Degree of delayed neurotoxic signs in male chickens given a single dose of leptophos

Dose (mg/kg)	No. of chickens	Ataxia		Death		Mortality after 60 days (%)
		No. of chickens	Days after dosing	No. of chickens	Days after dosing	
140	9			1	1	11
160	9			1	1	11
180	9			1	1	33
		1	9	1	15	
		1	13	1	23	
500	5	2	8	1	16	80
				1	20	
		2	10	2	22	
1000	5	5	8	1	16	100
				3	20	
				1	22	
1500	5	5	8	1	10	100
				1	14	
				1	16	
				2	20	
2000	5			1	1	100
		4	8	2	16	
				2	18	
2500	5	4	8	1	1	100
				3	16	
				1	18	
3000	5	5	8	1	15	100
				4	18	

that a compound showing such activity might produce the same effect in man, leptophos requires careful consideration before it is allowed to be freely used.

Zusammenfassung. Nachweis, dass Leptophos eine sehr niedrige akute Toxizität für männliche Hühnchen hat und einen neurotoxischen Effekt bei Dosen von 180–300 mg/kg verursacht. Dagegen haben Cyolane und Cytrolane eine hochakute Toxizität und verursachen nach oraler Verabreichung keine Neurotoxizität.

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On the Specificity of Dopamine Release by Amantadine

Amantadine causes its beneficial effects in Parkinsonian patients through an unknown mechanism, although it has been suggested that it acts through release of dopamine[1]. Amantadine has been reported[2] to increase both the synthesis and release of dopamine in the rat striatum in vitro and to increase the efflux of dopamine from brain structures in cats, most likely the caudate nucleus[3]. Comparable effects, as in the case of dopamine, have been reported for norepinephrine, both in vitro and in vivo[4]; however, relatively high doses of amantadine were necessary to show these effects in vivo. Lower doses of amantadine have been reported to cause release of dopamine in dopamine-loaded dogs[1], and it seemed of interest to determine whether amantadine could also be shown to release norepinephrine under these in vivo conditions. Evidence is presented that doses of amantadine that release dopamine do not release norepinephrine.

Methods. Mongrel dogs (6–11 kg) of either sex were anesthetized with Na pentobarbital (35 mg/kg i.v.) and bilaterally vagotomized. Blood pressure was recorded with a Statham P23Db pressure transducer and cannula inserted into the femoral artery. Additions of compounds were made via the contralateral femoral vein. Rabbits (2.1–4.0 kg) were anesthetized with urethane (1.25 g/kg i.p.) and prepared in the same manner as dogs, except that some experiments were performed in non-vagotomized animals.

Drugs used in these experiments were amantadine-HCl (Philips-Duphar), dopamine-HCl, morphine-H_2SO_4, norepinephrine bitartrate and phenoxybenzamine-HCl (S K and F). Solutions of all compounds were freshly

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Table I. Effects of amantadine on mean blood pressure in anaesthetized dogs

Experiment	n	Blood pressure changes after amantadine (mm Hg)[a] (cumulative doses in mg/kg) 0.064	0.4	2.0	7.0	17.0
Amantadine after saline	7	0 ± 2	+ 1 ± 2	+11 ± 4	+10 ± 11	−21 ± 11
Amantadine after dopamine[d]	7	+9 ± 2[b]	+17 ± 5[c]	+40 ± 7[c]	+72 ± 7[c]	−22 ± 28
Amantadine after norepinephrine	6	0 ± 1	+ 1 ± 2	+11 ± 3	+ 8 ± 18	−47 ± 13

[a] (+), Increase in blood pressure; (−), decrease in blood pressure; [b] $p < 0.05$; [c] $p < 0.01$ by the students t-test. Values are ± S.D. [d] Values of amantadine after dopamine are compared with values of amantadine after saline. The dose of dopamine was 200 µg/kg and that of norepinephrine was kept constant in any one experiment at 2 or 4 µg/kg.

Table II. Effect of subsequent additions of dopamine and norepinephrine, prior to amantadine, on blood pressure in anaesthetized dogs[a]

	n	Blood pressure increase (mm Hg) upon the First	Second	Third	Fourth	Fifth	Sixth dose
Dopamine (200 µg/kg)	5	103 ± 12	109 ± 11	107 ± 10	116 ± 8	108 ± 13	–
Norepinephrine (2 or 4 µg /kg)	7	64 ± 6	72 ± 7	85 ± 6[b]	100 ± 7[b]	123 ± 9[c]	160 ± 10[c]

[a] The values in this table are from the same experiments as those summarized in Table II. [b] $p < 0.05$; [c] $p < 0.01$ by the students t-test.

made each day and weights are expressed in terms of the salts.

Results. When amantadine was injected in dogs 6–8 min after an i.v. dose of 200 µg/kg dopamine that gave an average pressor response of 108 mm Hg, there was a dose-related pressor response to amantadine. A dose of 0.064 mg/kg i.v. already produced an effect that was significantly greater than control (Table I). The time between the injection of amantadine and the following dose of dopamine (or saline or norepinephrine) was 24 min. In experiments where dopamine was replaced by norepinephrine, responses to amantadine did not differ from saline controls (Table I), even when the period between norepinephrine and amantadine injections was reduced to 2 min. Blood pressure responses to norepinephrine increased upon each subsequent addition, but those to dopamine were unchanged (Table II).

Other experiments were performed in which the order of administration of the 2 agents was reversed, i.e. the lowest dose of amantadine was injected, followed 2 min later by the standard dose of either dopamine or norepinephrine. After 24 min the next greater dose of amantadine was injected, followed again by the standard dose of the catecholamine. In these experiments ($n = 5$), responses to amantadine were again significantly greater than control when given in combination with dopamine, but not when given in combination with norepinephrine.

Dopamine elicited a depressor effect in the dog when it was given after the irreversible α-receptor antagonist phenoxybenzamine (10 mg/kg). A dose-response was determined for dopamine after phenoxybenzamine and after the subsequent addition of amantadine ($n = 4$). Amantadine (2.0 and 4.0 mg/kg) had no effect itself, nor did it affect the depressor dose-response curve to dopamine after phenoxybenzamine. The effect of repeated injections of a single dose of dopamine (200 µg/kg) was also studied after amantadine (0.064 to 17.0 mg/kg i.v.) in phenoxybenzamine (10 mg/kg) treated dogs ($n = 4$) in the same manner as the experiments presented in Table I. Depressor responses to dopamine were unchanged throughout the experiment. Morphine (15 mg/kg) was then given and the depressor response to dopamine was reversed, i.e. a pressor response was again observed, as has been previously reported[5].

The interaction between dopamine and amantadine was studied in rabbits, since dopamine causes a depressor effect in this species. Amantadine (0.32 to 10 mg/kg i.v.) also caused a depressor response in rabbits (5 to 15 mm Hg) but this was not dose-related. Dopamine (1.0 and 100 µg/kg) was tested before and after amantadine as in the dog experiments. No interaction between dopamine and amantadine was observed.

Discussion. Amantadine caused a greater blood pressure rise in dogs loaded with dopamine than with saline, which suggests that amantadine caused a release of dopamine; this is in agreement with results of GRELAK et al[1]. This effect was shown not to be due to a general release of catecholamines, since no differences from controls were observed after loading the animal with norepinephrine. The increased rise in blood pressure to each subsequent dose of norepinephrine but not dopamine confirms earlier reports[1,6] that amantadine blocks the uptake of norepinephrine and suggests that it does not block the uptake of dopamine.

Zusammenfassung. Nachweis, dass Amantadin bei mit Dopamin vorbehandelten Hunden Blutdrucksteigerung bewirkt, welche nicht vorhanden ist, wenn die Hunde mit Norepinephrin vorbehandelt wurden.

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