BIOCHEMICAL BASIS OF INFLAMMATION WITH SPECIAL REFERENCE TO ACUTE BACTERIAL MENINGITIS

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Bacterial meningitis (BM) in children still remains a diagnostic and therapeutic challenge in clinical practice. Several recent investigations in experimental models and human beings have enhanced the knowledge of the biochemical basis of BM. This has helped to understand the altered pathophysiology and offer possible therapeutic interventions in the future(l-3). These altered events result in the development of brain edema, increased intracranial pressure, reduced cerebral blood flow and brain injury(2). The agents involved in the mediation of the inflammatory processes in bacterial meningitis are listed in *Table I.*

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Received for publication: April 28, 1993; Accepted: February 23, 1994

I. Bacterial Products

The bacterial capsule, cell wall and lipopolysaccharides are implicated in the virulence of organisms causing BM. The bacterial capsule contributes to the invasiveness of the pathogens by evading their recognition and clearance by the host cells. Following bacterial cell lysis, the bacterial products; peptidoglycans and teichoic acid from gram positive, and lipopolysaccharides to Gram negative organisms are released into the CSF(l). These result in transient enhancement of inflammation, increased CSF permeability and further production of inflammatory mediators(2,4). These products also activate factor XII of the coagulation cascade and thus may lead to their consumption and disseminated intramuscular coagulation(5).

II. Inflammatory Mediators

(i) *Tumor Necrosis Factor α (TNF α)*

Recent evidences point to the growing family of cytokines which act as critical agents in CSF inflammation. These include tumor necrosis factor (Cachectin) and Interleukin-1 (IL-1) produced by the tissue macrophages, microglial cells of the brain and the Kupffers cells of liver(l,2).

The net effect of TNF ***a*** depends upon its concentration and its interaction with other inflammatory mediators. In physiologic concentration it helps in tissue healing, while excessive amounts may contribute to fatal endotoxemia(l,6). TNF ***a*** alongwith IL-1 is responsible for the passage of neutrophils into the CSF(1,2). TNF ***a*** becomes detectable early in CSF in BM caused by *S. pneumoniae, H. influenzae, N. meningitidis* and other Gram negative enteric

TABLE I—*Inflammatory Mediators in Acute Bacterial Meningitis*

1. Bacterial cell wall components
   - Capsule, cell-wall and lipopolysaccharides.
2. Inflammatory mediators
   - Tumor necrosis factor (Cachectin)
   - Interleukin 1 (IL-1)
   - Platelet activating factor (PAF)
   - Arachidonic acid metabolites
   - Others: Interleukins 6 & 8, macrophage inflammatory proteins, complement C 5a, amino acids.
3. Polymorphonuclear leukocytes.

organisms. High CSF levels of TNF *a* in BM have been associated with the occurrence of seizures, the exact cause of which is unclear at present(3). TNF *a* is not found in the CSF in viral meningitis or in CSF without infection(7).

(ii) Interleukin-1 (IL-1)

The cytokine, Interleukin-1, is believed to be one of the important mediators of tissue response to microbial invasion. It is produced by both the endothelial cells and the CNS macrophages. It was formerly known as endogenous pyrogen and has numerous actions resulting in fever, leucocytosis and increased acute phase reactants in BM(1,2). Two types of Interleukins: IL-la and IL-1/3, have been identified in humans and CSF levels of IL-lj3>500 pg/ml at the time of diagnosis have been reported to be associated with neurologic sequelae(l).

(iii) Platelet Activating Factor (PAT)

PAF is a glycerophosphocholine derivate and causes chemotaxis, platelet and neutrophil aggregation, increased vascular permeability and triggering of coagulation cascade with resultant neuronal damage(l,2).

(iv) Arachidonic Acid Metabolites

These are formed by the phospholipase A2 activation of membrane phospholipids of vascular endothelium and polymorphonuclear cells. This pathway leads to the production of Prostaglandins E2 and 12, thromboxanes and leukotrienes(l). TNF and IL-1 induce phospholipase A2 activity triggering the formation of these metabolites(l,5). High concentration of PGE2 in CSF correlates directly with duration of fever and CSF cell count, proteins and lactate levels(l).

(v) *Other Mediators*

The other mediators include complement factor C5a, interleukins 6 and 8, and other macrophage proteins, C5 acts as a chemotactic agent for WBC influx in CSF while the IL-6 production is induced by IL-1 and is considered to be potent agent for acute phase reactants in bacterial infections(l,8).

The present evidence also suggests that certain excitatory amino acids (glutamate

and aspartate) are associated with the cell excitation, neuronal calcium influx resulting in brain edema and injury(l).

III. Polymorphonuclear Leukocytes (PML)

The **PML** release the cytokines in response to the bacterial products which later act as inflammatory mediators. Thus, PML along with the endothelial cells and macrophages are the cellular targets which are in-between the bacterial products and the inflammatory mediators in the pathway of inflammation. Capillary endothelium- PML adherence is promoted by the TNF and IL-1. PML then migrate through the intercellular junctions by enzymatic digestion and this is turn increases the protein influx from the serum into the CSF(1,5).

In summary, the release of the bacterial products *(e.g.,* endotoxin, teichoic acid) stimulates the release of cytokines (TNF and IL). These cytokines promote endothelium and WBC interaction with the comcomitant production of PAF, PFE2 *etc.* These ongoing inflammatory changes produce damage to the vascular endothelium, alter metabolism, cause brain edema and ultimately result in brain injury(l,5) *(Fig. 1).*

Future Trends

The emerging knowledge of inflammatory mediators is likely to lead to result in other therapeutic strategies that may be effective in neutralizing endotoxin and re-

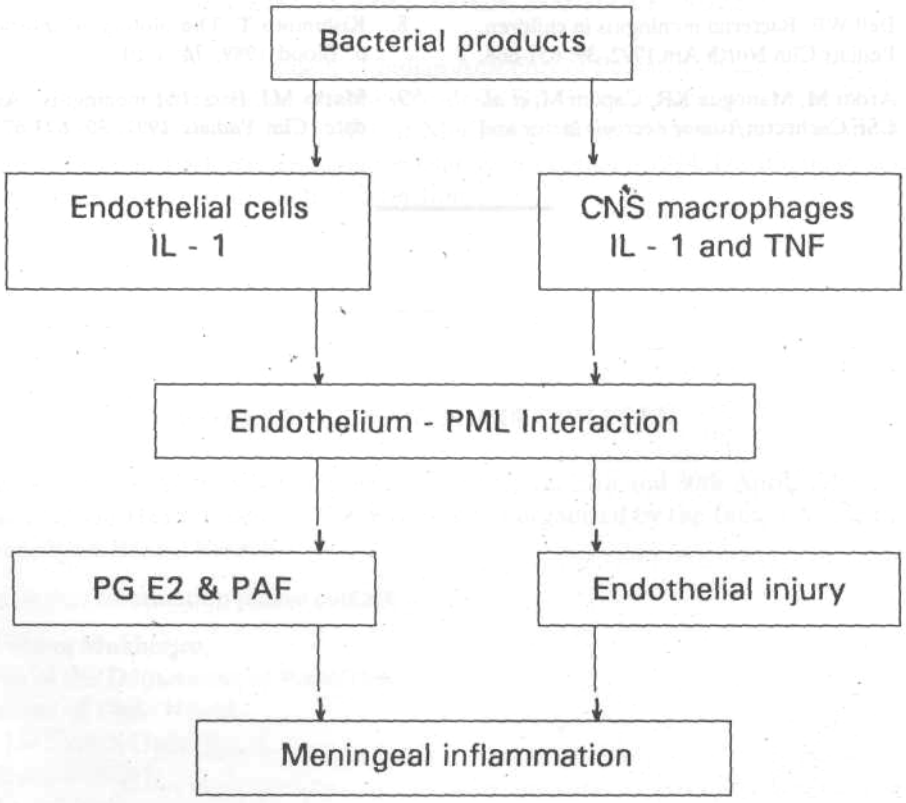

Fig. 1. Pathway for inflammation in acute bacterial meningitis.

duee further tissue injury(2,8,9). Presently, the beneficial effects of dexamethasone in *H. influenzae* meningitis are attributable to the reduction in cytokine formation in CSF(2,9). The potential therapies for future are those which reduce inflammatory mediators. Examples of these are monoclonal antibodies against cytokines, indomethacin and pentoxifylline (methyl xanthine derivative) which may improve the clinical outcome of bacterial meningitis(l,2,6).

REFERENCES

1. Mertsola M, McCracken GH Jr. Molecular pathophysiology of bacterial meningitis. Current concepts and therapeutic implications. J Pediatr 1990, 116: 671-684.
2. Bell WE. Bacterial meningitis in children. Pediatr Clin North Am 1992, 39: 651-668.
3. Arditi M, Manogue KR, Caplan M, *et al.* CSF Cachectin/tumor necrosis factor and platelet activating factor concentrations and severity of bacterial meningitis in children. J Infect Dis 1990, 162: 139-147.
4. Syrogiannapoulous GA, Hansen EJ, Erwin AL, *et al. H. influenzae* Type b lipooligosaccharide indu ces meningeal inflammation. J Infect Dis 1988, 157: 237-244.
5. Glauser MP, Zanetti G, Baumgarther JD, Cohen J. Septic shock pathogenesis. Lancet 1991, 338: 732-736.
6. Tracey KJ, Vlassare H, Cerami A. Cachectin/tumor necrosis factor. Lancet 1989, 1: 1122-1125.
7. Nadal D, Leppert D, Frei K, Fallo P, Lamche H, Fontana A. TNF factor in infectious meningitis. Arch Dis Child 1989, 62: 1274-1279.
8. Kishimoto T. The biology of interleukin 6. Blood 1989, 74: 1-10.
9. Marks MJ. Bacterial meningitis.: An up date. Clin Pediatr 1991, 30: 673-675.