for rats is 700–800 mg/kg. Compound II shows no activity in the motor acitivity test in rats at 100 mg/kg and a slight decrease in activity in mice at 100 mg/kg.

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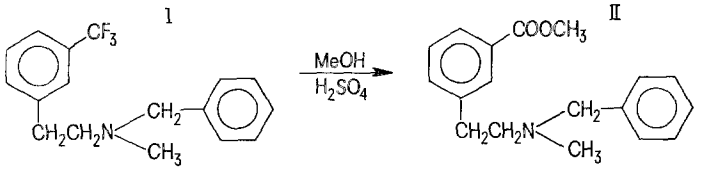

No potentiation of methamphetamine induced stimulation in the conditioned avoidance test is observed at 20 mg/kg p.o. This test is used to determine antidepressant activity. Tricyclic antidepressants typically cause potentiation of methamphetamine. The compound does not block monoamineoxidase in vitro at 10^{-3} *M* concentration.

However, in other tests, II retains a selective ability to stimulate the central nervous system. At high doses (150–200 mg/kg i.p.) convulsive side effects and motor tremors occur. The convulsions are manifested as leaping and rolling movements. Convulsions are followed by ataxia, a decrease of respiratory rate (gasping), cyanosis, and diuresis until the animal expires.

At low doses (4 mg/kg) II potentiates apomorphine induced gnawing. Furthermore, II promotes conditioned avoidance learning of the rat. For the majority of the experiments Holtzman rats of varying age groups were used. For each individual set of experiments a total of 12 to 20 animals were used, with half serving as controls and half receiving the drug. Experiments were repeated with fresh groups of rats whenever it was felt that it was desirable to do so. Results were found to be statistically significant.

More specifically, the performance of rats was tested using a number of different testing situations which included: escape response with the animal jumping to the safety of a raised ledge, the pole climbing test, a modification of the test described by COOK and WEIDLEY[3], and a passive avoidance test of our own design, all using electric foot shock as a negative stimulus. 10 mg/kg of II was given p.o. 1–1/2 to 2 h before the test in these experiments. In a typical experiment, avoidance (escape after receiving foot shock) was accomplished within the time limit by 13 control rats which received saline, as compared to 19 rats that had received 10 mg/kg of II ($n = 26$). Conditioned avoidance (escape prior to shock) was achieved by 6 control rats against 14 rats on II. A corridor type maze was used to determine drug effect on performance in a positive reinforced discrimination task. 50 rats were used for the maze experiments, 25 serving as controls, 15 receiving 10 mg/kg and 10 receiving 20 mg/kg of II. A positive dose response was observed in these trials. The percentage of rats that reached criterion after 4 min was 16% for controls and 29% for rats receiving 10 mg/kg of II and 40% for rats receiving 20 mg/kg of II. Animals were scored by number of errors committed, and total time elapsed to complete the task. Drug effect on retention was determined in the drug and non-drug state of the escape responses, and for the non-drug state in the maze situations.

Positive effects on certain parameters of intellectual performance in man are also observed. Clinical trials on over 100 subjects to date indicate improvement of learning (acquisition of verbal information), short term recall, long term recall and correlation. Learning and short term recall were measured using acquisition and retention of nonsense syllables as criterion. Long term recall and correlation (intellectual speed) were measured through the use of a word completion test.

Full reports of the chemistry and pharmacology of this new agent, and some of its analogues, will be presented in the near future[4].

Zusammenfassung. Es wurde 3-(2-Benzylmethylaminoethyl) Benzoesäuremethyl-Ester als neuer Typ einer wirksamen, das Zentralnervensystem aktivierenden Verbindung erkannt. Eine spezifische Wirkung auf Lernvorgang und Gedächtnis wurde festgestellt. Die Verbindung zeigt eine ausgesprochene spasmolytische Wirkung.

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[4] Manuscripts in preparation.

Contractile Filamentous Structures in Sertoli Cells of the Greek Tortoise (*Testudo graeca*)?

In recent years increasing interest has been paid to filaments which are supposed to form part of a contractile system in cells not identical with muscle cells. Bundles of filaments, which are assumed to be contractile, have been demonstrated, for example, in fibroblasts of duodenal villi of the rat[1], myoid cells (myofibroblasts[2]) in the peritubular connective tissue of the mammalian testis[2–5], and renal parenchymal and interstitial cells[6–9]. Now we have observed conspicuous bundles of filaments in Sertoli cells of *Testudo graeca*, which suggest that this cell type, apart from its overall role in spermatogenesis and maintaining the blood-tubulus barrier[10], may contribute to the contractility of seminiferous tubules.

Two sexually immature and 2 mature (spermatogenically active) specimens of *Testudo graeca* were perfused with phosphate-buffered glutaraldehyde and phosphate buffer. Testes were removed, postfixed with OsO_4 and embedded for electron microscopy. Thin sections were stained with uranyl acetate and lead citrate.

In immature animals sertoli cells exhibit scattered filaments[10], which partly insert in semidesmosomes. The peritubular tissue consists of 2–4 layers of elongated cells, which contain numerous free ribosomes, fragments of rough-surfaced ER, mitochondria of the crista-typus with an electron-dense matrix, but only few filaments. These cells seem to represent an intermediate stage between fibroblasts and myoid cells. They do not form an uninterrupted cellular sheath but only a loose framework which surrounds the seminiferous tubule. In adult, spermatogenically active animals, these cells have changed but little. Filaments are more prominent, but small inpocketings of the cell membrane, which have been described to be a characteristic feature of peritubular myoid cells[4,5], are only occasionally seen. Sertoli cells,

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