improved physical fitness favor the latter as the agent of choice. The postulated reduction of edema points to a possible wider therapeutic usefulness of oral gelatine.

Another peripheral observation of dietary gelatine supplementation is that initially it is accompanied by a feeling of well being and greater physical stamina both of which seem unrelated to the amelioration of urinary distress. These subjective effects were observed by individuals who did not exhibit demonstrable protein or other dietary deficiency. The high glycine content of gelatine may be more readily linked to these effects since glycine may enter numerous synthetic pathways, including that of steroids. Feeding of gelatine has been reported to induce great physical output and work endurance, an effect attributed to a more rapid synthesis of creatine[8] and was believed to be beneficial in the management of patients suffering from muscular dystrophy[11]. However, glycine is not a precursor of creatine[9], even though its ingestion induces prompt creatinuria[9–11]. The report that feeding of gelatine does not increase muscular strength[12] does not necessarily negate the finding of decreased muscular fatigue and greater work output[8].

An interesting and possibly valuable clue regarding the mode of action of gelatine in benign prostatic hypertrophy is the observation that ingestion of this substance increased the work output of men by 37% to 240% above the control training level but was without effect in women[8].

Résumé. La consommation journalière de 25 g de gélatine soulage rapidement les symptomes urinaires accompagnant l'hypertrophie prostatique bénigne. La gélatine peut être trés utile dans le traitement de ce désordre.

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Selective Destruction of Adrenergic Nerve Terminals by Chemical Analogues of 6-Hydroxydopamine

After it had been shown that 6-hydroxydopamine (6-OHDA) selectively destroys adrenergic neurons (terminals only if given to adult animals, whole neurons if given to new-born animals), this drug became a widely used experimental tool for studying both peripheral and central adrenergic mechanisms (for references see[1]).

The synthesis of analogues of 6-OHDA was designed to discover even more effective compounds and to learn more about the possible mechanism of action by comparing the chemical structure and probable formation of reactive oxidation products with the effect on adrenergic neurons.

In a first series of experiments male Wistar rats, weighing 100–110 g, were injected i.v. with 2×0.25 mmoles of the various amines (Table) at an interval of 20 h. On account of a general high toxicity, the dosage of several amines had to be reduced to 2×0.125 mmoles. 4 h after the last injection the animals were killed, the heart and brain rapidly removed and homogenized in 0.4 *N* $HClO_4$. The norepinephrine (NE) content was determined according to previously described procedures[2,3]. Those analogues of 6-OHDA, which had produced a marked depletion of NE in the short-term experiments, were further investigated to evaluate their ability to produce a long-lasting NE depletion. The treatment was the same as in the short-term experiments but the animals were killed 7 days after the last dose. The determination of the NE content was extended to salivary gland, spleen and vas deferens, whereas that of the brain was omitted, since in the short-term experiments none of the compounds studied had produced a marked reduction of the brain NE content. Those compounds which produced a long-lasting NE depletion were also investigated for possible ultramorphological changes in the adrenergic nerve terminals. The treatment was the same as for the biochemical studies but the animals were killed 24 h after injecting the last dose of the drug. The processing of the tissue samples for electronmicroscopy was performed as described previously[4].

The following groups of compounds (synthetized by Dr. A. LANGEMANN and U. FISCHER, Chemical Research Department, F. Hoffmann-La Roche & Co. Ltd., Basel) were compared (Table): a) α-methyl-6-OHDA; b) analogues of 6-OHDA in which one of the phenolic OH-groups is replaced by $-OCH_3$, $-NO_2$ or $-NH_2$; c) analogues of 6-OHDA in which the H-atoms of the aromatic nucleus are replaced by either halogen or CH_3; d) analogues of 6-OHDA with the substitution pattern on the nucleus differing from the 2, 4, 5-type.

The introduction of an α-methyl group, rendering the amine resistant to metabolism by monoamine oxidase, did not markedly increase the potency of 6-OHDA. This is in agreement with the observation that in the periphery pretreatment with monoamine oxidase inhibitors does not increase the effect of 6-OHDA (unpublished results). However, in the brain the effect of intraventricularly injected 6-OHDA is markedly potentiated after inhibition of monoamine oxidase, particularly the effect on the dopaminergic neurons[5]. *O*-Methylated derivatives and diphenols (see Table, compounds Nos. 3 and 17) produced neither a short nor a long-lasting depletion of NE, most probably due to a lack of transport through the neuronal membrane of the adrenergic neuron. Of the 2 nitrodiphenols, only compound No. 5 produced a short-lasting depletion, whereas compound No. 6 was ineffective. This finding was rather unexpected, since at least a partial metabolic conversion into the corresponding amine-derivatives could be expected. These latter compounds (Nos. 7, 8, 9) were not only highly efficient depletors of

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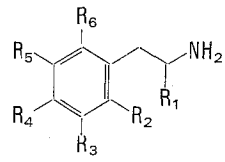

No.	R_1	R_2	R_3	R_4	R_5	R_6	dose (mmoles/kg)	Norepinephrine-content in % of controls						Ultrastructural changes in adrenergic nerves (heart, vas deferens)
								4 h	7 days					
								heart	brain	heart	salivary gland	vas deferens	spleen	
1	H	OH	H	OH	OH	H	2×0.25	7 ± 2	70 ± 8	15 ± 6	20 ± 4	29 ± 3	24 ± 6	degeneration
2	CH_3	OH	H	OH	OH	H	2×0.25	7 ± 2	82 ± 4	12 ± 2	16 ± 4	21 ± 2	8 ± 4	degeneration
3	H	OCH_3	H	OH	OH	H	2×0.25	89 ± 3	84 ± 7					
4	H	OH	H	H	OH	H	2×0.5	51 ± 4	110 ± 6	92 ± 5	99 ± 6	103 ± 11	96 ± 10	
5	H	NO_2	H	OH	OH	H	2×0.25	8 ± 3	102 ± 2	95 ± 7	91 ± 6	97 ± 6	81 ± 5	no degeneration
6	H	OH	H	NO_2	OH	H	2×0.25	87 ± 5	97 ± 4					
7	H	NH_2	H	OH	OH	H	2×0.125	16 ± 3	71 ± 7	20 ± 4	32 ± 5	42 ± 5	25 ± 7	degeneration
8	H	OH	H	NH_2	OH	H	2×0.125	< 1	76 ± 4	9 ± 3	30 ± 5	30 ± 3	16 ± 2	degeneration
9	H	OH	H	OH	NH_2	H	2×0.25	7 ± 1	107 ± 5	15 ± 1	35 ± 6	37 ± 2	12 ± 3	degeneration
10	H	OH	CH_3	OH	OH	H	2×0.25	97 ± 10	97 ± 5					
11	H	OH	Br	OH	OH	Br	2×0.25	115 ± 6	105 ± 5					
12	H	H	OH	OH	OH	H	2×0.25	10 ± 3	102 ± 4	98 ± 4	102 ± 4	81 ± 2	104 ± 4	no degeneration
13	H	OH	OH	OH	H	H	2×0.125	77 ± 2	92 ± 5					
14	CH_3	OH	OH	OH	H	H	2×0.25	78 ± 5	111 ± 7					
15	H	OH	OH	H	OH	H	2×0.25	< 1	85 ± 5	25 ± 3	49 ± 6	77 ± 5	33 ± 4	degeneration
16	H	OH	OH	H	NH_2	H	2×0.25	31 ± 5	89 ± 6	58 ± 5	63 ± 6	110 ± 11	74 ± 4	
17	H	OH	OCH_3	H	OH	H	2×0.25	83 ± 4	97 ± 3					
18	H	OH	OCH_3	H	NH_2	H	2×0.25	101 ± 8	94 ± 6					
19	H	OH	NH_2	H	H	OH	2×0.25	92 ± 5	85 ± 4					

The animals were injected i.v. with 2 doses of either 0.25 or 0.125 mmoles at an interval of 20 h. The animals were killed either 4 h or 7 days after the last dose. The norepinephrine content of the controls amounted to 977 ± 70 ng/h in the heart, to 500 ± 45 ng/g in the spleen, to 1380 ± 105 ng/g in the salivary gland, to 8753 ± 580 ng/g in the vas deferens and to 428 ± 8 ng/g in the brain.

NE but also produced a selective destruction of adrenergic nerve terminals similar to that produced by 6-OHDA, as shown by electronmicroscopy (Table). Additional substitutions on the aromatic nucleus by either methyl (No. 10) or Br (No. 11) abolished both short- and long-lasting NE depletion. 5-hydroxydopamine (No. 12) produced a marked short-lasting NE depletion without destroying adrenergic nerve terminals, which is in agreement with previous observations[6]. Another trihydroxyphenethylamine, 2-hydroxydopamine (No. 13) and its α-methyl congener (No. 14) exhibited minor depleting effects only. However, the latter two compounds could not be studied in the usual dose of 2×0.25 mmoles/kg on account of severe general toxicity. A long-lasting depletion of NE, accompanied by a destruction of adrenergic nerve terminals, was achieved by altering the substitution pattern from 2, 4, 5 into 2, 3 and 5-positions (No. 15). Here again the replacement of a hydroxy by an amino group (No. 16) did not alter the efficiency of the derivatives, whereas the corresponding methoxy-compounds (Nos. 17 and 18) were inactive. Compound No. 19, substituted at position 2, 3 and 6 exhibited no effect on the NE content.

From the type of substitution leading to a selective destruction of adrenergic nerve terminals, one might conclude that the redox potential of these compounds, in addition to their affinity to the neuronal amine pump, is one of the essential factors determining whether a chemical sympathectomy occurs or not. This is in accordance with the available information on the mechanism of action of 6-OHDA, that the uptake and accumulation in the adrenergic neurons is an absolute prerequisite for the destructive effect of 6-OHDA, whereas accumulation in the storage vesicles is not necessary[1,7]. On account of its low redox potential, 6-OHDA is easily oxidized to highly reactive intermediates, which undergo covalent bindings with nucleophilic groups of proteins and other biologically essential macromolecules which are thus denatured[7]. On account of the highly efficient transport of 6-OHDA into the adrenergic neuron, the density of the covalent bindings formed is highest in the adrenergic neurons[1,7]. At present it cannot be decided as to what extent the formation of H_2O_2 is also involved in the damaging effect of 6-OHDA[8] in addition to the covalent binding of its oxidation products[1,7].

Zusammenfassung. Verschiedene chemische Analoge von 6-Hydroxydopamin bewirken ebenfalls eine selektive Zerstörung der adrenergen Nervenendigungen. Es werden die Beziehungen zwischen der chemischen Konstitution und der Fähigkeit zur chemischen Sympathektomei diskutiert.

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