*Results.* The effect of reserpine on MSMR evoked from extensor GS nerves was investigated in 6 cats. In all experiments, 5 h after i.v. injection of reserpine (4 mg/kg) marked reduction of MSMR amplitude was observed (figure 1). Thus, in 6 experiments, L-Dopa (30 mg/kg i.v.) completely antagonized the reserpine-induced decrease in the monosynaptic spike height (figure 1). The L-Dopa induced antagonism on reserpine effect appeared within 20–30 min of the injection of L-Dopa. Pimozide (3 mg/kg i.v.) antagonized the L-Dopa induced recovery (increase) in the MSMR spike after reserpine (figure 2). These experiments were performed on 6 cats.

*Discussion.* Results obtained clearly demonstrate that reserpine and L-Dopa alter spinal neuronal activity. Because the time sequence of reserpine-induced decrease of the MSMR is correspondent with the time sequence of the reserpine-induced neuronal depletion of catecholamines[9], it seems probable that catecholamines in the spinal cord determine in some way the size of the motoneurons-pool which take part in the MSMR. On the other hand, the recovery (increase) of the monosynaptic spike amplitude following L-Dopa is a reflection of the rise in recruitment of motoneurons which are at monosynaptic input disposal. This effect seems to be due to a neuronally restored content of catecholamines (DA and/or NA) synthesized centrally from L-Dopa[10]. Pimozide was reported to be a DA-receptor blocking agent without any apparent NA-receptor blocking ability in the central nervous system[11]. In fact, antagonizing action of pimozide on the L-Dopa-induced recovery (increase) of monosynaptic spike after reserpine, strongly indicates that dopaminergic receptors could be involved in the action L-Dopa on spinal MSMR. Further study will be done to prove or disprove definitely this assumption.


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## Changes in gentamicin pharmacokinetics after reduction of renal parenchyma


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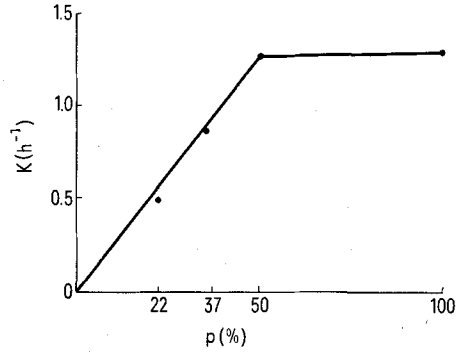
*Summary.* The relationship between the elimination constant of gentamicin and the percentage of functioning nephrons in rats cannot be characterized by a simple linear relation. The results support the assumption that gentamicin elimination per residual nephron increased.


The decrease of renal function caused by various pathological processes is associated with a decrease of the elimination constant (and an increase of biological half-life) of drugs, which are eliminated from the body predominantly by the kidneys. The elimination constant of many drugs decreases in linear relation to the decrease of glomerular filtration rate[1]. However this renal function does not decrease in a simple linear relation to the number of functioning nephrons[2]. We have attempted to study the relationship between changes in the elimination constant (K) of gentimicin and the percentage of functioning nephrons.




Elimination constant of gentamicin in rats with different amount of renal parenchyma. K = elimination constant (total); p = % of remaining renal parenchyma.

*Methods.* In our experiments we used female SPF rats of the Wistar strain. Before the experiment, their weight was about 200 g. The renal parenchyma was reduced to 50, 37, 22 and 0% of the normal amount (for details see table). After the operation, the rats were fed a high protein diet. On postoperative day 11, gentamicin was administrated i.m. in doses 6 mg/kg. Gentamicin concentrations in serum were measured by the technique described earlier[3].

The amount of remaining renal parenchyma expressed as percentage of the initial value (p) was calculated according to the formula:

$$p = \frac{KW - E}{KW} \times 100 \qquad (1)$$

Where KW = weight of both kidneys, E = weight of the extirpated tissue. The values of K and biological half-life were calculated in the usual way[4]. As the K of gentamicin in rats is given practically only by its renal excretion (see the K value after bilateral nephrectomy), this value may be regarded as the renal elimination con-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stant of gentamicin. The K value of gentamicin may therefore be taken as the sum of the mean value of elimination constant of each nephron (k). If we denote the number of functioning nephrons as N, this assumption may be expressed by the following aquation:

$$K = N \times k \quad (2)$$

The present findings indicate that compensatory hypertrophy in adult rats is not attended by an increase in N[5]. If we presume that, in normal conditions, there is a direct relation between KW and N, changes in k after reduction of renal parenchyma may be calculated according to the formula:

$$\frac{k_R}{k_N} = \frac{K_R}{K_N} \times \frac{KW}{KW - E} \quad (3)$$

where $K_R$ and $k_N$ = elimination constant per nephron in reduced and in normal renal parenchyma, respectively. $K_R$ and $K_N$ = elimination constant after reduction of renal parenchyma and under normal conditions, respectively.

*Results.* The results obtained are summarized in the table. The reduction of the number of nephrons to 50% caused no changes in K of gentamicin, as compared with healthy animals. If the reduction of p was more than 50% of the normal value, the K value decreased in linear relation to p (see figure). Calculated $k_R/k_N$ showed the value of elimination constant per nephron for gentamicin in residual nephrons to be 1.73–1.95 times higher than in normal nephrons. In other words, the elimination constant of gentamicin per nephron under these conditions approximately doubled.

*Discussion.* The results based on the renal elimination of gentamicin indicate that the reduction of the number of functioning nephrons to 50% of the normal value was fully compensated by the residual nephrons. Calculations of the elimination constant per residual nephron indicate that the increase of gentamicin elimination per nephron can be maximally doubled. The mechanism underlying the increase of gentamicin elimination by residual nephrons cannot be explained on the basis of these experiments. Theoretically, the increase in glomerular filtration rate and the changes in tubular transport of gentamicin should be taken in account.

Pharmacokinetic parameters of gentamicin in rats with reduced renal parenchyma

| | (KW–E)× 100/KW[a] | K[b] ($h^{-1}$) | $t_{0.5}$[c] (h) | $k_R/k_N$[d] – |
|---|---|---|---|---|
| With both kidneys (normal rats) | 100 | 1.29 | 0.52 | 1.00 |
| After unilateral nephrectomy | 50 | 1.26 | 0.55 | 1.95 |
| After unilateral nephrectomy and resection of proximal pole of second kidney | 37 | 0.87 | 0.80 | 1.81 |
| After unilateral nephrectomy and resection of proximal and distal poles of second kidney | 22 | 0.49 | 1.41 | 1.73 |
| After bilateral nephrectomy | 0 | 0.032[e] | 22.00[e] | – |

[a] See formula 1; [b] elimination constant; [c] half-life; [d] see formula 3; [e] 20 h after bilateral nephrectomy. Number of animals in all groups was not less than 25.

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## A tissue-selective prostaglandin $E_2$ analog with potent antifertility effects

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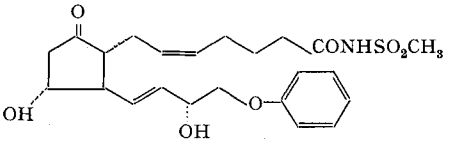
*Summary.* N-methanesulfonyl 16-phenoxy-ω-tetranor $PGE_2$ is a prostaglandin analog which is markedly more tissue selective than $PGE_2$. This compound is 10–30 times more potent than $PGE_2$ in animal models which are considered relevant to antifertility effects in humans. In pharmacological tests which are believed to be predictive for side effects in humans, the compound has potency either equal to or less than that of $PGE_2$.

Achievement of tissue selectivity and metabolic stability are important requirements for the realization of the potential therapeutic usefulness of prostaglandins[1,2]. To this end, one line of research pursued in our laboratories has been the modification of the carboxyl terminus of the prostaglandins. These studies have shown that replacing the carboxyl group in $PGE_2$ by a methylsulfonyl carboxamido group results in the complete retention of uterine smooth muscle stimulant activity, while other $PGE_2$-like effects are markedly diminished. Parallel investigations have established that appropriate alterations in the ω-chain of prostaglandins greatly affect potency. This report describes the relevant properties of a $PGE_2$ analog modified in both the α- and ω-chain, which appears to fulfill the criteria of a potentially useful agent for fertility control in humans, based on its abortifacient potency, metabolic stability, and selectivity of action.

The compound, N-methanesulfonyl 16-phenoxy-ω-tetranor $PGE_2$ carboxamide, CP-34,089 (ZK 57 671), is a white, crystalline powder, melting at 78.5–80 °C, which is sparingly soluble in water (0.5 mg/ml) and readily soluble in ethanol (> 100 mg/ml).




CP-34,089 (ZK 57 671)

The antifertility effects of CP-34,089 were compared with those of $PGE_2$ in 3 experimental models (rat, guinea-pig, and rhesus monkey), which distinguish between luteo-