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Influence of Adrenergic Blocking Drug [N-Ethyl-N-(2-bromoethyl)-1-naphthylenemethylamine • HBr] On Pyrogenic Reaction.*

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An important mechanism of the febrile response to pyrogen is vasoconstriction[1-3] with reduction of skin temperature.[2,4-10] The site of action of pyrogen in the production of fever is central rather than peripheral since such fever is prevented by certain lesions of the central nervous system.[11-13] Pyrogen induced vasoconstriction and fever are mediated in part *via* the sympathetic nervous system, partial or complete removal of which modifies or prevents such vasoconstriction[2,5] and delays and reduces fever.[14] Evidence is here presented that N-Ethyl-N-(2-bromoethyl)-1-naphthylenemethylamine • HBr,† a potent adrenergic blocking agent,[15-17] reduces the febrile response of the dog to pyrogenic material.

Five dogs received intravenous injections of 50 mcg/kg of "Pyromen,"‡ a purified pyrogenic material obtained from pseudomonas aeruginosa. Six dogs were injected intravenously with 3 mg/kg of N-Ethyl-N-(2-bromoethyl)-1-naphthylenemethylamine • HBr 30 minutes prior to the injection of pyrogen. Five days later the order was reversed and dogs previously pre-treated with blocking agent now served as their own controls and vice versa.

Rectal temperatures were determined at 30 minute intervals and data from the experiments on these 11 dogs are given in Table I. The first value is the average temperature during the 6 hour period following injection of pyrogen, and the second is the maximum temperature recorded during the pyrogenic reaction. Both are expressed as increments over basal temperature. Paired comparisons show the mean responses of the two experimental periods to be significantly different. The reduction in average response accomplished by the blocking agent is of the order of 25%.

These studies imply only slight participation of the sympathetic nervous system in the pyrogenic reaction. However, while the dose of N-Ethyl-N-(2-bromoethyl)-1-naphthylenemethylamine • HBr is sufficient to cause complete reversal of the blood pressure response to injected epinephrine in the dog, its potency in preventing sympathetic nerve mediated

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‡ Supplied by Baxter Laboratories, Inc., through the courtesy of Dr. N. M. Nesset.

TABLE I.
Effect of Adrenergic Blocking Agent on Pyrogenic Response in Normal Dogs.

Dog No.	Avg temp. increment over 6 hr (°C)		Maximum increment in temp. (°C)	
	Control	Pre-treated	Control	Pre-treated
1	1.50	1.33	2.05	1.94
2	0.89	0.83	1.33	1.22
3	1.39	0.61	1.72	1.11
4	1.11	1.05	1.67	1.50
5	2.05	1.05	2.55	1.61
6	1.72	1.33	2.10	1.78
7	1.83	1.33	2.44	1.89
8	1.45	1.22	2.50	1.61
9	1.56	1.28	2.16	1.72
10	1.55	1.33	2.22	1.89
11	1.11	0.67	2.11	1.16
Avg	1.469	1.094	2.077	1.585
Probability	<0.01		<0.01	
Significance	High		High	

All temperatures are rectal and are expressed as increments over basal temperature determined during pre-pyrogen control period.

vasoconstriction in the skin is unknown.

In order to further test the role of the sympathetic nervous system in the pyrogenic reaction, the effect of the adrenergic blocking agent on the pyrogenic reaction was determined in curarized dogs. Under such conditions the major portion of the fever following injection of pyrogen is due to reduced heat loss.[18] Since the curarized dog cannot reduce heat loss by reduction of ventilation or reduction of radiating surface, it may be assumed that vasoconstriction is the mechanism of the fever.

Crystalline d-tubocurarine§ was given intravenously in an initial dose of 1.5 mg/kg followed by hourly intramuscular injections of 0.5 mg/kg. Artificial respiration by means of a Starling-Palmer pump was adjusted to give a ventilation-oxygen consumption ratio of approximately 20. Rectal temperatures were obtained by means of a recording resistance thermometer. Room temperature was maintained at 27 ± 1°C.

Fifteen minutes after curarization 10 dogs were given 3 mg/kg of N-Ethyl-N-(2-bromoethyl)-1-naphthylenemethylamine · HBr by slow intravenous infusion. After a control period of approximately 1 hour these 10 dogs and 13 curarized control dogs were given 50 mcg/kg of pyrogen intravenously.

Data for the 13 control and 10 pre-treated animals are shown in Table II. Several values representative of the pyrogenic reaction are given. The first is the latent period or the period from injection of pyrogen to onset of fever. One effect of the adrenergic blocking agent appears to be significant prolongation of this latent period. The duration of the period of rising temperature is not significantly different in the two groups of dogs. The third value, the maximum increment in temperature during the pyrogenic reaction, is significantly lower in the group of dogs pre-treated with blocking agent. The mean response for the group is 52% less than that of the control. The fourth value, the average increment in temperature during the period of rising temperature, is significantly lower in the group of animals pre-treated with the blocking agent. The mean response of the pre-treated group of animals is 55% less than that of the controls.

Thus the adrenergic blocking drug produces 2 alterations of the pyrogenic reaction in curarized dogs. It delays the onset of the response and reduces its magnitude. The last entry in Table II is a single figure which portrays both of these processes. This figure is the average increment in temperature during the 2 hour period following the injection of pyrogen, and it is significantly lower in the

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§ Supplied by Abbott Laboratories, through the courtesy of Dr. R. K. Richards.

TABLE II.
Pyrogenic Reaction in 10 Curarized (Control) and 13 Curarized Dogs (Pre-treated) with Adrenergic Blocking Agent.

Latent period (min.)		Duration of rising temp. (min.)		Max. temp. post-inj. (°C)		Avg temp. during period of rising temp. (°C)		Avg temp. during 2 hr post-inj. (°C)	
Control	Pre-treated	Control	Pre-treated	Control	Pre-treated	Control	Pre-treated	Control	Pre-treated
20	90	110	230	1.61	1.72	1.01	.87	.73	.08
10	110	220	130	1.89	.89	1.11	.54	.52	.02
20	20	160	250	2.83	2.22	1.60	1.11	.86	.39
20	20	280	90	1.67	1.75	.98	1.16	.58	.93
20	30	110	10	1.61	.06	1.01	.05	.72	.04
20	180	150	10	1.39	.33	.79	.40	.44	.00
20	20	150	100	1.11	.25	.82	.18	.54	.14
20	20	180	30	1.61	.14	1.20	.14	.84	.07
20	30	110	120	1.22	.50	.73	.31	.52	.17
20	90	170	140	1.92	.86	1.42	.43	.88	.04
20		140		3.00		1.92		1.18	
30		160		1.64		1.19		.64	
20		190		1.97		1.23		.62	
Avg									
20	61	163.9	111.0	1.805	.872	1.155	.519	.698	.188
Probability									
<0.01		0.10		<0.01		<0.01		<0.01	
Significance									
High		None		High		High		High	

All temperatures are rectal and are expressed as increments above basal temperature determined during pre-pyrogen control period.

group of animals pre-treated with blocking agent. The average response of the pre-treated group is 73% less than that of the control. On closer inspection of the individual dogs in the group of animals pre-treated with blocking agent, it is apparent that only 2 of them showed febrile reactions of any consequence and the reaction can be said to have been essentially abolished in the remainder.

It is concluded that a potent adrenergic blocking drug reduces the febrile response to the injection of pyrogenic material. In most curarized dogs the reaction is nearly abolished and greatly delayed in onset, but in two of them a nearly normal pyrogenic reaction was observed.

Assuming that the present drug alters the pyrogenic reaction because of its ability to block adrenergic nerves, then partial inhibition of the febrile response to pyrogen by this drug may be interpreted in several ways. The adrenergic blocking action of the drug may be only partial, or adrenergic nerve mediated vasoconstriction may contribute only partially to the pyrogenic reaction.

The febrile response in curarized dog is due in large part to vasoconstriction. Thus, partial reduction of the pyrogenic reaction under these conditions implies either incomplete adrenergic blocking action on the part of the drug or participation in the febrile response of a non-sympathomimetic vasoconstrictor substance.

In line with the latter interpretation are the observations that complete sympathectomy modifies but does not prevent the pyrogenic reaction in the cat[14] and that after complete sympathectomy and adrenal inactivation, the ears of some rabbits still showed delayed vasoconstriction associated with the rise in body temperature.[8]

Summary. A potent adrenergic blocking drug, N-Ethyl-N-(2-bromoethyl)-1-naphthylenemethylamine · HBr, has been shown to reduce and alter the febrile response of normal and curarized dogs to the intravenous injection of a purified pyrogenic material obtained from pseudomonas aeruginosa. This evidence is interpreted as supporting the hypothesis that the pyrogenic reaction is due, at least in part, to a reduction in heat loss caused by adrenergic nerve mediated vasoconstriction in the skin.