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Reprogramming the Host Response in Bacterial Meningitis: How Best To Improve Outcome?

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INTRODUCTION

Sixty years after their discovery, antibiotics remain virtually the only weapons against bacterial meningitis (126). Antibiotic therapy has changed meningitis from a uniformly fatal disease to a frequently curable one. However, the outcome is still often unfavorable, with a mortality of 5 to 10% and permanent neurologic sequelae occurring in 5 to 40% of survivors, depending on patient age and pathogen (5, 9, 31, 44). Recent scientific progress has resulted in an effective polysaccharide-protein conjugate vaccine against *Haemophilus influenzae* that has reduced the current incidence of bacterial meningitis to ≈4.0 per 100,000 population in most developed countries (140, 161). There are also effective conjugate vaccines against *Streptococcus pneumoniae* and *Neisseria meningitidis* type C (87, 145). Maternal immunization with group B streptococcal (*Streptococcus agalactiae)* conjugate vaccine may present a feasible strategy to reduce neonatal group B streptococcal disease incidence (14, 103). Development of a group B meningococcal conjugate vaccine has been hindered by the potential risks of autoantibodies that cross-react with glycosylated host antigens. New vaccine candidates discovered during the sequencing of the group B meningococcal genome offer promise of an effective and safe vaccine against group B *N. meningitidis*, which would result in a significant further reduction in morbidity and mortality from bacterial meningitis (52). At present, however, physicians depend on early antibiotic therapy in the remaining cases of meningitis to avert dismal outcomes (6, 127, 166).

Two-thirds of meningitis-related deaths are attributable primarily, or at least in part, to central nervous system complications; the remainder result from systemic complications, such as septic shock (113). Increased insight into the pathophysiology of bacterial meningitis has shown that the inflammatory host response to bacterial products continues after the bacteria are killed with antibiotics. This host response regrettably affects host tissues and contributes significantly to central nervous system injury (83, 90, 97, 137). Thus, the addition of anti-inflammatory or neuroprotective agents would be expected to protect against tissue injury associated with meningeal inflammation. While this is a logical hypothesis, real-life experience with modulation of the host inflammatory cascade, such as in clinical sepsis trials, has yielded mixed results and demonstrated that the setting is so complex that predicting the benefit of any intervention is very tricky (39).

Adjuvant use of corticosteroids in clinical trials in bacterial meningitis has demonstrated that there is an opportunity to protect against tissue injury and thereby improve outcome. Corticosteroids have been used against bacterial meningitis since the 1950s, even though initial clinical studies with meth-

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ylprednisolone failed to demonstrate any benefit in children with meningitis; it is important to note that no mention was made of hearing evaluation in these patients. As concluded in a recent meta-analysis, adjuvant dexamethasone therapy, which is more potent than methylprednisolone, in children with *H. influenzae* type b meningitis significantly reduces neurologic sequelae, most notably severe hearing loss (number needed to treat, 12) (89). Extending the efficacy of corticosteroids to adults and to meningitis due to other pathogens has remained much debated, however, because the results from several small trials showed no clear benefit of this intervention.

Following the introduction of the *H. influenzae* type b vaccine, the clinical use of corticosteroids in bacterial meningitis became more controversial, and additional clinical trials of sufficient size were warranted to resolve this issue (30). A recently completed, large clinical trial in adult patients shows that early dexamethasone treatment initiated before or with the first dose of antibiotics improves outcome (25). The effect was especially strong in patients with pneumococcal meningitis (number needed to treat 4 to 10). Adjuvant dexamethasone treatment did not result in an increased risk of serious adverse events, such as gastrointestinal bleeding. Studies in the developing world, where presentation to hospital is often delayed, showed that adjuvant steroid treatment could not improve outcome in this setting (96, 123). These results indicate that corticosteroids are only beneficial when administered early in the course of the disease.

The clinical efficacy of corticosteroids is proof of the principle that reduction of injury to the central nervous system can be achieved by modulation of the host response. Other avenues of benefit may also exist. For example, although tissue injury, such as disruption of the blood-brain barrier, cerebral edema, and mild neuronal injury, always occurs in meningitis, some patients survive the disease and recover fully. This illustrates the natural capacity of the body to repair injured tissues, at least in part. Strengthening of the body's repair systems may present a second major avenue to achieving benefit and reducing permanent tissue damage in the central nervous system. The molecular dissection of cell maintenance and repair mechanisms has given important leads to therapies that might enhance the body's innate repair response.

CELLULAR DYSFUNCTION IN MENINGITIS

Endothelium of the blood-brain barrier

The cerebral microvascular endothelium has unique ultrastructural properties, such as continuous intercellular tight junctions and a slow rate of fluid endocytosis, that enable it to function as a high-resistance barrier to circulating macromolecules, also called the blood-brain barrier. Disruption of the blood-brain barrier is a hallmark event in the pathophysiology of bacterial meningitis. Disturbance of cerebral endothelial function results in the development of vasogenic cerebral edema in 30% of cases and cerebral herniation in 6 to 8% of clinical cases in some series (113). Cerebral edema and resultant increased intracranial pressure impair tissue perfusion and are associated with a high risk of death or severe neurologic sequelae. Bacterial toxins in blood or cerebrospinal fluid (CSF), such as gram-negative lipopolysaccharide (LPS), gram-positive peptidoglycan, and cytotoxins, engage Toll-like receptors of endothelia and activate their downstream signaling cascades. The endothelial cells then release mediators, such as tumor necrosis factor alpha (TNF-α), nitric oxide, and matrix metalloproteinase-2 (MMP-2), which increase endothelial permeability (63, 76, 125). The endothelium expresses multiple leukocyte adhesion molecules and presents chemotactic factors such as interleukin-8 (IL-8) when activated by inflammatory mediators. This combination promotes neutrophil adherence and transendothelial migration. Upregulation of tissue factor on the endothelial surface induces a procoagulant state and stimulates thrombus formation. Cerebrovascular events such as thrombosis and hemorrhage are frequently found in autopsy cases (113).

Endothelial activation and vascular inflammation have a negative impact on cerebral blood flow. Vasculitis characterized by subintimal infiltration of cerebral blood vessels by neutrophils causes narrowing of the vascular lumen and vasospasms (112, 113). Release of vasoconstrictive agents, such as the endothelins, and vasodilatory agents, such as nitric oxide, causes loss of autoregulation of cerebral perfusion pressure. In the face of systemic hypotension, these events further decrease cerebral perfusion (121).

The Neuron

In bacterial meningitis, hypoxia, neurotoxic bacterial products, and host mediators combine to cause neuronal injury. Whether the damage is bacterial or leukocyte derived, the final toxic element is often the free radical. These oxidants, including reactive oxygen intermediates and reactive nitrogen intermediates, have direct toxic effects on neurons (53). Activation of apoptotic and necrotic cell death pathways causes neuronal loss that may result in permanent neurologic sequelae or even death (63, 76, 77, 99, 114, 125, 151, 153). Neuronal apoptosis in the granular layer of the hippocampal dentate gyrus and necrosis of pyramidal cells in the hippocampus are frequently found in the brains of patients who died from bacterial meningitis. Studies applying magnetic resonance imaging in survivors of bacterial meningitis often demonstrate hippocampal atrophy (37).

The cascade of pathophysiologic events during bacterial meningitis is summarized in Table 1. Focal damage in other brain regions such as the neocortex and brain stem is less common. Long-term sequelae due to these processes of neuronal death include deafness, intellectual and cognitive impairment ranging from severe intellectual disability to educational deficits and behavioural problems, and less commonly epilepsy, spasticity, or focal neurologic deficits. (9, 12, 15, 24, 44, 140).

POTENTIAL INTERVENTIONS

Protect against Injury

Neutralize bacterial toxins. Clinical outcome in bacterial meningitis is directly related to concentrations of bacteria and bacterial antigens in the CSF (34, 90, 137). Because the CSF contains few humoral and cellular defenses, bacteria multiply freely before being detected, releasing toxic components such as lipopolysaccharide (LPS), peptidoglycan, and teichoic acid,

TABLE 1. Phases in the pathophysiology of bacterial meningitis

Time (h postinfection)	Pathophysiologic events	Clinical symptoms
0	Bacteria and bacterial products accumulate in CSF	None
4	Release of inflammatory mediators and cytokines	Fever
8–24	Blood-brain barrier disruption; development of cerebral edema; transendothelial migration of leukocytes; more proinflammatory and toxic mediators; followed by impaired cerebral blood flow, elevated intracranial pressure, and vasculitis	Elevated CSF protein; meningism/neck stiffness; elevated CSF leukocytosis; possible systemic complications; followed by altered mental status, focal symptoms, and seizures
24–48	Neuronal injury	Focal symptoms; hearing loss; paralysis; cognitive impairment; death

which elicit a strong inflammatory response. Bacterial hemolysins and cytotoxins have direct lethal effects on host tissues. Bacterial lysis associated with killing by bactericidal antibiotics releases a pulse of toxic bacterial components comparable to the Jarisch-Herxheimer phenomenon in syphilis (38, 155). One should be aware, however, that the amount of toxins released from untreated bacteria that continue to grow is considerably greater (38). One strategy to minimize exposure of the brain to bacterial toxins is to minimize the release of toxic bacterial compounds. It is possible to lower the amount of bacterial toxins released by choosing bactericidal antibiotics that act by inhibiting RNA or protein synthesis or DNA replication (rifamycins, macrolides, clindamycin, ketolides, and quinolones) (16, 100). However, assessment of the effectiveness of different antibiotic therapies is challenging, and at present insufficient data are available to recommend a change in empirical antibiotic therapy (67, 126).

Neutralization of proinflammatory bacterial products is a second logical strategy to prevent harmful effects. However, in practice the potential of this approach is limited because no single agent neutralizes both gram-positive and gram-negative bacterial products. Preliminary studies evaluating antibody neutralization of the gram-positive pneumococcal cell wall have not been followed by successful clinical studies (153). Neutralization of the lipid A moiety of LPS in gram-negative bacterial meningitis by intrathecal administation of neutralizing antibodies, polymyxin B, or recombinant fragments of bactericidal/permeability-increasing protein (rBPI) (an endogenous LPS-neutralizing protein) has been studied in several animal models of bacterial meningitis. All these agents had only limited efficacy when administered at clinically relevant timepoints in live-infection models (150; I. Lutsar, I. R. Friedland, H. Jafri, L. Wubbel, W. Ng, F. Ghaffar, and G. H. McCracken, Jr., Abstr. 38th Intersci. Conf. Antimicrob. Agents Chemother., abstr S117-B B-38, 1998). Therefore, this type of adjuvant treatment is likely to fail in clinical practice, most probably because the treatment is given too late following the unleashing of the inflammatory cascade. This conclusion seems to be supported by the disappointing results of clinical trials evaluating LPS neutralization in gram-negative sepsis (43, 79, 174).

For most pathogens, the bacterial toxins that trigger host cell apoptotic responses have not been identified. Studies with pneumococcus have identified two toxins responsible for permanent loss of neurons in the hippocampus. Pneumolysin, a pore-forming toxin, and hydrogen peroxide produced by the bacterium induce apoptosis by the release and translocation of mitochondrial apoptosis-inducing factor (19). For group B streptococcus, an important pathogen in neonatal meningitis, hemolysin has recently been identified as the toxin that triggers host cell apoptosis (129). Since these toxins do not have structural homology, a strategy to neutralize them has not been forthcoming. Targeting of bacterial toxins is summarized in Fig. 1.

Reprogram the inflammatory response. The highly evolved systems of innate and adaptive immunity generally allow the host to detect microbial invaders and to initiate an inflammatory response to dispose of the invaders without destroying host tissues. However, in central nervous system infection, because neuronal cells have little regenerative capacity, damage to host tissues as a side effect of the inflammatory response is more prominent. Experimental work has demonstrated that the presence of dead bacterial material in the CSF elicits such a strong inflammatory response that severe neuronal injury or death may result. Since modern antibiotic therapy ensures rapid killing of invading bacteria in clinical patients, some components of the inflammatory response may no longer serve a critical role in an effective inflammatory response. When making a comparison to warfare, it is like bombing a city and destroying it once the enemy has already been defeated. Obviously this does not mean the whole sophisticated immune system has become useless. Just attenuating or reducing the

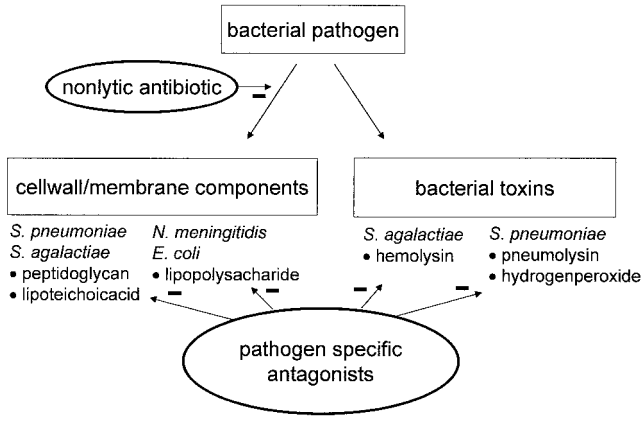

FIG. 1. Targeting of bacterial cell wall, cell membrane components, and toxins to prevent injury. Use of nonlytic antibiotic agents may minimize the release of toxic components following initiation of antibiotic therapy. Different organisms and different bacterial substances require separate neutralizing antagonists, making a uniform strategy difficult to design.

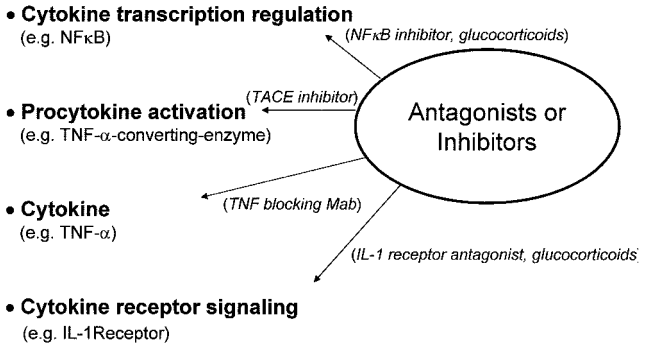

FIG. 2. Interventions aimed at cytokines may target different levels: regulation of cytokine production via interference with transcriptin factors, interference with procytokine activation by proteolytic enzyme inhibition, direct blocking of the cytokine, and interference with the cytokine receptor or signaling pathway.

immune response will delay effective clearance of bacterial debris and tissue healing. However, within the context of modern bactericidal antibiotic therapy, reprogramming the inflammatory response, leaving some helpful components in place and changing other harmful components of the cascade, may improve outcome. What exact balance in the inflammatory response constitutes "good" versus "bad" is hard to predict.

(i) Reset the cytokine balance. Cytokines are key regulators of the immune response, switching on and off whole cascades of events. These cytokines are released by macrophages, microglia, astrocytes, ependyma, and endothelia. Four major avenues exist to intervene in the inflammatory response at the cytokine level: inhibition of transcription of the cytokine gene, blockage of the cytokine itself or by cleavage to activate the procytokine, and antagonism of the cytokine receptor and its downstream signaling pathways, as summarized in Fig. 2. The maximum benefit of interference with any cytokine can be predicted by studies in knockout mice lacking the specific cytokine gene or transgenic mice displaying altered expression of a certain mediator.

Neutralizing cytokine antibodies and endogenous cytokine inhibitors have been tested in animal models as adjuvant agents. TNF-α and IL-1β antagonists (antibodies) reduced meningeal inflammation in most animal models when instilled into the CSF space at the beginning of the infection (128, 135, 149). Endogenous inhibitors of cytokines, such as recombinant IL-1 receptor antagonist and soluble TNF receptor, were effective against cytokine-induced meningitis but failed to have a significant effect against LPS-induced meningitis. This important finding highlights the functional overlap between mediators (104) that frustrates the design of simple therapeutic interventions. This could perhaps have been predicted by results in knockout mouse models. In a live pneumococcal meningitis model without antibiotic therapy, knockout mice deficient in TNF-α (but still expressing TNF-β) did not show any decrease in meningeal inflammation and experienced greater growth of *Streptococcus pneumoniae* in the bloodstream, yet studies in TNF receptor-deficient mice did show decreased meningeal inflammation but no benefit in terms of reducing neuronal injury (172). These opposite results again demonstrate the functional overlap between different mediators and the probable conclusion that individual targets within the cytokine cascade are not currently a fruitful area of pursuit in the development of adjuvant therapies for meningitis.

An alternative target for cytokine inhibition may be found in enzymes involved in the activation of procytokines. TNF-α is produced as membrane-associated pro-TNF-α and cleaved to its active soluble form by TNF-α-converting enzyme, a metalloproteinase closely related to matrix metalloproteinases. Experiments in the neonatal rat model of bacterial meningitis showed significantly downregulated CSF levels of TNF-α by combined inhibition of matrix metalloproteinases and TNF-α-converting enzyme with a broad-spectrum hydroxamic acid-based metalloproteinase inhibitor (BB-1101). In addition, the incidence of seizures, mortality, and neuronal injury was significantly decreased (71). Current inhibitors of TNF-α-converting enzyme have a low potency, necessitating the use of high doses; however, it is expected that modifications will result in improved agents (10).

Similarly, IL-1β is formed by the cleavage of its precursor pro-IL-1β by caspase-1. Treatment of rabbits and rats with experimental pneumococcal meningitis with the caspase-1 inhibitor z-VAD-fmk (benzyloxycarbonyl-Val-Ala-Asp-fluoromethyl ketone) resulted in a reduced inflammatory response, with lower fever, CSF white blood cell counts, and intracranial pressure, fewer cerebrovascular changes, and less neuronal apoptosis. This response is probably affected at least partially by reduced IL-1β activation (64). Caspase-1 is further involved in activation of the apoptotic cell death pathway (17).

Although disruption of the activity of individual cytokines has been disappointing in gaining neurological benefit in meningitis, several avenues have suggested that broader-spectrum interventions have promise. These approaches include enhancing the native anti-inflammatory cascade, inhibiting several cytokines by single agents, and blocking global transcription factors. Anti-inflammatory cytokines such as IL-10 and transforming growth factor beta downregulate the host inflammatory response. Therapeutic administration of IL-10 has been studied in animal models. Early intravenous administration of IL-10 was consistently effective in modulating meningeal inflammation (59, 105), and transforming growth factor beta inhibited cerebrovascular changes and brain edema in bacterial meningitis (115). Since these downregulators have effects on many positive inflammatory cascades, they offer more potential for benefit in a true-life, clinical setting.

This concept can be modeled pharmacologically in the case of thalidomide. In addition to its well-known sedative and teratogenic effects, thalidomide possesses significant and unique anti-inflammatory activities. It inhibits TNF-α and IL-8 production by LPS-stimulated monocytes but does not interfere with the production of IL-6 and IL-1β. Experiments have shown that thalidomide can reduce peak CSF TNF-α levels by 30 to 50% in conjunction with sustained inhibition of CSF pleiocytosis (21). In animal models of tuberculous meningitis, thalidomide greatly enhanced survival and decreased brain pathology (152). However, a clinical trial of thalidomide as an adjuvant treatment of tuberculous meningitis was halted prematurely because of concern about adverse effects. A 6-month outcome analysis of the 47 children included in the study showed a worse outcome for children receiving adjuvant thalidomide therapy (138, 139).

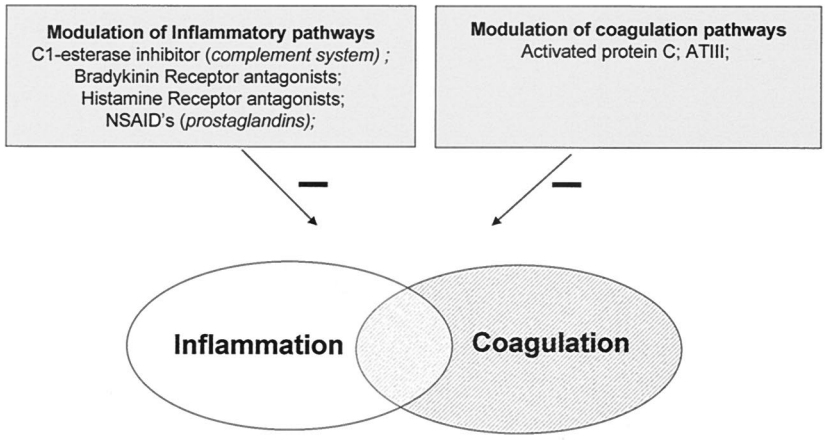

FIG. 3. Interference with inflammatory pathways may target a whole spectrum of noncytokine mediators. Several mediators influence both the inflammatory and coagulation cascades. NSAID's. nonsteroidal anti-inflammatory drugs. ATIII, antithrombin III.

Intervention at the transcription level regulates the expression of many cytokines at once. NF-κB is an important transcription factor, first recognized for its role in the immune system. Various anti-inflammatory drugs including corticosteroids and anti-inflammatory cytokines such as IL-10 inhibit the NF-κB pathway. In resting cells, the NF-κB heterodimer remains in the cytoplasm, where it is associated with inhibitory IκB proteins. Stimuli from outside the cell activate IκB via phosphorylation and induce its proteolytic degradation, leading to translocation of NF-κB to the nucleus, which results in a concerted activation of target genes. Pharmacological manipulation of NF-κB activation was recently investigated in experimental meningitis-associated central nervous system complications and clinical symptoms. Two agents were tested, the NF-κB inhibitor *N*-acetyl-leucinyl-leucinyl-norleucinial, which interferes with IκB proteolysis, and BAY 11-7085, which inhibits IκB phosphorylation. Both agents improved clinical status and reduced the increase in intracranial pressure, blood-brain barrier permeability, CSF pleiocytosis, and changes in vascular status (58). Importantly, inhibition of NF-κB may protect against neural cell death (136). Given the broad involvement of NF-κB in cell regulation, it is expected that systemic inhibition will also affect nonimmune cells. The present challenge is to examine which components of the NF-κB signaling pathway can be inhibited without causing unacceptable side effects.

It must be appreciated that single mediators often induce many effects and that there is considerable functional overlap between different mediators. This explains why inhibition of one mediator, once the concentration of a second mediator is above a critical level, cannot prevent the progression of inflammation (128). It is therefore unlikely that inhibition of a single proinflammatory mediator will prove useful in clinical practice.

(ii) Noncytokine mediators. Inflammation activates the coagulation cascade. Not surprisingly, therefore, advanced bacterial meningitis is associated with thrombosis and ischemia. Thus, modulation of inflammatory or coagulation pathways may have a broader impact than suspected from the primary target, as illustrated in Fig. 3. Several clinical trials testing the therapeutic effect of different anticoagulant agents in sepsis have been performed following promising increases in survival in animal studies. One of these agents, recombinant activated protein C, significantly reduced mortality in adult patients with severe sepsis (13, 39). Activated protein C, a component of the natural anticoagulant system, is a potent antithrombotic serine protease with substantial anti-inflammatory properties. However, sepsis trials testing other anticoagulants such as antithrombin III have all failed (168).

Why activated protein C was effective where antithrombin III failed puzzles many people in the field. Sepsis therapy with protein C is not perfect, however. Because of the anticoagulant activity of activated protein C, the administration of this drug might increase the risk of hemorrhage, and further studies to assess safety in different categories of sepsis patients will be needed. Activated protein C may pose too big a risk in meningitis patients because intracranial bleeding is associated with such poor outcome.

Several plasma enzyme systems are activated during inflammation and have been inhibited in experimental models. These include the complement system (P. G. J. Zwijnenburg, T. van der Toll, C. E. Hack, S. J. H. van Deventer, J. J. Roord, and A.M. van Furth, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr 1600, 1999), the vasoactive nonapeptide bradykinin (82), and the vasoactive amine histamine (170). At present, the results of these studies are inconclusive. Complement inhibition might limit endothelial injury, and results from a clinical trial with C1-esterase inhibitor in sepsis show some improvement in clinical status, but the data are still limited (22, 57). Bradykinin and histamine are likely to be too early in the cascade of mediators in bacterial meningitis to be of clinical significance as therapeutic targets.

During inflammation, cytokines stimulate phospholipase A2, which acts on membrane phospholipids, releasing arachidonic acid and glycerophosphocholine. Arachidonic acid is metabolized to cyclooxygenase products (prostaglandins and thromboxanes) and lipooxygenase products (leukotrienes). Inhibition of the lipooxygenase pathway of arachidonic acid metabolism (leukotrienes) by nordihydroguaiaretic acid did not significantly decrease meningeal inflammation in an animal model of meningitis. In contrast, inhibition of cyclooxy-

TABLE 2. Selected strategies to target leukocyte influx

Phase of leukocyte influx	Target	Agent class
Leukocyte attraction (chemotaxis)	Chemokines, e.g., IL-8, MCP-1	Monoclonal antibodies
Leukocyte activation	cAMP production up	A_{2A} adenosine receptor agonist
	cAMP degradation down	Phosphodiesterase inhibitors, e.g., pentoxifylline
Leukocyte adhesion and migration	Selectin class of adhesins	Carbohydrate antagonist, e.g., fucoidin
	Integrin class of adhesins	Monoclonal antibodies, peptides

genases (prostaglandins and thromboxanes) by the nonsteroidal anti-inflammatory drug oxindanac was effective and even reduced permanent sequelae and death in rabbits. The cyclooxygenase inhibitors indomethacin and diclofenac sodium also reduced inflammation, but not as effectively (155, 159). Oxindanac was more effective than corticosteroids in experimental meningitis in rabbits; however, to our knowledge, the drug has not been clinically developed, possibly because of the risk of side effects (154).

(iii) Leukocyte attraction, activation, and adhesion. Should we stop leukocytes? By analogy to other sites of infection, one would intuitively infer a beneficial role for neutrophils. However, early experimental work has suggested detrimental effects of the leukocyte response and inflammatory exudate in the CSF space. Moreover, the absence of humoral immune components in the CSF prevents opsonization of bacteria and subsequent effective phagocytosis and killing by neutrophils. Indeed, in vivo comparison of leukopenic with nonleukopenic rabbits demonstrated that neutrophils fail to stop bacterial multiplication in the CSF (32). The mean duration of survival after intracisternal inoculation of pneumococci was actually longer in leukopenic dogs than in normal nonleukopenic controls (62 versus 47 h) (111). Still, the presence of neutrophils limited the magnitude of bacteremia as a consequence of meningitis, which may have clinical significance, since bacteremia is associated with a worse outcome (34).

A large in vivo study by Giampaolo et al. examining the interrelationships of sequential CSF bacterial titers and leukocyte counts in nonneutropenic rabbits produced somewhat contradictory results (40). In this study, a high CSF leukocyte count on day 1 prior to antibiotic therapy correlated negatively with the bacterial titer in the CSF, suggesting reduction of bacterial multiplication by CSF leukocytes. This study also showed an association of higher CSF leukocyte counts prior to therapy with greater chances of survival. These latter results are similar to the findings in clinical case series, in which bacterial meningitis patients with an initial low CSF leukocyte count, before initiation of antibiotic therapy, generally have a worse outcome than patients with initially higher CSF leukocyte counts (66, 166). However, the study by Giampaolo et al. also showed that continued CSF leukocyte elevation after initiation of antibiotic therapy was associated with a greater chance of death, indicating detrimental effects of CSF pleiocytosis in the context of effective antibiotics.

Previous experimental studies have demonstrated that the number of leukocytes in the meninges immediately adjacent to the cerebral cortex contributes significantly to death (88). Early in vitro studies demonstrated direct cytotoxic effects of leukocytes on cerebral cortex tissue (36). On autopsy, cortical leukocyte infiltration and ventricular empyema are frequently found (113). Since the combined evidence suggests that neutrophils are not very efficient in bacterial phagocytosis and killing in the CSF environment and that persistent CSF pleiocytosis following initiation of antibiotic therapy is associated with a worse outcome, inhibition of leukocyte recruitment into the CSF compartment when initiating antibiotic therapy seemed worthy of exploration. Three avenues to decreasing white blood cell influx into the CSF have been examined: inhibition of attraction, adherence, and activation, as summarized in Table 2.

The process of leukocyte attraction to the site of infection is regulated by chemotactic substances such as complement factor C5a, platelet-activating factor, and chemotactic cytokines called chemokines. The chemokines are subdivided into several families according to structural features related to the relative positions of their cysteine residues. Chemokine receptors belong to the seven-membrane-spanning G-coupled protein receptor family (85). Chemokines are produced at sites of inflammation and are then presented at the luminal side of endothelial cells, sometimes on surface heparan sulfates (92). The CSF of patients with bacterial meningitis contains detectable levels of the C-X-C chemokines (IL-8) and C-C chemokines (monocyte chemotactic protein 1 [MCP-1], macrophage inflammatory proteins MIP-1α and MIP-1β) (144). In experimental models of meningitis, systemic neutralization of IL-8 had a sustained effect, and neutralization of MCP-1 reduced macrophage infiltration, whereas systemic neutralization of MIP-1α or MIP-2 with antibody temporarily reduced neutrophil influx into the CSF. Intrathecal neutralization of IL-8 had no effect on immune cell recruitment (27, 28, 102). Because of multiplicity and overlap between chemokines, it will be difficult to make a good formula to stop attraction of leukocytes.

Processes such as integrin-mediated leukocyte adhesion and release of mediators require leukocyte activation. High levels of the intracellular second-messenger cyclic AMP (cAMP) prevent leukocyte activation. Drugs can influence intracellular cAMP levels either by increasing the synthesis of intracellular cAMP or by preventing the breakdown of cAMP. The level of cAMP can be increased by stimulation of inhibitory leukocyte receptors such as the adenosine receptor A_{2A}. Indeed, treatment with an A_{2A} adenosine receptor agonist (WRC-0470) inhibited pleiocytosis and reduced blood-brain barrier disruption in a rat model of LPS-induced meningitis (146). Degradation of intracellular cAMP can be inhibitid by phosphodiesterase inhibitors, such as the type IV phosphodiesterase inhibitor rolipram. In addition, the phophodiesterase inhibitor pentoxifylline (a methylxanthine derivative) reduced inflammation in the subarachnoid space in several models of bacte-

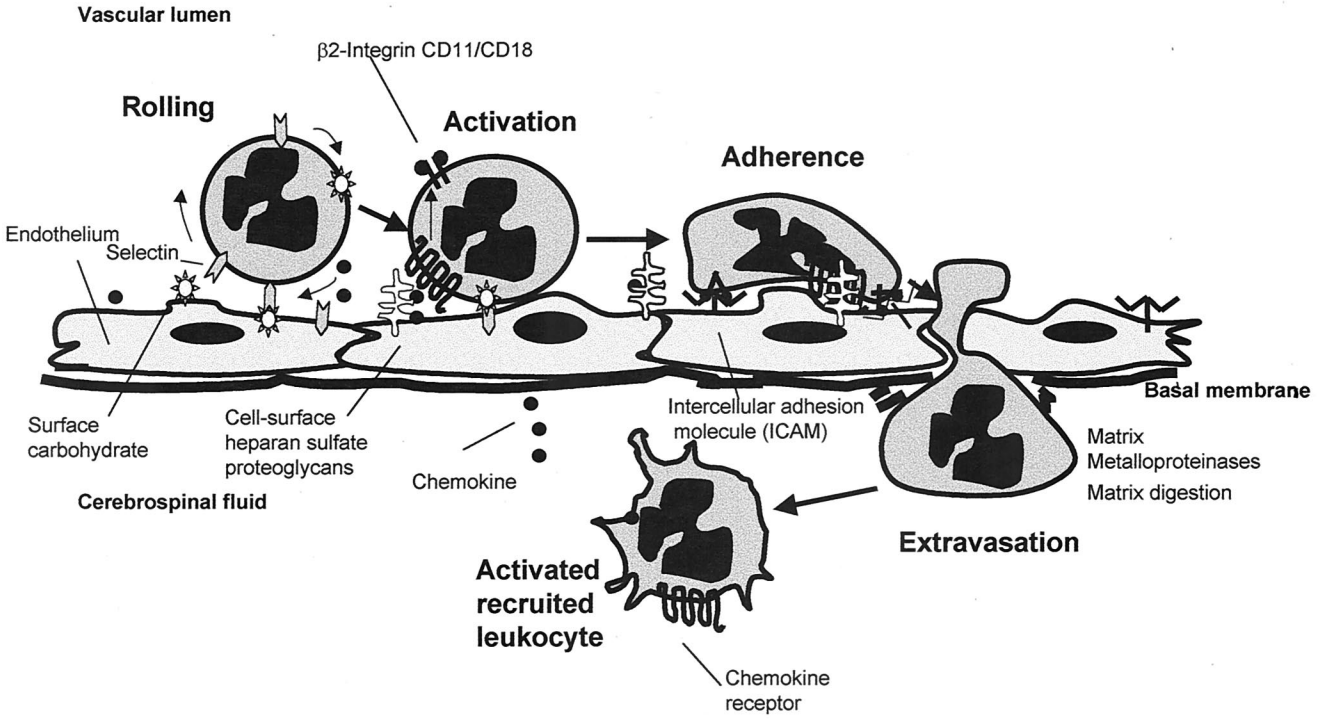

FIG. 4. Process of neutrophil transendothelial migration. Initially the neutrophil is slowed and rolls down the endothelium, following thethering by an interaction of endothelial E-selectin and P-selectin with the leukocyte CD15 sialyl Lewis-X carbohydrate moieties and an interaction of L-selectin with endothelial cell carbohydrate moieties. Chemokine binding to receptors on leukocytes activates leukocyte adhesins of the integrin family, such as the $\beta_2\alpha_M$ integrin CD18/CD11b. Simultaneously, mediators such as IL-8 upregulate the endothelial adhesins of the immunoglobulin superfamily (e.g., intercellular adhesin molecule 1 [ICAM-1]) which bind CD18 on the leukocyte, initiating diapedesis into the cerebrospinal fluid. Matrix metalloproteinases released by the leukocyte digest intercellular tight junctions and the basal membrane during diapedesis.

rial meningitis but had no significant effect on blood-brain barrier permeability or neuronal damage (106, 133, 175). New xanthine derivatives such as lisofylline, which have a similar mode of action, are less toxic, making their clinical use more feasible (165). Newly discovered regulators of neutrophil activation, such as inosine monophosphate, may lead to the development of other effective inhibitors of neutrophil activation (124). Since these drugs will affect leukocytes both in the bloodstream and in the CSF, this seems a promising strategy.

Leukocyte migration into the CSF involves the interaction of leukocytes with the vascular endothelium via several sets of surface adhesion molecules. The process of leukocyte transmigration is illustrated in Fig. 4.

Selectin-mediated rolling of leukocytes is essential for the transendothelial migration of neutrophils, as elegantly demonstrated in selectin-deficient mice (148). Several proinflammatory mediators, such as histamine, stimulate the upregulation of endothelial selectins and promote rolling of leukocytes. Interference with activation of the histamine (H1) receptor in a rat model of bacterial meningitis temporarily inhibited leukocyte rolling in the early phase of meningitis (170). In addition, several carbohydrate agents prevent the selectin-mediated rolling of leukocytes and inhibit neutrophil migration into the CSF in models of meningitis. These agents include heparin (171), the polysaccharide fucoidin (3, 42), and the polysaccharide glucuronoxylomannan from the capsule of the yeast *Cryptococcus neoformans*. Glucuronoxylomannan decreased TNF-α levels in the CSF, an effect not studied for the other polysaccharide agents (80). Though rolling is the initial phase of leukocyte transmigration, inhibition of rolling by fucoidin at the time of antibiotic treatment still affected CSF neutrophil numbers, suggesting that treatment with fucoidin may be relevant in the late phase of the disease, which is the important phase clinically (41).

TABLE 3. Cellular dysfunction contributes to exacerbation of pathophysiology

Dysfunctional cell type	Pathophysiologic event	Effect
Endothelium	Disruption of bood-brain barrier	Vasogenic edema, increased intracranial pressure, compromised cerebral bloodflow, cerebral herniation
	Procoagulant state	(Micro)thrombi, ischemia
Smooth muscle	Loss of cerebral autoregulation	Cerebral hypo-/hypertension
	Vasoconstriction	Cerebral ischemia
Neuron	Increased release of excitatory amino acids	Excessive stimulation, metabolic disturbances, cellular edema

The β_2-integrin (CD11a/CD18; CD11b/CD18) and intercellular adhesion molecule-1 (ICAM-1)-dependent phase of leukocyte endothelial transmigration can be inhibited by antibodies or peptides blocking the CD18 complex or ICAM-1 (130, 131, 157, 169). Blockage of CD18-mediated adhesion in an animal model prevented CSF pleiocytosis and protected against enhanced blood-brain barrier permeability and brain edema without changing the efficacy of bacterial killing by ampicillin. Antibodies against leukocyte adhesion molecules have already been used successfully in clinical trials as treatment for primarily lymphocyte-dependent illnesses, including transplant rejection and inflammatory bowel disease (23, 45). An additional target for intervention may be the structural tight junction components. Antibodies against the cerebral endothelial tight junction component junctional adhesion molecule inhibited leukocyte recruitment in a model of cytokine-induced meningitis in mice (26) but not in a model of infectious meningitis. Moreover, in the latter model, complement-mediated endothelial damage induced by the antibody treatment was observed (69). Since the effects of activated leukocytes in the CSF are very wide-ranging, further evaluation of strategies to interfere with leukocyte actions still seems worthwhile.

Conserve cellular function. (i) Blood-brain barrier and increased intracranial pressure. In bacterial meningitis, the pathophysiologic changes are much broader than the above-mentioned direct toxic effects of bacteria, release of proinflammatory mediators and activation of leukocytes. As a result of the inflammatory response, many cell types, including endothelium, smooth muscle cells, and neurons, dysfunction and contribute to aggravation of the condition, as summarized in Table 3. This vicious circle poses a major risk for death or neuronal damage. One cause of an unfavorable outcome of bacterial meningitis is cerebral edema and increased intracranial pressure. At present, the only clinical treatments for cerebral edema and elevated intracranial pressure are corticosteroids, infusions with hyperosmolar mannitol solutions, and mechanical hyperventilation. All these treatment strategies are controversial. Although corticosteroids reduce tumor-associated edema, it is unclear whether their beneficial effect in bacterial meningitis is related to edema reduction. Mannitol has been shown to reduce intracranial pressure in experimental models of meningitis and has been used in the clinic (84, 93, 147). However, its use is debated because of possible paradoxical effects (46, 55). Similarly, mechanical hyperventilation will reduce cerebral blood flow and thus intracranial pressure but may inadvertently worsen cerebral ischemia (7).

Vasogenic edema is caused by the leakage of plasma proteins into tissue following disruption of the blood-brain barrier. Many of the inflammatory mediators mentioned above contribute to this disruption of the blood-brain barrier. Vasoactive mediators such as vascular endothelial growth factor (VEGF) are released in response to bacterial toxins and proinflammatory mediators (163). VEGF is intrathecally released from invading neutrophils in the CSF in bacterial meningitis (164). VEGF induces the formation of transcellular canals called vesiculo-vacuolo organelles and causes loss of intercellular tight junctions (35, 167). Blocking VEGF reduces cerebral edema in experimental cerebral ischemia, but the role of VEGF in blood-brain barrier disruption in bacterial meningitis awaits further evaluation (162).

Furthermore, degrading enzymes such as the matrix metalloproteinases are implicated in disruption of endothelial tight junctions and the blood-brain barrier during leukocyte diapedesis. Matrix metalloproteinases are a family of zinc-dependent endopeptidases that are released in inactive form and are regulated by endogenous tissue inhibitors of metalloproteinases. Disruption of the blood-brain barrier in experimental meningitis can be modulated by administration of matrix metalloproteinase inhibitors such as batimastat (BB-94) and hydroxamic acid-type inhibitors (GM-6001 and BB-1101) (78, 109). Broad-spectrum hydroxamic acid-based inhibitors simultaneously inhibit proteolytic activation of pro-TNF, thereby inhibiting the progression of inflammation (75).

In addition to vasogenic edema, interstitial edema resulting from decreased CSF outflow and cellular edema due to cellular injury contribute to brain edema. Intracellular calcium is an important mediator of inflammatory cellular responses, and calcium channel antagonists have been demonstrated to modulate the production of cytokines and reactive oxygen intermediates and reduce cellular injury. In an experimental pneumococcal meningitis model, nimodipine, a calcium channel blocker, reduced intracranial pressure. In patients with subarachnoid hemorrhages, nimodipine reduced the proportion of ischemic neurologic deficits and improved overall outcome (33). However, nimodipine failed to protect the brain from ischemic stroke in the clinical setting (47). Because nimodipine also induces cerebral vasodilation, which lowers cerebral perfusion pressure, hypotension and shock are regarded as contraindications for its use. Possible effects on cerebral blood flow in meningitis require further experimental evaluation (108).

(ii) Protecting cerebral blood flow. In bacterial meningitis, the cerebral blood flow initially increases as a result of vasodilating neuropeptide release and then steadily decreases due to vasoconstriction and the pressure of surrounding cerebral edema (7, 118, 158). In the early phase of pneumococcal meningitis, dilation of pial vessels and increased blood flow are initiated by endogenous vasodilating neuropeptides such as substance P. Treatment with the substance P antagonist spantide reduced pial arteriolar dilatation (120). The vasodilatator effects of substance P seem to be mediated, at least in part, by nitric oxide production. Early pial vasodilatation is associated with stimulation of endothelial inducible nitric oxide synthase and neuronal nitric oxide synthase activity. Nitric oxide freely diffuses into the cytosol and stimulates guanylate cyclase, which transforms guanylate triphosphate into cyclic guanylate monophospate, raising the intracellular cyclic GMP levels and causing relaxation of smooth muscle cells. Nitric oxide antagonists (7-nitroindazole and *N*-nitro-L-arginine) prevent early pial vasodilatation in experimental models, which suggests that nitric oxide is a potential therapeutic target (107). However, the early timing of inhibitor administration is crucial, because administration of the inhibitor later in the disease process exacerbates hypoperfusion (72, 142).

During bacterial meningitis, cerebral autoregulation is lost, and systemic changes in mean arterial pressure influence cerebral blood flow (95). This loss of cerebral autoregulation is due at least in part to cerebral arteriolar dilatation and can be restored by hyperventilation (94). Decreased blood flow is me-

diated by vasoconstrictive agents such as endothelins, the levels of which are significantly elevated in the CSF of patients with bacterial meningitis (60). The vasoconstrictive effects of endothelins may contribute to ischemic neuronal injury, because an endothelin antagonist (bosentan) significantly reduced neuronal injury in experimental meningitis. The protective effect of bosetan was independent of an effect on nitric oxide production (121). These results should be confirmed in further experiments, especially because bosetan treatment was associated with a substantial increase in spontaneous deaths, even though the increase in mortality did not reach statistical significance. Studies with endothelin B receptor-deficient rats and autopsy studies of humans and rabbits suffering pneumococcal meningitis indicate that endothelin may also function to increase neuronal survival (29).

Cerebral blood flow can be further compromised by the activation of platelets and the induction of a procoagulant state on the endothelial surface. Cerebrovascular complications and focal ischemia are frequently found on autopsy (113). Decrease in cerebral blood flow is accompanied by a steady increase in intracranial pressure and CSF lactate concentration, which is a sign of deleterious metabolic changes. In clinical practice, fluid restriction in bacterial meningitis patients for fear of of inappropriate antidiuretic syndrome has long been the standard of care. Experimental work on the effects of the hydration status on cerebral blood flow and CSF lactic acidosis has demonstrated better outcome with no fluid restriction (160). This important conclusion is supported by some small clinical studies (122, 143).

(iii) Neurotoxicity and intrinsic cellular death pathways. Oxidants such as reactive oxygen species and reactive nitrogen intermediates are terminal mediators of brain damage in bacterial meningitis (62). These highly reactive instable molecules are cytotoxic through their inactivation of enzymes, damage to membrane ion transporters, and initiation of lipid peroxidation (76). In addition, they cause damage to DNA, causing single- and double-strand breaks, which activate poly(ADP-ribose) polymerase 1. Excessive activation of poly(ADP-ribose) polymerase 1 causes futile consumption of intracellular energy stores, cellular dysfunction, and eventually necrotic cell death (65).

Experimental and endogenous antioxidants (α-phenyl-*tert*-butyl, superoxide dismutase, catalase, the 21-aminosteroid U74389F, and uric acid) (54, 73, 81, 83, 116, 117, 119) and several clinically used antioxidants (*N*-acetylcysteine, desferoxamine, and trylizad mesylate) (8) reduce brain edema, cortical damage, and changes in cerebral blood flow in experimental meningitis. Assessment of the effect on hippocampal neurons produced conflicting results, varying from reduction of apoptosis by α-phenyl-*tert*-butyl in group B streptococcal meningitis to aggravated apoptosis and learning deficits with the same agent in pneumococcal meningitis (73, 81). Inhibition of poly(ADP-ribose) polymerase 1 by 3-aminobenzamide also reduces central nervous system complications (65). Interference with reactive oxygen species and reactive nitrogen intermediates as terminal mediators of meningitis-associated central nervous system cell damage holds much promise for future therapeutic interventions. When agents prove protective for brain function in clinical trials of cerebral ischemia, they will be excellent candidates as adjunctive therapy in bacterial meningitis.

Inflammation-induced production of excitatory amino acids (glutamate, aspartate) causes neuronal damage due to excessive stimulation. The excitatory amino acids activate cells by opening receptor-operated calcium channels, resulting in elevated intracellular calcium levels and metabolic changes which lead to cellular edema and neuron death. Stimulation of excitatory amino acid receptors (such as the NMDA [*N*-methyl-D-aspartate] receptors) contributes to inflammation by activation of inflammatory gene expression (50). In the neonatal rat group B streptococcus meningitis model, kynurenic acid, an NMDA receptor antagonist, significantly reduced neuronal injury in the cortex and hippocampus compared to that seen in control animals (74). In an experimental model of pneumococcal meningitis, an NMDA antagonist (HU-211) reduced brain edema and blood-brain barrier impairment even when given together with antibiotics as late as 18 h after infection (11). However, NMDA blockade could not reduce ischemic or traumatic brain damage in several animal models, and depending on the timing of inhibition, NMDA blockage may even increase neuronal cell death (49). Moreover, the results of clinical trials evaluating the supposed protective efficacy in ischemic brain damage have been disappointing (70). Blockade of another glutamate receptor subtype, the α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor) to date seems very promising in experimental studies but has not yet been tested in experimental meningitis or clinical trials in other neurologic diseases (49).

Nonpharmacological therapies may also effectively improve the outcome of bacterial meningitis. For example, hypothermia, which is clinically applied in neurosurgery to lower metabolism in the brain and to make the brain less vulnerable to neuronal damage, has been tested in an experimental meningitis model. Hypothermia successfully reduced meningitis-induced changes, particularly the increased intracranial pressure (2). However, the differential effects of hypothermia on outcome demand further investigation. Inflammatory mediators in the CSF trigger the activation of caspases, a specific class of proteases involved in cell survival. Activation of caspases ultimately results in neuronal apoptosis. Bacterial meningitis may cause apoptotic cell death in specific areas of the brain, as evidenced by the presence of apoptotic neurons in the hippocampus at autopsy (101, 176). This neuronal loss may explain some of the learning and memory difficulties seen in survivors of meningitis.

In animal experiments, treatment with the caspase inhibitor z-VAD-fmk greatly reduced the extent of meningitis-associated apoptosis (17). Caspase antagonist therapy still reduced neuronal damage and CSF white blood cell counts when started 8 h postinfection, but since the largest increase in CSF white blood cell counts in a rabbit model of pneumococcal meningitis occurred from 12 h postinfection onward, further evaluation of the window of opportunity is needed (156). Other investigators have shown the efficacy of z-VAD-fmk when administered up to 6 h after infection in a rat model of pneumococcal meningitis (64). The relevance of caspase-1 for both inflammation and apoptosis in bacterial meningitis has been studied in a caspase-1-deficient knockout mouse model of meningitis. However, the results are conflicting (64; M. V. Mering, A. Wellmer, U. Michel, and R. Nau, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr 431, 2000).

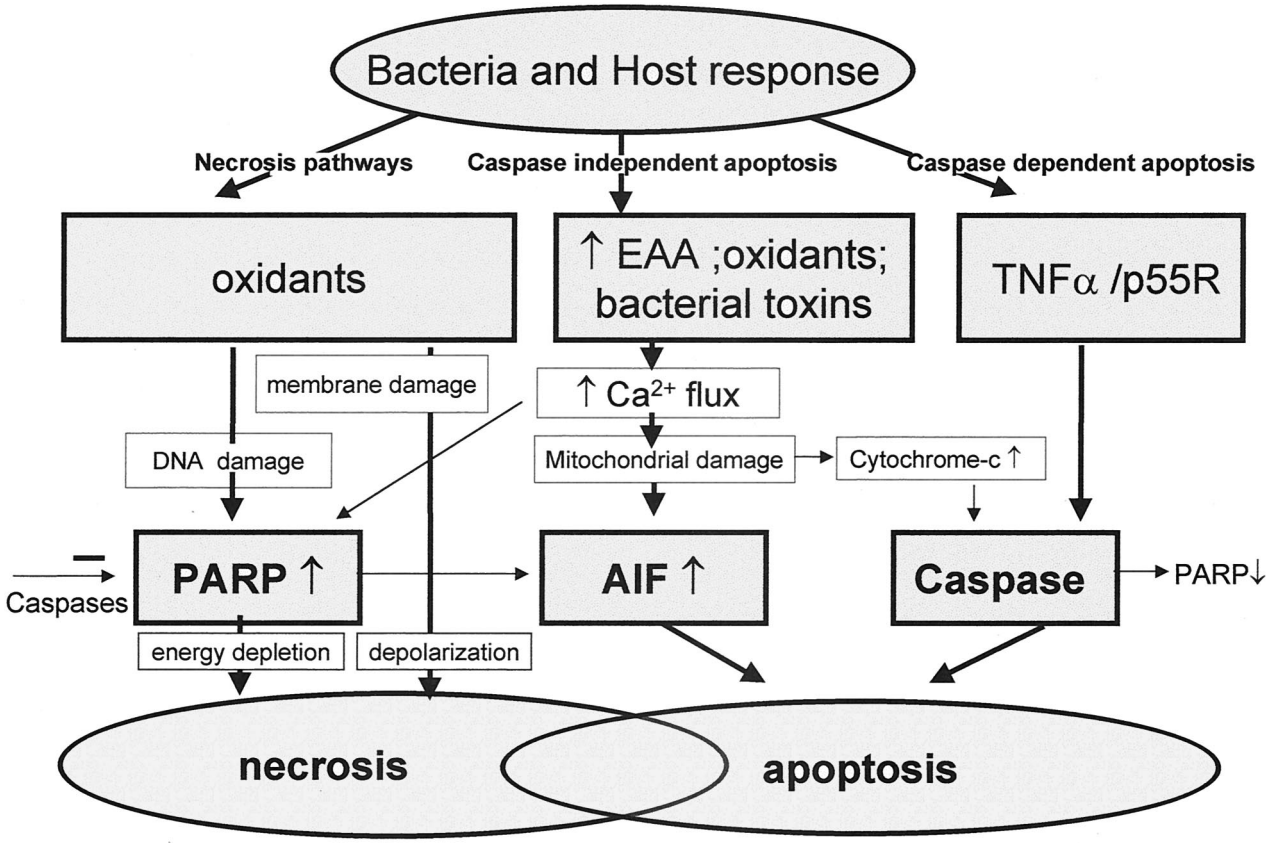

FIG. 5. Neuronal cell death pathways may be divided into necrotic pathways, caspase-independent apoptotic pathway, and caspase-dependent apoptotic pathway. Bacterial and host oxidants cause damage to cell membranes via lipid peroxidation, leading to loss of membrane integrity and depolarization and finally necrotic cell death. Oxidants also cause DNA damage, resulting in the energy-consuming activation of the poly(ADP-ribose) polymerase (PARP). When DNA repair is futile because of the magnitude of the damage, massive energy depletion will cause necrotic cell death. Oxidants, high concentrations of excitatory amino acids (EAA), and bacterial toxins such as the pneumolysin of *S. pneumoniae* or the hemolysin of *S. agalactiae* all cause increased cytosolic free calcium levels. This may result in PARP activation and contribute to necrotic death but primarily causes damage to the mitochondrial outermembranes with PARP-dependent release of apoptosis-inducing factor (AIF). Free cytosolic apoptosis-inducing factor will move into the nucleus and cause chromatin condensation and apoptotic cell death. Release of inflammatory mediators such as TNF-α in response to the invading bacterial pathogens will result in activation of caspases. This results in activation of the apoptotic pathway and will also inhibit necrosis through inactivation of PARP. Release of cytochrome *c* from mitochondria following mitochondrial damage in response to increased cytosolic free calcium levels also causes activation of caspases and apoptotic death. As indicated in the figure, several crossroads exist between the different death pathways. In many cases, both necrotic and apoptotic cell death may be revealed on histologic examination.

Since neuronal apoptosis is the final common pathway of many damaging factors, the components of the apoptosis pathway are attractive novel targets for adjuvant neuroprotective therapy (20). It must be kept in mind, however, that there are many pathways to apoptosis, both caspase dependent and independent. Thus, the involvement of the individual pathways must be compared in order to choose agents with the most potential benefit. For instance, in pneumococcal infection, an equal contribution of caspase-dependent and -independent pathways suggests that at least two inhibitors would be needed (18). The different neuronal cell death pathways and their interactions are summarized in Fig. 5.

Enhance Repair

Endothelial recovery. When inflammation subsides, restoration of blood-brain barrier integrity is important because continuing vasogenic edema and leakage of potentially harmful molecules such as excitatory amino acids from the blood into the CSF and cerebral tissue will sustain metabolic disturbances in the brain. The mechanisms responsible for endothelial repair have long remained elusive. Until recently, vascular endothelial growth factor (VEGF), a hypoxia-inducible, angiogenic factor, was the only proven specific and critical factor for endothelial growth and blood vessel formation. The advance in genetic techniques has resulted in the discovery of a whole series of new growth factors acting on the vascular endothelium, including new members of the VEGF family, four members of the angiopoietin family, and at least one member of the ephrin family (173). Furthermore, it has become clear that many other growth factors that are not vascular endothelium specific are important for blood vessel growth and repair, such as transforming growth factor beta.

A challenging new concept in the understanding of blood vessel formation is the recruitment of bone marrow-derived endothelial progenitor cells to sites of angiogenesis (86). The possible role of these cells in repairing damaged and leaky

TABLE 4. Strategies to enhance repair

Cellular target	Aim	Potential agents
Endothelium	Restore blood-brain barrier Limit vasogenic edema Protect composition of CSF and interstitial fluid in brain	Endothelial growth factors, e.g., angiopoietin
Neurons	Stimulate recovery Prevent neuron loss Replace dead neurons Stimulate recruitment of endogenous progenitor cells	Growth factors, e.g., transforming growth factor beta, VEGF Growth factors, e.g., epidermal growth factor, fibroblast growth factor 2

vessels following inflammation and possibly ischemia has to be studied further. Experimental work has demonstrated how angiopoietin 1 administration protects the adult vasculature from damage and leaks induced by inflammation and VEGF. The role of signaling mechanisms from astrocytes or other cells in maintaining and restoring the defined characteristics of the blood-brain barrier are still poorly understood and require further study (48, 110, 132). It is expected that these new insights will result in therapeutics that improve vascular repair, which might limit the development of cerebral edema and cerebrovascular complications in the context of bacterial meningitis.

Neurotrophic factors. Neurotrophic growth factors may have therapeutic potential to protect brain tissue from damage. For instance, receptors for VEGF are present on neuronal cells. VEGF promotes survival of neuronal cells in culture and stimulates axonal outgrowth and survival of mouse dorsal root ganglions in vivo, but also protects neuronal cells from the effects of hypoxia (51). Many of the neurotrophic growth factors have additional critical roles for many other systems. For instance, VEGF may also assert negative effects, since it may induce vascular permeability and vasogenic edema (162). VEGF can be detected in the CSF of bacterial meningitis patients, suggesting that it may have a biological role in bacterial meningitis (164).

In general, proinflammatory cytokines are neurotoxic. Some anti-inflammatory cytokines, such as transforming growth factor beta, possess neurotrophic functions. Transforming growth factor beta 2 has additional beneficial effects, since it inhibits cerebrovascular changes and brain edema in bacterial meningitis (115).

The functions and therapeutic potential of neurotrophic and neuroprotective factors have drawn much research attention in recent years (1). However, the list of neurotrophic growth factors is long, and it remains an enormous challenge to determine the exact effects and potential of the individual factors and their interactions, and much research is needed before therapeutic applications can be expected.

Neuronal regeneration. Recently, it has become evident that, even in adults, neurons are continuously born from endogenous stem cells and added to the dentate gyrus throughout life. This process is regulated by several growth factors important in neuronal development, e.g., epidermal growth factor and Sonic hedgehog (68). Hippocampal pyramidal cells can be replaced by endogenous progenitors which migrate into the hippocampus to generate new neurons, although this potential for regeneration declines with age (56, 98, 141). The dentate gyrus and hippocampus are the primary sites of neuron loss in clinical meningitis. In animal experiments, intraventricular infusion of growth factors (e.g., fibroblast growth factor 2 and epidermal growth factor) augments the regenerative response in the hippocampus following ischemia, providing hope for the concept that this endogenous regenerative potential may be applied therapeutically to ameliorate hippocampal atrophy (98). Other animal experiments have shown how an enriched environment providing adequate stimulation improves hippocampal neurogenesis and behavioral performance (56). Potentially, this source of neuronal self-renewal may one day be fully employed. Several strategies to enhance the body's repair mechanisms are summarized in Table 4.

FUTURE PROSPECTS

Considering ways to improve outcome in bacterial meningitis, the experience gained in sepsis and stroke research has to be taken into account. The retrospective evaluation of several unsuccessful clinical trials has taught us the value of thorough preclinical evaluation. When all available preclinical data are reexamined, it seems that some of the drugs that failed in clinical trials for stroke or sepsis did not have a reasonable chance to succeed when these trials were initiated. Since well-designed clinical trials to evaluate the effect of adjuvant agents in bacterial meningitis require an enormous effort from many people, it is of utmost importance that drugs proposed for such trials undergo sufficient preclinical evaluation to select the most promising candidates (30). Researchers need to be aware of the limitations of different animal models, and methods to assess data from several animal experiments are available (61, 91, 134). Guidelines of adequate preclinical drug evaluation such as those developed for stroke research are relevant to prevent futile trial efforts in bacterial meningitis, which may damage the execution of more promising future trials (4).

Knowledge of the effects of timing during the course of disease and the optimal dose agents often seems to be crucial to reaching a beneficial effect. As mentioned above, many mediators may be beneficial early in the disease process or at low doses but may have detrimental effects later or in higher doses. For instance, corticosteroids protect clinically against unfavorable outcome when administered early but have no effect when administered later during the course of disease (89, 96, 123). Successes in related conditions, such as adjuvant treatment with activated protein C for severe sepsis, should not be simply assumed to apply to bacterial meningitis as well (13).

Unlike antibiotic therapy, the effectiveness of adjuvant therapy may be very different in sepsis or meningitis. It is important to appreciate the differences in pathology between these different diseases, which are likely to translate to different risk-benefit profiles for individual agents. In the case of activated protein C, the risk of intracranial bleeding in bacterial menin-

gitis may outweigh other beneficial effects, such as a decrease in ischemic events. However, clinical experience with protection against injury or enhancement of cellular repair in sepsis and stroke may help select agents to evaluate for bacterial meningitis. For some substances, such as neuroprotective agents, it is probably best to first await successes in clinical stroke trials, which allow faster patient recruitment.

Based on the compiled experimental evidence, it seems unlikely that inhibition of a single proinflammatory mediator will prove useful in clinical practice. Encouraging results have been found with several avenues that simultaneously reprogram a broader range of mediators. Particularly exciting are the adjustment of cytokine combinations such as effectuated by inhibition of the NF-κB signal pathway and the results with leukocyte activation inhibitors. Equally promising are strategies to interfere with oxidant-mediated damage processes, to inhibit neuronal apoptosis, and to enhance endothelial and neuron repair.

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