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SEVERE IMPAIRMENT OF CHOLINERGIC AND ADRENERGIC RESPONSIVENESS IN *Bordetella pertussis* VACCINATED RATS

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In Western Europe a high percentage of all children of 3 months of age are vaccinated against whooping cough with *Bordetella pertussis*. Post-vaccinal reactions sometimes occur, including serious complications like permanent neurological damage, convulsions, coma and shock (Hannik and Cohen, 1979). Whether the cardiovascular system is primarily involved in the side effects has never been thoroughly investigated.

The present study was carried out to characterize the pharmacological effects on receptor functioning within the autonomic nervous system with respect to blood pressure and heart rate. Male rats (Riv: TOX) weighing 275-325 g, were injected intraperitoneally with either saline or whole cell pertusis vaccine (10^{11} micro-organisms per 100 g body weight). Four days after vaccination the animals were anesthetized with urethane (1 g/kg i.p.) and blood pressure was recorded continuously form a canulated carotid artery. Heart rate was derived from the blood pressure trace by a cardiotachometer. Drugs were infused in a volume of 200 μl over a period of one minute via a cannula in the jugular vein.

In the pertussis-treated animals the blood pressure decrease induced by the selective β_2-sympathomimetic agent salbutamol was significantly reduced while the pressor response evoked by the α_1-adrenergic agonist methoxamine was strongly potentiated (table 1). Moreover, the reflex bradycardia after administration of methoxamine was nearly absent in the vaccinated group.

The pressor response induced by a high dose (100 μg/kg) of the selective α_2-agonist B-HT 920 as well as the depressor response of a low dose of this drug (1 μg/kg) were significantly reduced in the treated group. The bradycardia elicited by both doses of B-HT 920 was profoundly inhibited (table 1).

A pronounced impairment of cholinergic transmission after pretreatment with pertussis vaccine was demonstrated by the complete blockade of bradycardia induced by the muscarinic agent arecoline (table 1). Even nearly toxic doses (> 300 μg/kg) of this agonist in control rats did hardly provoke a negative chronotropic effect in pertussis treated animals. Furthermore the hypotensive effect of arecoline was significantly reduced in the treated group.

Our recent studies demonstrate that a heat-labile component of the pertussis vaccine seems to be the predominant cause of the changes in autonomic receptor function since after heating of the vaccine at 1 h (80°C) the effects completely disappeared. Interestingly, it was observed that the diastolic blood pressure was significantly lower in pertussis-treated animals than in control animals. However, differences in basal values do not influence the results presented (to be published).

These results might suggest a severe impairment of vascular β_2-, α_2-adrenergic and muscarinic receptors upon treatment with pertussis vaccine. Moreover, a muscarinic block in the heart was

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TABLE 1

Effect of different agonists upon diastolic blood pressure and heart rate in urethane-anesthetized rats 4 days after either saline or *B. pertussis* treatment. Absolute control values for diastolic pressure amounted to 89 + 5 mm Hg (n = 30) for the control group and 69 ± 4 mm Hg (n = 30) for the treated group respectively. Initial values for heart rate were 383 ± 15 b.p.m. (n = 30) and 398 ± 9 (n = 30) for control respectively treated rats respectively.

Drug	Dose (μg/kg)	% change in diastolic blood pressure		% change in heart rate	
		Control	Pertussis-treated	Control	Pertussis-treated
Salbutamol	10	−33 ± 2	−9 ± 2 [a]	−4 ± 1	0
B-HT 920	1	−18 ± 4	−8 ± 3 [a]	−8 ± 2	0 [a]
B-HT 920	100	+39 ± 6	+15 ± 2 [a]	−15 ± 3	−4 ± 1 [a]
Arecoline	100	−56 ± 5	−17 ± 2 [a]	−61 ± 5	−4 ± 1 [a]

[a] Significantly different ($P < 0.05$) from respective control estimated by Student's t-test. Each drug was tested in 6 rats ($\bar{x} \pm$ S.E.M.). + = increase; − = decrease.

evident. It seems likely that the α_2-adrenergic hyporesponsiveness is not only restricted to peripheral vascular receptors but might occur at a central level as well, since the centrally mediated hypotensive effect and bradycardia induced by low doses of B-HT 920 was antagonized. The absence of a reflex bradycardia after administration of methoxamine points towards an interrupted baroreceptor reflex which might be well explained by the prominent atropine-like action of pertussis vaccine.

The precise mechanism involved in the impairment of the autonomic responsiveness remains to be calculated. However, since a c-AMP pathway appeared to be a common feature for cholinergic, α_2- and β_2-adrenergic transmission (Hazeki and Ui, 1981) a defect in this pathway rather than specific actual receptor blockade can be suggested. Since cholinergic transmission is also known to be mediated by a c-GMP pathway a disturbance at this level cannot be excluded as yet. The potentiated (opposite) effect of methoxamine in pertussis treated rats cannot be explained at present, since α_1-receptor responses possibly are not mediated by the c-AMP-pathway.

In conclusion, the present study extends the current information about various biological effects due to pertussis-induced β-adrenoceptor blockade (Munoz and Bergman, 1978; Szentivanyi, 1968). The results demonstrate that in the circulatory system of the rat pertussis vaccine produces β_2- and α_2-adrenergic and cholinergic hyporesponsiveness accompanied by α_1-adrenergic hyperresponsiveness. It is suggested that disturbance of signal transfer from adenylate cyclase-coupled receptors to system(s) generating intracellular c-AMP might be the underlying cause.

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References

Hannik, C.A. and H. Cohen, 1979, Pertussis vaccine in The Netherlands in: C.R. Manclark and J.C. Hill (eds.), International Symposium on Pertussis (U.S. Government Printing Office, Washington D.C.) p. 279.

Hazeki, O. and M. Ui, 1981, Modification by islet-activating protein of receptor-mediated regulation of cyclic AMP accumulation in isolated rat heart cells, J. Biol. Chem. 256, 2856.

Munoz, J.J. and R.K. Bergman, 1978, *Bordetella pertussis*: immunological and other biological activities (Marcel Dekker, New York) p. 235.

Szentivanyi, A., 1968, The beta-adrenergic theory of the atopic abnormality in bronchial asthma, J. Allergy 42, 203.