The present study has provided evidence that the tecto-pulvinar projection is originated from SC cells innervated by retinal W-type cells. The previous findings[14,15] that neurons in cat Pul_m are sensitive only to complex visual stimuli (figured stimuli and/or moving stimuli) may be accounted for, at least partly, by the fact that these pulvinar neurons are stimulated indirectly by retinal W-type ganglion cells which are known to have complex visual properties[16,17].

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2 Present address: Department of Physiology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan.
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Histamine release in dogs by Emulphor EL620[1]

J.W. Constantine and W.S. Lebel

Department of Pharmacology, Pfizer Central Research, Pfizer Inc., Groton (Connecticut, 06340, USA), 18 July 1978

Summary. A vehicle containing ethanol and Emulphor EL620 lowers blood pressure and increases heart rate in morphine-chloralose anesthetized dogs. These effects are associated with histamine release caused by Emulphor EL620.

Emulphor EL620 is a polyoxyethylated vegetable oil which has been recommended as a component in an i.v. formulation for Δ^9-tetrahydrocannabinol[2,3], and this formulation has been used in studies of the pharmacological effects of cannabinoids[4–8]. Since Cremophor-EL, which is similar to Emulphor EL620, causes release of histamine in dogs[9], we investigated the formulation[3] containing Emulphor EL620 for this effect.

Methods. Mongrel dogs of either sex, 6–12 kg b.wt, were anesthetized with sodium pentobarbital, 35 mg/kg i.v. (18 dogs) or with morphine, 1 mg/kg i.m., followed by chloralose, 100 mg/kg i.v. (30 dogs). A cannula was placed into a fermoral artery for measurement of blood pressure with a transducer (Statham, model P23G) and the electrical output of this operated a biotachograph (Narco Biosystems, model B1200) for measurement of heart rate; both variables were recorded continuously with a physiograph (Narco-Biosystems, model 4CFM). Where appropriate, blood pressure, heart rate and latent period are expressed as the average ±SD. 6 pentobarbital and 10 morphine-chloralose anesthetized dogs were injected twice, 20 min apart, with ethanol, 0.03 ml/kg i.v. Each dose was twice the amount of ethanol administered in the formulation containing Emulphor EL620. The latter was prepared in a formulation[3] consisting of 5% Emulphor EL620, 5% ethanol and 90% sodium chloride solution (0.9%) for injection into a femoral vein. Injections were given twice, 20 min apart, and the dose of ethanol and Emulphor EL620 in each was 0.015 ml/kg. In 4 additional morphine-chloralose anesthetized dogs, 5 ml of blood was drawn from a femoral vein at 6 and 1 min before, and 1, 7 and 20 min after injection of the formulation (3 dogs) or compound 48/80, 1 mg/kg i.v. (1 dog). In 1 other dog, the formulation was given twice with a 10-min interval between treatments; blood was drawn at 6 and 1 min before, and 1 min after the 1st dose, and at 2 and 10 min after the 2nd dose. All blood samples were centrifuged for 5 min at 374×g; the plasma was separated and frozen until analyzed for histamine.

The assay for plasma histamine was adapted from the procedure of Beaven et al.[10]. The histamine in a 50-µl sample was labelled by methylation with tritiated S-adenosyl methionine using histamine methyl transferase isolated from guinea-pig brain[11]. The radiolabeled histamine was measured with a Beckman LS-250 scintillation spectrometer. The lower level of sensitivity of the assay was 4 ng histamine base/ml of plasma.

Results. There were no effects on blood pressure or heart rate in any of the dogs injected 2 times with ethanol, at a dose twice that administered in the formulation containing Emulphor EL620. We thus conclude that the effects described below for the formulation are due to Emulphor EL620.

In each of 12 pentobarbital anesthetized dogs, Emulphor EL620, 0.015 ml/kg i.v., caused sustained hypotension. The average blood pressure was 129±4.5 mm Hg (range, 110–160 mm Hg) before treatment, and was decreased an average of 60±3.5% (range, 38–85%). Heart rates averaged 143±51 beats/min, and, in 9 of the dogs, there was an average increase of 16±4.8% (range, 2–45%), followed by a sustained decrease of 21±2.3% (range, 14–35%); in the remaining 3 dogs, there was only a sustained decrease of 29±5.3% (range, 10–37%). The latent period, i.e., the time from injection of Emulphor EL620 to onset of cardiovascular changes, averaged 1.8±0.14 min (range, 1.5–2.5 min). After a 20-min interval, all 12 dogs were again given Emulphor EL620, 0.015 ml/kg i.v., and it had no further effect.

In 20 morphine-chloralose anesthetized dogs, blood pressure and heart rate averaged 113±3.2 mm Hg (range, 95–130 mm Hg) and 97±2.4 beats/min (range, 85–120 beats/min), respectively. In 15 of the dogs, Emulphor EL620, 0.015 ml/kg i.v., caused sustained decreases in blood pressure averaging 32±2.9% (range, 13–43%) and sustained increases in heart rate averaging 85±6.3% (range, 35–139%).

In 2 of the remaining 5 dogs, blood pressure and heart rate were not affected and, in another 2, blood pressure was unchanged, but there was either a transient (+41%) or a sustained (+70%) increase in heart rate. In the 5th dog blood pressure was increased transiently by 17% followed by a sustained decrease of 13%, and there was a sustained increase in heart rate of 95%. For the 18 of 20 dogs in which

Effect of compound 48/80 or Emulphor EL620 on blood pressure (BP), heart rate (HR) and plasma histamine concentration (HIST) in morphine-chloralose anesthetized dogs

a	Dog No.	Variable	Time (min) before and after treatment −6	−1	0	1	7	15	20
	1	BP (mm Hg)	120	120		80	35	45	45
		HR (beats/min)	80	75	Compound 48/80 (1 mg/kg i.v.)	180	175	205	210
		HIST (ng/ml)	<4	<4		>1000	697	-	405
	2	BP (mm Hg)	110	110		110	110	110	110
		HR (beats/min)	60	60	Emulphor EL620 (0.015 ml/kg i.v.)	60	155	105	80
		HIST (ng/ml)	<4	<4		<4	132	-	35
	3	BP (mm Hg)	100	100		100	100	75	80
		HR (beats/min)	90	90	Emulphor EL620 (0.015 ml/kg i.v.)	90	195	185	175
		HIST (ng/ml)	<4	<4		<4	154	-	59
	4	BP (mm Hg)	100	100		100	115	120	105
		HR (beats/min)	80	80	Emulphor EL620 (0.015 ml/kg i.v.)	80	205	175	170
		HIST (ng/ml)	<4	<4		<4	70	-	28

b	Dog No.	Variable	Time (min) before and after 1st treatment −6	−1	0	1	7	9	10	12	20
	5	BP (mm Hg)	130	135		140	145	155		120	125
		HR (beats/min)	80	80	Emulphor EL620	80	80	95	Emulphor EL620	130	85
		HIST (ng/ml)	<4	<4	(0.015 ml/kg i.v.)	<4	-	-	(0.015 ml/kg i.v.)	203	53

Emulphor EL620 caused a cardiovascular change, the latent period averaged 2.3±0.2 min (range, 1.5-3.5 min). At 20 min after the 1st treatment, all 20 dogs were again given Emulphor EL620, 0.015 ml/kg i.v., and there was either no effect or no further change in blood pressure or heart rate.

In an additional 5 dogs, anesthestized with morphine-chloralose, blood pressure, heart rate and plasma histamine were determined before and after treatment with compound 48/80 (1 dog) or Emulphor EL620 (4 dogs). Compound 48/80, 1 mg/kg i.v., lowered blood pressure by 71%, increased heart rate by 75% and caused a marked increase in plasma histamine concentration (dog No. 1, table, a). In 3 of the animals treated with Emulphor EL620, 0.015 ml/kg i.v., blood pressure was either unchanged, decreased by 25% or increased by 20%; heart rates were increased by 158, 116 and 156%, respectively, and the latent periods were 3.0, 3.5 and 3.0 min, respectively. Plasma histamine concentrations were increased at 7 and 20 min, but not at 1 min, after treatment (dogs Nos. 2-4, table, a). In the other dog, Emulphor EL620 had no effect on blood pressure or heart rate, and there was no detectable change in plasma histamine concentration 1 min after treatment. After a 10-min interval, this animal was given Emulphor EL620, 0.015 ml/kg i.v., and following a latent period of 1.5 min, blood pressure was lowered by 23% and heart rate was increased by 37%. Plsma histamine concentration was 203 and 53 ng/ml at 2 and 10 min after the second treatment, respectively (dog No. 5, table, b).

Discussion. Our results indicate that the pronounced fall in blood pressure and increase in heart rate in dogs following intravenous injection of solvent containing Emulphor EL620 is due, at least partly, to released histamine. Since the other component (ethanol) in the solvent had no cardiovascular effects we conclude that the effects observed with the solvent are due to Emulphor EL620. Lorenz et al.[9] have shown that Cremophor-EL, a compound similar to Emulphor EL620, lowers blood pressure and releases histamine in dogs and cats, but causes neither of these effects in pig or man. However, in the latter there is histamine release when certain anesthetics, which themselves do not cause release, are administered dissolved in Cremophor EL (see review by Lorenz[12]).

Emulphor EL620 has been used as one of the components in the solvent system for cannabinoids in studies of their pharmacological effects[4-8]; in 1 of these[4], the solvent itself caused 'profound' decreases in blood pressure in 43% of pentobarbitol-anesthetized dogs, but a subsequent injection of solvent had no effect. In the present study, the 1st injection of Emulphor EL620 (0.015 ml/kg i.v.) lowered blood pressure and increased heart rate in each of 12 pentobarbital-anesthetized dogs, and there was no further effect following a 2nd injection. The cardiovascular effects of Emulphor EL620 were not as consistent in morphine-chloralose anesthetized dogs as in those anesthetized with pentobarbital; it lowered blood pressure and increased heart rate in 16 of 20 animals, and increased heart rate in 2 others. Of the 4 dogs in which histamine release was determined, Emulphor EL620 increased heart rate in all animals, but lowered the pressure in only 2; nevertheless, histamine was released in each of the 4 animals. Although we did not determine histamine release in the pentobarbital-anesthetized dogs, the latent period following the injection of Emulphor EL620, and the nature of its cardiovascular effects suggest that histamine was released. We think that Emulphor EL620 should not be included in an i.v. formulation for drug studies in dogs.

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