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Dexamethasone Aggravates Hippocampal Apoptosis and Learning Deficiency in Pneumococcal Meningitis in Infant Rats

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ABSTRACT

In an infant rat model of pneumococcal meningitis the effect of dexamethasone on neuronal injury in the hippocampus and on learning disability after recovery from the disease was examined. Treatment with dexamethasone or vehicle was started 18 h after infection, concomitant with antibiotics. Neuronal apoptosis in the hippocampal dentate gyrus 34 h after infection was significantly aggravated by dexamethasone treatment compared with vehicle controls ($p = 0.02$). Three weeks after acute pneumococcal meningitis, learning capacity of animals was assessed in the Morris water maze. The results showed a significantly impaired learning performance of infected animals treated with dexamethasone compared with vehicle controls ($p = 0.01$). Dexamethasone had no effect on hippocampal injury or learning in uninfected controls. Thus, dexamethasone as adjuvant therapy increased hippocampal cell injury and reduced learning capacity in this model of pneumococcal meningitis in infant rats. **(*Pediatr Res* 54: 353–357, 2003)**

Abbreviations

CSF, cerebrospinal fluid
DG, dentate gyrus
MMP, matrix metalloproteinase
PBN, alpha- phenyl-tert-butyl nitrone
TACE, tumor necrosis factor alpha converting enzyme

Inflammation in the subarachnoid and ventricular space is the hallmark of bacterial meningitis and appears to be responsible for much of the pathophysiologic consequences of the disease (1–3). Therapy with highly active antibiotics is only partially effective in preventing death and the development of neurologic sequelae in patients with bacterial meningitis (4, 5). Even with optimal treatment, mortality remains high in certain patient groups and up to 40% of the survivors of meningitis suffer from neurologic sequelae, including sensory-motor deficits, cerebral palsy, seizure disorders, mental retardation, and learning impairments (6–8).

Given the harmful effect of the inflammatory reaction, anti-inflammatory adjuvant treatment with dexamethasone has been tested in several controlled clinical trials (9–11). A recent meta-analysis concluded that the drug is effective in preventing hearing loss in *H. influenzae* meningitis and has some beneficial effects on hearing and neurologic sequelae in pneumococcal meningitis when given before or at the time of the first antibiotic dose (11). However, in most of the individual trials, these benefits were either marginal or could not be detected at all (12). Furthermore, *H. influenzae* meningitis has virtually disappeared in countries that have implemented programs with conjugated vaccines in infants and children (13). Consequently, the use of dexamethasone has remained controversial (12, 14, 15).

Two brain structures prominently affected in bacterial meningitis are the cortex and the hippocampus. Neuronal apoptosis in the hippocampal dentate gyrus has been observed in humans dying from bacterial meningitis (16) and in animal models of meningitis (17–20). Neuropsychological evidence in humans and animal models suggests that damage to the hippocampus impairs learning and spatial memory (21–23). We have recently shown that the extent of learning dysfunction is related to the extent of hippocampal apoptosis in infant rats with pneumococcal meningitis (17, 19)

A study in adult rabbits with pneumococcal meningitis has suggested that the number of neurons undergoing apoptosis in the hippocampal formation was increased when antibiotic treatment was combined with dexamethasone therapy (18). However, the outcome of adjuvant dexamethasone in a model of infant meningitis and the effect on learning dysfunction as a consequence of bacterial meningitis has not been studied to date. Together with the questions surrounding the benefits of

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dexamethasone in patients with bacterial meningitis, this prompted us to study the effect of the drug in our model of pneumococcal meningitis in infant rats. Specifically, we examined whether dexamethasone influenced apoptotic injury in the dentate gyrus and whether this was associated with an effect on learning capacity after recovery from acute meningitis.

MATERIALS AND METHODS

Model of meningitis. The animal studies were approved by the Animal Care and Experimentation Committee of the Canton of Bern, Switzerland, and followed National Institutes of Health guidelines for the performance of animal experiments. Nursing Sprague-Dawley rat pups were infected on postnatal day 11 ($n = 142$) by intracisternal injection with 10 μL of saline containing an inoculum of $\log_{10}$ 6.5 $\pm$ 0.6 cfu/mL *Streptococcus pneumoniae* (17, 19, 24, 25). Uninfected animals ($n = 62$) were injected intracisternally with 10 μL of sterile, pyrogen free saline. At 18 h after infection, animals were weighed and assessed clinically. To document meningitis, 10 μL of cerebrospinal fluid was obtained by puncture of the cisterna magna and cultured quantitatively.

Treatment. All infected animals ($n = 142$) received antibiotic treatment (ceftriaxone 100 mg/kg s.c. bid; Roche Pharma, Reinach, Switzerland) following CSF collection at 18 h. Antibiotic treatment was continued for 2 doses in infected animals subsequently examined histopathologically ($n = 38$) and for 5 d in animals subjected to learning testing ($n = 104$). Animals to be assessed histopathologically ($n = 38$ for meningitis; $n = 14$ for uninfected controls) were randomized for treatment with dexamethasone (0.7 mg/kg s.c. q8h from 18 to 34 h after infection; $n = 16$ for meningitis; $n = 8$ for controls) or vehicle ($n = 22$ for meningitis; $n = 6$ for controls). Animals to be assessed for learning performance were randomized for treatment with dexamethasone (0.7 mg/kg s.c. q8h for 4 d; $n = 34$) or vehicle ($n = 70$) concomitant with the first antibiotic dose. Data presented here combine two separate experiments using the same protocol. In the first trial, normal saline was administered as vehicle to control animals (infected controls, $n = 31$; uninfected controls, $n = 31$). In the second trial, control animals received PBS containing 1% Tween 80 (0.2 mL s.c.) as vehicle (infected controls, $n = 52$; uninfected controls, $n = 32$) because in this trial another drug was tested concomitantly with dexamethasone, which had to be dissolved in PBS/Tween (17). Treatment with NaCl *versus* PBS/Tween did not result in significant differences in hippocampal histopathology or learning performance either in uninfected or in infected control animals. However, for both the infected and uninfected control group, animals treated with NaCl or PBS/Tween had to be combined to make the differences between the three treatments (uninfected; infected vehicle treated; infected dexamethasone treated) statistically significant.

Effect of treatment on bacterial killing in CSF. In eleven infected animals (dexamethasone, $n = 5$; PBS/Tween, $n = 6$) repeated cisternal punctures were performed at 18, 22, and 30 h post-infection. CSF bacterial titers were determined quantitatively by serial dilution to assess the influence of dexamethasone therapy on the decline of bacterial titers in CSF following initiation of antibiotic therapy.

Histopathology. At 34 h post-inoculation, infected animals treated with dexamethasone ($n = 10$), uninfected animals treated with dexamethasone ($n = 8$) and infected ($n = 19$) and uninfected controls ($n = 6$) were killed with an overdose of pentobarbital. Animals dying spontaneously before 34 h ($n = 9$) were not evaluated. Immediately after euthanasia, animals were perfused *via* the left ventricle with 15 mL of 4% paraformaldehyde in PBS (pH 7.4). Brains were removed, post-fixed and snap-frozen at -60°C in methylbuthane and cut at 45–60 μm intervals on a cryotome to obtain four coronal sections of the hippocampal region. Sections were mounted on gelatinized glass slides for staining. After dehydration, sections were Nissl stained with cresyl violet and coverslips were fixed with Entellan® (Merck, Darmstadt, Germany). Neuronal injury in the dentate gyrus was evaluated as described previously (24). Apoptosis in the granule cell layer of the hippocampus, defined as cells showing markedly shrunken, condensed or fragmented nuclei (Fig. 1) was counted at 400x in 3 visual fields for each of the four blades of the dentate gyrus. An average per dentate gyrus (six visual fields) per animal was

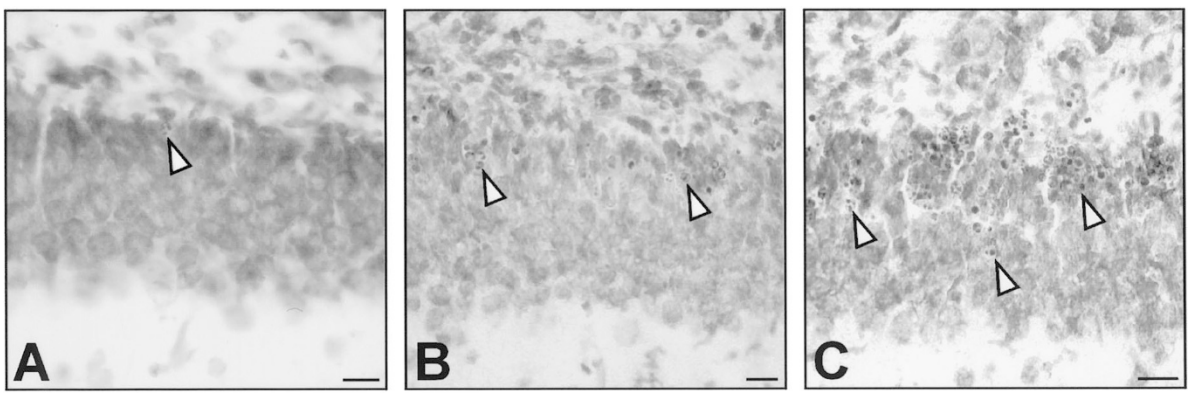

Figure 1. Hippocampal dentate gyrus histology of infant rats suffering from pneumococcal meningitis at 34 h after infection. *A*) In the dentate gyrus of uninfected controls physiologic occurrence of neuronal apoptosis is sporadically visible by the formation of condensed and fragmented nuclei (*arrowhead*). *B*) In infected vehicle treated rats formation of apoptotic bodies is characteristically observed in the inner rim of the dentate gyrus (*arrowheads*) at 34 h after infection. *C*) Treatment with dexamethasone markedly increased the occurrence of apoptotic bodies (arrowheads) in the hippocampal dentate gyrus. Cresyl violet; original magnification $\times$ 300; bar 50 μm.

calculated from all slides evaluated. Histopathologic evaluations were done by an investigator blinded to the clinical, microbiologic and treatment data of the animals.

Assessment of learning function. Testing of spacial learning and memory based on visual clues was performed in the Morris water maze, as previously described (17, 19). Before the test, gross vestibulomotor dysfunction was excluded using a rotating rod, as described (17, 19). For assessment of learning function, time and distance to reach a submersed, for the rats invisible platform was determined by registering the swim patterns with the video tracking system Ethovision® (Noldus Information Technology, Wageningen, Netherlands).

Thirty-two day old survivors of meningitis ($n = 85$; 19/104 infected animals died or had to be killed for ethical reasons before the age of 32 d) treated with dexamethasone ($n = 28$) or vehicle ($n = 57$) and uninfected control animals ($n = 48$) were transferred to the test room where they were given 24 h to acclimatize in 12 hourly light/dark cycles. Animals were provided with water and food ad libitum. From day 1 to 4 animals performed five training trials per day with the invisible platform in a fixed position throughout the test. The rats were put into the water at randomly assigned entry points with their head directed toward the wall of the tank. If an animal found the platform within 90 s, it was allowed to stay on it for 15 s before it was put back to the cage. Otherwise the rat was guided to the platform by hand and was allowed to stay on it for 15 s. Between trials animals rested 45 min.

Statistical methods. Normally distributed variables were expressed as mean ± SD. Differences between groups were analyzed by *t* test or ANOVA and the Newman-Keuls posthoc test for multiple comparison in the case of multiple groups. Survival curves were analyzed using the Kaplan-Meier method. Incidence of seizures, spontaneous death and cortical injury were compared using Fisher's exact test. Hippocampal apoptosis was analyzed with the Mann-Whitney rank-sum test. Distances moved in the water maze task were compared with repeated-measures ANOVA, and pair wise comparison was done with the Tukey-Kramer adjustment. SAS Version 8.0 (SAS Institute Inc., Cary, NC, U.S.A.) software was used.

RESULTS

Characteristics of disease. By 18 h after infection, meningitis was documented in all infected animals by positive CSF cultures for *Streptococcus pneumoniae*. Animals subsequently treated with dexamethasone and infected control animals had similar bacterial titers in CSF ($\log_{10}$ 7.7 ± 0.6 *versus* 7.7 ± 0.7 cfu/mL, p = n.s.). The decline of CSF titers after the first dose of ceftriaxone in animals treated with dexamethasone *versus* controls was similar at 22 h ($\log_{10}$ 3.4 ± 2.5 *versus* 3.4 ± 3.0; p = n.s.) and 30 h (sterile in both groups). Spontaneous death occurred in 37% of dexamethasone treated animals and in 35% of infected controls (p = n.s.). Seizures were observed with the same frequency in infected controls (15%) and dexamethasone treated animals (14%; p = n.s.). The known effect of dexamethasone therapy on catabolism was reflected in a decreased weight at the age of 32 d, when surviving animals were tested for motor and learning function. Dexamethasone treated animals weighted significant less than vehicle treated animals both among the infected (90.1 ± 11.1 g *versus* 112.8 ± 12.2 g; $p < 0.001$) and uninfected groups (68.0 ± 7.6 g *versus* 120.7 ± 15.8 g; $p < 0.001$) (26). No weight differences were present at the time of infection (data not shown).

Histopathology. Previous studies have shown that in this model of bacterial meningitis neuronal cells in the subgranular zone of the dentate gyrus undergo apoptosis (17, 19). In the present study, apoptosis in the dentate gyrus was more frequent in the infected dexamethasone treated animals than in infected controls (median [range] 56.6 [2.63–132.1] *versus* 5.5 [0—31.9], $p < 0.01$) (Fig. 1 and 2). In uninfected animals, there was a slight, nonsignificant increase in apoptosis in the hippocampus in animals treated with dexamethasone compared with controls (Fig. 2). Injury to the cortex was relatively minor, such that the previously documented beneficial effect of dexamethasone on this form of injury could not be evaluated in the present study (27).

Learning assessment. All animals had normal vestibulomotor function based on their ability to stay on the rotating rod. The distance to reach the platform decreased in all groups of animals over the four test days ($p < 0.001$). Uninfected controls improved their learning significantly faster than infected control animals ($p < 0.001$) (Fig. 3). Furthermore, among infected animals, those treated with dexamethasone had significantly reduced learning capacity compared with infected controls ($p = 0.01$; Fig. 3). Among the uninfected controls, there was no measurable effect of dexamethasone treatment on performance in the water maze learning test (data not shown).

DISCUSSION

In the present study, we found that dexamethasone, which has been shown to have some beneficial effects as adjuvant

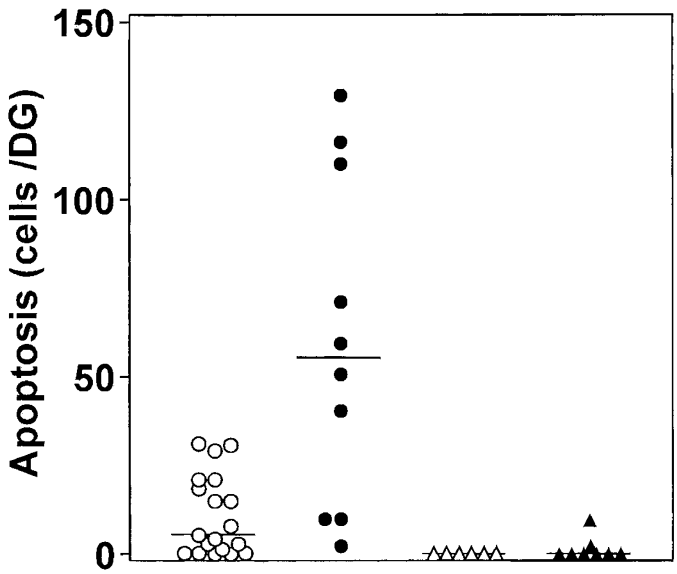

Figure 2. Effect of dexamethasone on hippocampal apoptosis in infant rats with pneumococcal meningitis. Dexamethasone significantly increased apoptosis in infected animals ($p < 0.01$, Mann-Whitney rank-sum test). In uninfected animals no effect was observed. (○, infected vehicle treated; ●, infected dexamethasone treated; △, uninfected vehicle treated; ▲, uninfected dexamethasone treated).

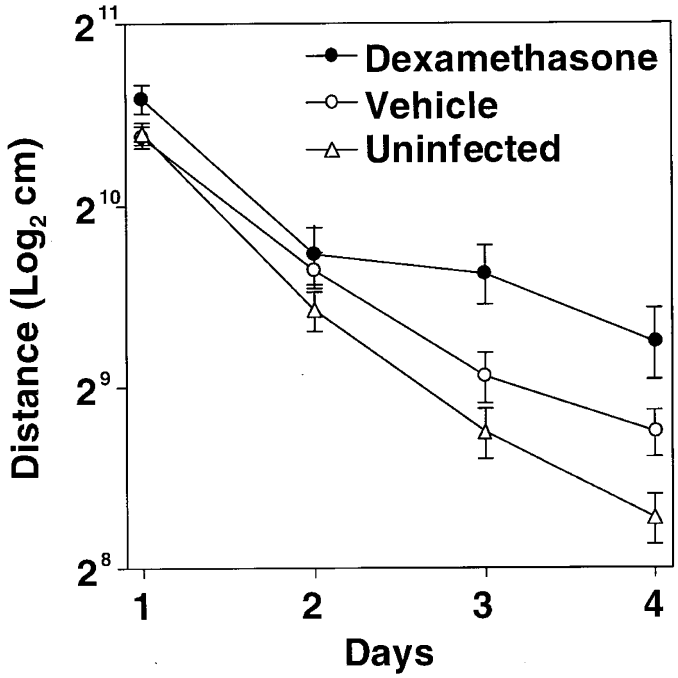

Figure 3. Assessment of learning capacity by Morris water maze 3 wk after infection (analysis of the distance to reach platform. Uninfected control animals learned significantly faster than infected animals ($p < 0.001$). Adjuvant therapy of meningitis with dexamethasone led to inferior performance compared with vehicle treated animals ($p = 0.01$). ANOVA, pair wise comparison with Tukey-Kramer adjustment.

therapy in bacterial meningitis (9, 11, 28), led to an increase in apoptotic cell death in the hippocampal dentate gyrus of infant rats with pneumococcal meningitis. These findings expand on the previous observation in adult rabbits with pneumococcal meningitis, where dexamethasone also led to an increase in hippocampal neuronal apoptosis (18). Thus, in two different experimental systems, infant rats and adult rabbits, there is an association between dexamethasone treatment and hippocampal neuronal apoptosis. More importantly, the present study demonstrates that the increase in hippocampal apoptosis induced by adjuvant therapy with dexamethasone was associated with reduced learning capacity in the Morris water maze test, which assesses spacial learning and memory based on visual cues (17, 19).

The results of the present study are similar to a previous study from our laboratory, in which the brain-penetrating antioxidant PBN also increased dentate gyrus apoptosis and at the same time reduced performance in the water maze test (17, 19). Studies using different experimental probes with different molecular mechanisms strengthen the contention that apoptotic neuronal death in the dentate gyrus has a negative effect on spacial learning in experimental pneumococcal meningitis and suggest that the details of this association warrant further studies.

Neurons of the hippocampal regions show a high density of glucocorticoid receptors (29) and there are complex interactions between systemic corticosteroid levels and cell viability of hippocampal neurons (30). Recent studies indicate that stimulation of the high affinity mineralocorticoid receptor shifts the balance between pro- and anti-apoptotic factors of the *bcl*-2 gene family in favor of cell survival, while stimulation of the low affinity glucocorticoid receptor has the opposite effect (30). In keeping with these observations, treatment of rats with the glucocorticoid dexamethasone induced apoptosis in the hippocampus, especially in the dentate gyrus and CA1 and CA3 regions (31, 32). Also, chronic corticosteroid (prednisone) treatment in patients with systemic disease in a retrospective study appeared to deteriorate hippocampus-dependent explicit memory (33).

Apoptotic cell death in the dentate gyrus in experimental pneumococcal occurs in a caspase-3 dependent fashion (34, 35). However, little is known about the stimuli that lead to the induction of this cell death pathway. Among various adjuvant therapies tested in the pneumococcal meningitis model in infant rats, only the use of a combined MMP/TACE inhibitor has reduced the extent of apoptotic injury and the associated impaired performance in the Morris water maze (17).

The basis for the adverse effects of dexamethasone remains currently unclear. Importantly, administration of dexamethasone in the dosing schedule used in this study had no effect on hippocampal cell death or functional performance in uninfected animals. Thus, the adverse effect of the drug was only unmasked by the presence of meningitis. This could indicate an increased susceptibility of dentate gyrus neurons to the effects of steroids during meningitis. The present observations raise, in addition to questions regarding the molecular mechanisms, several important clinical questions. Prominently, efforts should be made to explore the possibility that dexamethasone has similar adverse effects on hippocampal structure and function in humans with bacterial meningitis treated with dexamethasone. While the controlled clinical studies have made attempts to assess neurologic outcome, the methods used for this assessment and the follow-up time may not have been sufficient to reliably detect more subtle effects of corticosteroids on hippocampal functions. It is also not known whether the observed effect is age-dependent. In rodents, older animals appeared to be more susceptible to steroid-induced apoptosis, but no similar data are available for humans (36).

CONCLUSION

In summary, the present study confirms previous experimental observations that adjuvant therapy with dexamethasone for bacterial meningitis may increase neuronal damage to the hippocampus and demonstrates for the first time that this increase in neuronal loss is associated with functional deficits in learning. Important questions regarding the basic mechanisms of this observation and its clinical significance are raised by these observations. For example, adjuvant therapy of bacterial meningitis with dexamethasone has been shown to reduce severe hearing loss in children, which also might influence overall learning performance in survivors (11). The potential to preserve hearing capacity by giving dexamethasone needs to be balanced against the possibility of inducing hippocampal damage by this treatment. Future studies must carefully assess the possible effects of dexamethasone on hippocampal function in patients with meningitis.

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