pH 4.5, containing phenolphthalein glucuronide to a final concentration of 0.006 *M*. A unit of β-glucuronidase represents the amount of the enzyme necessary to hydrolyze one μg of the substrate per h under the conditions of assay. Serum cholesterol levels were measured by the method of ZLATKIS et al.[15].

The results are presented in the Table. It is evident that Vitamin A exerted a moderate hypocholesteremic effect (7 to 43%) on rabbits fed 0.2% chloesterol. The severity of the average atherosclerosis was reduced by 31% in the aortic arch and 61% in the abdominal aorta. Half of the rabbits fed Vitamin A plus cholesterol were free of atherosclerotic lesions as were 4 of the 9 rabbits fed cholesterol alone. We have shown that cholesterol feeding increases the level of aortic β-glucuronidase. The level of β-glucuronidase in the sera of rabbits fed cholesterol was no different from that observed in control rabbits: Administration of Vitamin A to cholesterol-fed rabbits significantly reduced serum β-glucuronidase levels suggesting a possible lysosome stabilizing effect of this Vitamin. Since aortic β-glucuronidase levels were not determined, we cannot say if increased levels of this enzyme in the artery would have been reflected in blood levels. The results in the Table (groups B and C), however, suggest that aortic and serum levels of β-glucuronidase may not be correlated.

Further experiments are planned to clarify the role of Vitamin A in the establishment and progression of atherosclerosis[16, 17].

Résumé. La vitamine A a eu un effet hypocholestérimique modéré (7 à 43%) sur des lapins nourris de 0.2% cholestérol. La gravité de l'athérosclérose moyenne fut réduite de 31% dans la crosse aortique, et de 61% dans l'aorte abdominale. L'administration de vitamine A aux lapins nourris de cholésterol a réduit les niveaux de sérum β-glucuronidase d'une manière significative, il est donc possible que cette vitamine ait une influence stabilisatrice sur le lysosome.

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Effect of vitamin A on atherosclerosis and serum β-glucuronidase levels in rabbits

	Group		
	A	B	C
Number	10/10	9/10	10/10
Vitamin A Acetate, 25×10^6 U/100 g diet	+	−	−
Cholesterol, 0.2%	+	+	−
Serum Cholesterol, mg/dl			
Day 125	299 ± 44[a]	323 ± 48	82 ± 5
Day 220	412 ± 45	464 ± 103	111 ± 13
Day 365	219 ± 40	384 ± 74	61 ± 4
Serum β-Glucuronidase (units/ml)			
Day 125	9.6 ± 2.2	13.1 ± 1.9	13.7 ± 1.7
Day 220	7.5 ± 0.9[b]	15.0 ± 1.3	15.3 ± 3.7
Avg. Atheromata			
Arch	1.1 ± 0.5	1.6 ± 0.6	0
Thoracic	0.5 ± 0.2	1.3 ± 0.5	0

[a] Standard error [b] A vs B, $p < 0.001$.

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Influence of Anticholinergic-Antiparkinsonian Agents on the Effects of Narcoanalgesic Drugs in the Rat

There are numerous references in the bibliography about relations between action mechanisms of narcoanalgesic drugs (morphine, meperidine, etc.) and neurohumoral agents (acetylcholine, catecholamines, serotonin, etc.)[1-4]. Experiments carried out in our laboratory also confirmed such relations[5]. In recently performed assays we found also a marked influence of central cholinergic blocking agents (commonly known as antiparkinsonian drugs) on the analgesic and conditioned avoidance suppressing effects of morphine and meperidine in the rat.

Material and methods. The analgesic effect was tested on rats with the method of JANSSEN et al.[6] (Immersion of tail of rats in hot water – in our experiments 51 °C ± 0.5 –, measuring the lapse of time until the tail is withdrawn by the animal). The time between immersion and withdrawal of tail was measured on untreated

Table I. Analgesic effects on rats (expressed in sec)

	Animals without pretreatment	Animals pretreated with narcoanalgesics for 15 days
Control	4.5 ± 0.5	4.5 ± 0.5
	Morphine sulphate	
Alone	10 ± 1	4.5 ± 1
Combined with methixene	21 ± 2	23 ± 3
Combined with biperiden	33 ± 4	36 ± 4
Combined with ethapropazine	30 ± 4	32 ± 4
Combined with caramiphene	29 ± 3	33 ± 5
Combined with atropin sulphate	10 ± 2	4 ± 0.5
	Meperidine	
Alone	11 ± 2	4 ± 0.5
Combined with biperiden	23 ± 3	25 ± 4

animals and 60 min after an i.p. injection of 8 mg/kg of morphine sulphate or 90 mg/kg of meperidine in Wistar male rats of 150–200 g. In every assay 15 animals were used.

The specific suppression of conditioned avoidance response was tested on rats of similar conditions by the method of Cook and Weidley[7]. This method is based on training of rats to climb on a pole in a chamber with a grid floor after receiving electric stimuli in the form of shocks to the feet. The pole provides a safety area. The trained rats are then conditioned associating the shocks with the sound of a buzzer. The conditioned animals climb on the pole if the buzzer sounds. This conditioned response can be blocked by different drugs, especially neuroleptics and narcoanalgesics. Rats that received previously such drugs will not climb on the pole when stimulated by the buzzer alone. The minimal effective dose (ED_{50}) is that which suppresses the response in 50% of the treated animals (16 in each assay).

Tolerance to the analgesic effect was produced by daily i.p. injections of 8 mg/kg or morphine sulphate or 90 mg/kg of meperidine during 15 days. Tolerance to the conditioned avoidance response blocking action was obtained after injecting 15 mg/kg of morphine sulphate during a similar period.

Antiparkinsonian drugs (methixene, biperiden, ethapromazine and caramiphene, 10 mg/kg) were injected i.p. 15 min before the injection of the narcoanalgesic drug. They showed alone no analgesic or conditioned response suppressing effects.

Results. Table I shows the influence of methixene, biperiden, ethapropazine and caramiphene on the analgesic effect of morphine sulphate and meperidine. It can be seen that the effect of both drugs is significantly enhanced by a previous injection of an antiparkinsonian drug (Student's t-test: $p < 0.001$). Atropin was without effect. The tolerance to the analgesic effect seemed to be interrupted.

Table II shows the results obtained in assays of the conditioned avoidance response. It can be seen that the blocking effect of morphine is diminished after a 15 days pretreatment with the same drug. The efficacy was then restored by an injection of methixene or biperiden and also atropin. The quaternary atropin derivative was ineffective.

Table II. Conditioned avoidance suppressing effect of morphin sulphate in rats (measured by the minimal effective dosis in mg/kg)

Pretreatment	Combination with antiparkinsonian drugs	ED_{50}
Without pretreatment	No antiparkinsonian drugs	15 ± 3
Pretreatment with morphine	No antiparkinsonian drugs	32 ± 4
Pretreatment with morphine	Methixene	16 ± 4
Pretreatment with morphine	Biperiden	13 ± 3
Pretreatment with morphine	Atropin sulphate	13 ± 4
Pretreatment with morphine	Methylatropin sulphate	29 ± 5

Zusammenfassung. Nachweis, dass die zentral wirksamen, anticholinergischen Agentien (Antiparkinson-Substanzen: Methyxen, Biperiden, Ethaproperazin, Caramiphen) sowohl die analgetischen Effekte von Morphin und Meperidin als auch ihre hemmende Wirkung auf konditionierte Reaktionen erhöhen.

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