PLATELET FUNCTIONS IN BRONCHIAL ASTHMA

THESIS

Submitted in Partial Fulfilment for The M.D. Degree in INTERNAL MEDICINE

BY

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1985
TO MY DEAR FATHER
THIS WORK IS DEDICATED
ACKNOWLEDGEMENT

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ABBREVIATIONS

PAF : Platelet activating factor.
cAMP: Cyclic adenosine monophosphate.
SC : Sodium cromoglycate.
SRS-A: Slow-reacting substance of anaphylaxis.
H₁ : Histamine one.
H₂ : Histamine two.
M.W.: Molecular weight.
IgE : Immunoglobulin E.
IgG : Immunoglobulin G.
C.M.I.: Cell-mediated immunity.
D.T.H.: Delayed-type hypersensitivity.
Ca : Calcium.
GP : Glycoprotein.
ADP : Adenosine diphosphate.
PDGF: Platelet-derived growth factor.
TGF : Transforming growth factor.
EGF : Epidermal growth factor.
DTS : Dense tubular system.
OCS : Open canalicular system.
CPU-S: Colony-forming-units-spleen.
CPU-Meg: Colony-forming-units-megakaryocytes.
DMS : Demarkation membrane system.
MRC : Megakaryocytes.
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CFU-Meg: Colony-forming-units-megakaryocytes.
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INTRODUCTION AND AIM OF WORK
Nicholas et al. (1981) suggested that the platelets have a release reaction referring to the secretion of certain substances stored in the intracellular organelles. Serotonin, a potent bronchoconstricting substance, was demonstrated to be one of these substances.

In 1980, Arnoux et al., succeeded in isolating platelet-activating factor (PAF-acether) from rabbit, rat and human alveolar macrophages stimulated with the Ca++ ionophore A 23187. In 1983, Denjean et al., reported that PAF-acether had a potent bronchoconstrictive effect and can be responsible for the acute attacks of bronchoconstriction.

The aim of the present work is to study the blood platelets in bronchial asthma. Different types of bronchial asthma will be studied. Variation in the platelet shape, count, and functions with the changes in the physiologic state of the lungs will also be studied.

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REVIEW
OF
LITERATURE
BRONCHIAL ASTHMA

Definition:

Although major advances have been made in recent years to clarify the immunopharmacology and pathophysiology of asthma, still there is no point in attempting to seek agreement on definitions for the clinical use of the word asthma (Corrao, 1980).

In terms of function it could be regarded as a state of airway obstruction rather than a disease, and that being dynamic and reversible (Turner-Warwick, 1962).

Asthma has been also defined as a disease characterized by wide variations over short periods of time in resistance to flow in the airways of the lungs (Turner-Warwick, 1978).

The definition did not include any statement regarding aetiology, host characteristics, immunological or neurological mechanisms since triggering factors were numerous and target organ responses were variable (Turner-Warwick, 1972).
Asthma could be defined also as intermittent, rapidly developing and spontaneously resolving bronchial obstruction, always consisting of bronchial muscular spasm, but sometimes, it was also associated with oedema and hypersecretion. (Herzheimer, 1975).

Although the attacks of asthma were characteristically intermittent and reversible, they might become persistent with only minor variations. In this case, the diagnosis would be made by indirect evidence that wide variability has been presented in the past, and confirmed by later observation of the clinical course including the response to treatment. (Scadding, 1976).
RECEPTOR PHARMACOLOGY OF RESPIRATORY SMOOTH MUSCLE

Table (1) summarizes much of the current knowledge concerning airway smooth muscle pharmacology.

A) Cholinergic receptors:

Throughout the respiratory tree, cholinergic stimulation is a potent constrictor influence. However, distal airways are not innervated by parasympathetic nerves, and since acetylcholine does not circulate systemically the role of cholinergic receptors in peripheral airways remained undefined. (Nadel et al., 1971).

B) Adrenergic receptors:

Both alpha and beta-adrenergic receptors are present. The beta-adrenergic receptors on airway smooth muscle are almost exclusively of the beta_2-adrenergic subtype, the pharmacologic stimulation of which promotes smooth muscle relaxation and airway dilatation. Catecholamines do reach the systemic circulation as a result of
adrenal secretion, therefore, unlike the distal
cholinergic receptors, the beta$_2$-adrenergic recep-
tor of distal airways can be stimulated under
physiologic conditions (Leff and Munoz, 1981). The
endogenous neural transmitter of sympathetic activ-
ity is norepinephrine. Despite the relatively
weak beta$_2$-adrenergic activity of this catecholamine,
norepinephrine has been shown to cause substantial
airway smooth muscle relaxation in canine trachea
in situ (Himori and Taira, 1976).

Prior investigations have shown that stimulation
of sympathetic nerves that directly innervate res-
piratory airways causes very little airway relaxa-
tion. It has been suggested that physiologic symp-
athetic influences on bronchomotor tone are of
little significance (Kneussl and Richardson, 1978).
However, these studies failed to take into account
adrenal secretion, which may be responsible for
at least 80 percent of the sympathetic bronchodil-
lator response (Leff and Munoz, 1981).
On the opposite side of beta-adrenergic receptors, alpha-adrenergic receptors in airway smooth muscle promote bronchoconstriction.

Under physiologic conditions, both alpha- and beta-adrenergic stimulation occur simultaneously, since norepinephrine and epinephrine possess both intrinsic alpha- and beta-adrenergic activity. Because beta adrenergic receptor density greatly outweigh alpha adrenergic effects, sympathetic stimulation resulting from either direct innervation or endogenous circulating catecholamines causes net relaxation of airway smooth muscle. (Leff and Muncz, 1981).

C) Non-adrenergic inhibitory nerves:

A class of non-adrenergic inhibitor nerves has been defined in some species including man. Airway relaxation caused by these nerves is not antagonized by propranolol, and this system is therefore, distinct from the sympathetic nervous system. The neurotransmitter has been thought to be a purine (Richardson and Beland, 1976). However, Irvin et al. (1980) suggested that adenosine analogues may not be the
mediators responsible for non-adrenergic inhibition of bronchomotor tone. There is also no distinct evidence that the non-adrenergic inhibitory system serves a physiologic homeostatic function in antagonizing bronchoconstriction.

* * *
<table>
<thead>
<tr>
<th>System</th>
<th>Effect on Airway Smooth Muscle (SM)</th>
<th>Airways Innervated</th>
<th>Humoral Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasymathetic</td>
<td>Constrictor</td>
<td>&gt; 9 generations (Vagus nerve); peripheral airways not innervated</td>
<td>All airways</td>
</tr>
<tr>
<td>Histamine</td>
<td>Constrictor</td>
<td>No direct innervation</td>
<td>Histamine is released from respiratory mast cells; tissue concentration of histamine increases from trachea to periphery</td>
</tr>
<tr>
<td>H₁</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H₂</td>
<td>May partially inhibit mast cell release of histamine; may have a dilator effect on human airway SM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathetic alpha (α₁, α₂)</td>
<td>Constrictor</td>
<td>~6 generations; not significant without beta-blockade</td>
<td>Major resistance airways; significance in distal airways unknown; causes constriction after beta-blockade</td>
</tr>
<tr>
<td>Beta₄</td>
<td>Dilator</td>
<td>~3 generations; not of major importance</td>
<td>All airway SM. Causes substantial bronchodilation resulting from adrenal secretion</td>
</tr>
<tr>
<td>Non-adrenergic inhibitory</td>
<td>Dilator</td>
<td>Major resistance airways? Others?</td>
<td></td>
</tr>
</tbody>
</table>

Alan 1982.