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REVIEW ARTICLE

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Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside

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Abstract Central nervous system toxicity following administration of beta-lactam antibiotics, of which penicillin is the prototype, is a potential cause of morbidity and mortality. In recent years, important advances have been made in the pathogenesis of antibiotic-related neurotoxicity. This review focuses on the experimental and clinical aspects of neurotoxicity caused by beta-lactam antibiotics. The purpose is to provide an update on the pathogenesis, mechanism, and clinical manifestations of the neurotoxicity, along with an overview of the relationship between antibiotic structure and convulsive action. In particular, some of the prevailing ideas about pathogenesis are highlighted, including theories of the mechanism of pathogencity. A better understanding of antibiotic-related neurotoxicity, as derived from animal models and human clinical experience, would be of value in facilitating more efficient and safer use of antimicrobial compounds.

Introduction

Epileptogenic properties of penicillin were first described in 1945 by the classic works of Johnson and Walker [1–4]. In their seminal animal experiments involving macaque monkeys and cats [1, 3], the animals were noted to appear listless and uninterested in their surroundings shortly after administration of penicillin to the cerebral cortex. At times, the animals exhibited myoclonic jerks and tonic–clonic seizures accompanied by electroencephalographic manifestations of convulsion. In human subjects, historically, benzylpenicillin was used for treatment of bacterial meningitis via the subarachnoid space or the intraventricular route. The potential neurotoxicity of penicillin administered in large quantities intrathecally had been documented since the 1940s, when a case of seizure was reported after inadvertent intrathecal instillation of 500,000 U of penicillin [3]. The risk of neurotoxicity after parenteral administration of the antibiotic was further established after demonstration of a progressive increase in cerebrospinal fluid drug concentration with cephalad progression in the subarachnoid space [5]. This was then borne out nearly 6 decades ago by clinical observation among 15 individuals who developed seizures and other central nervous system adverse events after intravenous penicillin [6].

Since then, adverse effects of penicillin and beta-lactam antibiotics on the central nervous system have become more widely recognized. Clinical manifestations include confusion, disorientation, twitching, somnolence, myoclonus, and, notably, convulsions ranging from generalized tonic clonic seizures to nonconvulsive status epilepticus [7–9]. Important advances have recently shed light on the pathogenesis of neurotoxicity induced by beta-lactam antibiotics, providing insight into this disorder as well as implications for diagnostic and preventive measures. We review here these recent investigations that hold promise for clinical practice.

Theories of pathogenesis

The most widely accepted theory on the pathogenesis of convulsions induced by penicillin and related beta-lactam compounds involves the interference or inhibition of gamma-aminobutyric acid (GABA) binding to $GABA_A$ receptors, a member of the ligand-gated ion channel superfamily [10]. The $GABA_A$ receptor complex, present both at synapses and outside of synapses on neurons, consists of a hetero-pentamer that forms an integral part of the chloride channel. At least 19 different subunits of the mammalian $GABA_A$ receptors are thus far described according to the subunit amino-acid sequence homology. Most, if not all, of these isoforms with different subunit compositions are ligand-gated chloride channels involved in inhibitory synaptic transmission. In other words, a

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reduction in GABA-mediated inhibition on the inward chloride current permits excitatory cortical afferents to produce central nervous system excitation or trigger epileptiform discharges [11]. As illustrated in Fig. 1, the chloride influx is closely modulated by variable ligand binding to various binding sites of the transmembrane $GABA_A$ receptor complex. Noteworthy is the fact that positive modulators of $GABA_A$ receptors, such as benzodiazepines and barbiturates, are more efficacious than phenytoin to treat convulsions induced by beta-lactam antibiotics [12]. This observation lends credence to the role of $GABA_A$ receptors in antibiotic-induced neurotoxicity.

The proposed mechanism underlying the inhibitory effect of beta-lactam antibiotics on chloride current, as mediated by $GABA_A$ receptors, has been studied both in vivo and in vitro. Among the mechanisms associated with different classes of antibiotics, penicillin antagonism at the $GABA_A$ receptors is the most well characterized prototype. In experimental models using rat brain membranes, penicillins inhibited specific [^{3}H] GABA binding, in keeping with the assumption that penicillins are weak GABA receptor antagonists [13]. By means of the extracellular patch clamp recording technique to study the gating of GABA receptor chloride channels in mouse spinal cord neurons, penicillin was shown to produce a concentration-dependent reduction in the duration that $GABA_A$ receptor channels were open [14]. Penicillin appears to bind within the $GABA_A$ chloride ionophore channel to reduce the inward chloride currents (Fig. 1). This is mediated by a reduction in the mean duration that GABA receptor channels are open, despite an increase in the frequency of channel opening. Furthermore, penicillins might directly antagonize the binding of GABA to the $GABA_A$ receptor [15]. A postulated indirect antagonistic action of penicillin at the $GABA_A$ receptors derived from another earlier study of the interaction between penicillin derivatives and the affinity of benzodiazepine [^{3}H] flunitrazepam for the benzodiazepine receptor [16]. These in vivo data demonstrated a strong correlation between the affinity of the penicillin derivatives for the benzodiazepine receptor, as given by the IC50 values, and their neurotoxicity.

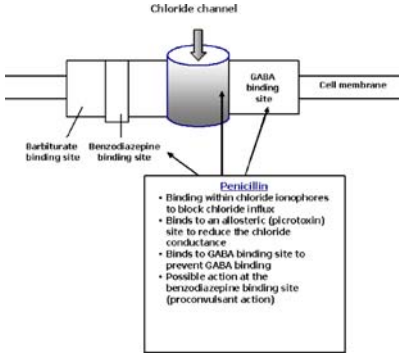

Fig. 1 Schematic representation of the transmembrane gamma-aminobutyric acid (GABA) subtype A ($GABA_A$) receptor, which is thought to be an assembly of different subunits. Potential interaction of penicillin with various binding sites of the $GABA_A$ receptor complex that mediates the chloride ion channel is indicated

The era of molecular medicine provides further insight into the mechanism of penicillin neurotoxicity, through the use of cloning techniques to identify the genes that encode for the $GABA_A$ receptor subunits. In a mutational study, a single mutation of a murine $GABA_A$ receptor drastically abolished the inhibitory effect of penicillin [17]. The same point mutation in the $GABA_A$ subunit had been reported to abolish the inhibitory effect of the classical noncompetitive inhibitor picrotoxin [18]. Taken together, the site-directed mutagenesis of the $GABA_A$ subunit appears to suggest that penicillin acts on a site identical or adjacent to that of picrotoxin (Fig. 1) in the channel pore of the $GABA_A$ receptor.

Although studies of GABA modulation have yielded useful information, there are other plausible mechanisms of penicillin neurotoxicity that occur in the absence of GABA. More recently, another model has been proposed to suggest that penicillin plugs the chloride channel pore and holds the receptor in an open conformation but prevents ion conduction until it is removed [19].

Furthermore, evidence is accumulating of different mechanisms of $GABA_A$ receptor inhibition by various beta-lactam antibiotics. Whilst penicillin is thought to inhibit $GABA_A$ receptors in a noncompetitive and voltage-dependent manner, not all beta-lactam antibiotics act in the same manner. Previous binding studies and electrophysiological data, for instance, suggested direct antagonistic action at the $GABA_A$ receptor complex to account for the epileptogenic effects of the cephalosporins [11, 15, 17, 20, 21].

Relationship between antibiotic structure and neurotoxicity

Cognizant of these mechanisms, we will examine the relationship between the molecular structures of various beta-lactam antibiotics and the potential of these antibiotics to cause neurotoxicity. The familiar basic structure of penicillin consists of a 5-member thiazolidine ring and a 4-member beta-lactam ring that carries a secondary amino group at the C-6 position. Cephalosporins differ in their basic structure from the penicillins in that they contain a 6-member thiazolidine ring fused to the beta-lactam portion. The beta-lactam ring is thought to be essential for the antibacterial structure, whereas the side chain largely determines the antibacterial spectrum and pharmacologic properties. Interestingly, the epileptogenic properties have been traced to the beta-lactam ring; an enzymatic cleavage of this ring has resulted in the loss of epileptogenic activity [22, 23]. The enzyme penicillinase catalyzed the hydrolysis of the beta-lactam ring of penicillin and abolished the epileptogenic properties of benzylpenicillin in vivo, when directly applied to the adult cat cerebral cortex, and that application of penicillinase to already established penicillin-induced epileptogenic foci shortened the duration of the focal discharge [23]. In retrospect, recognition of this phenomenon dated back to the fundamental work by

Walker et al. [1], who reported that the convulsive effects of penicillin could be minimized in a proportionate manner by inactivating penicillin, by means of boiling, autoclaving, or enzyme degradation. The hypothesis that the structure of beta-lactam antibiotics plays an underlying role in drug neurotoxicity is further supported by the fact that the penicillin beta-lactam ring shares a structural similarity with the inhibitory neurotransmitter GABA.

Aside from the central role of the beta-lactam ring, subsequent studies further demonstrated the epileptogenic activity derived from the thiazolidine ring [24], as well as substitutions at positions 3 and 7 of the side chain (Fig. 2) [22, 25–27]. For the purpose of evaluating the relationship between antibiotic structure and the activity of various antibiotics, drug exposure experimental models in the form of the in vitro hippocampal slice technique is among the most commonly used means [22, 24]. The major advantages include the absence of the blood–brain barrier and a testing condition with a well-defined concentration of antibiotic. Such studies permit a comparison of various beta-lactam antibiotics in terms of neurotoxicity. On the basis of comparative studies of different beta-lactam antibiotics, the likelihood of antibiotic-associated neurotoxicity has been tested and tabulated in Table 1 [11, 21, 24–30]. Furthermore, the rank orders of convulsive activities of these antibiotics were found to correlate closely with those of inhibitory potencies on [^{3}H] muscimol binding (a specific radiolabeled ligand for the $GABA_A$ receptor) and GABA-induced currents of $GABA_A$ receptors in vitro [21]. These results, in turn, support the role of GABA-mediated inhibition of neurotransmission in the pathogenesis of antibiotic-related neurotoxicity.

A special circumstance meriting comment is the neurotoxicity caused by another class of novel beta-lactam antibiotics, i.e. carbapenems [31]. The parent compound of imipenem most probably shares the GABA-mediated mechanism with penicillins, although the role of the beta-lactam ring is less well defined in the former. Instead, the high incidence of neurotoxicity with the imipenem-cilastatin combination might have been related to the strength of basicity of the amino group in the side chain on the second carbon atom; this side chain is more basic (as

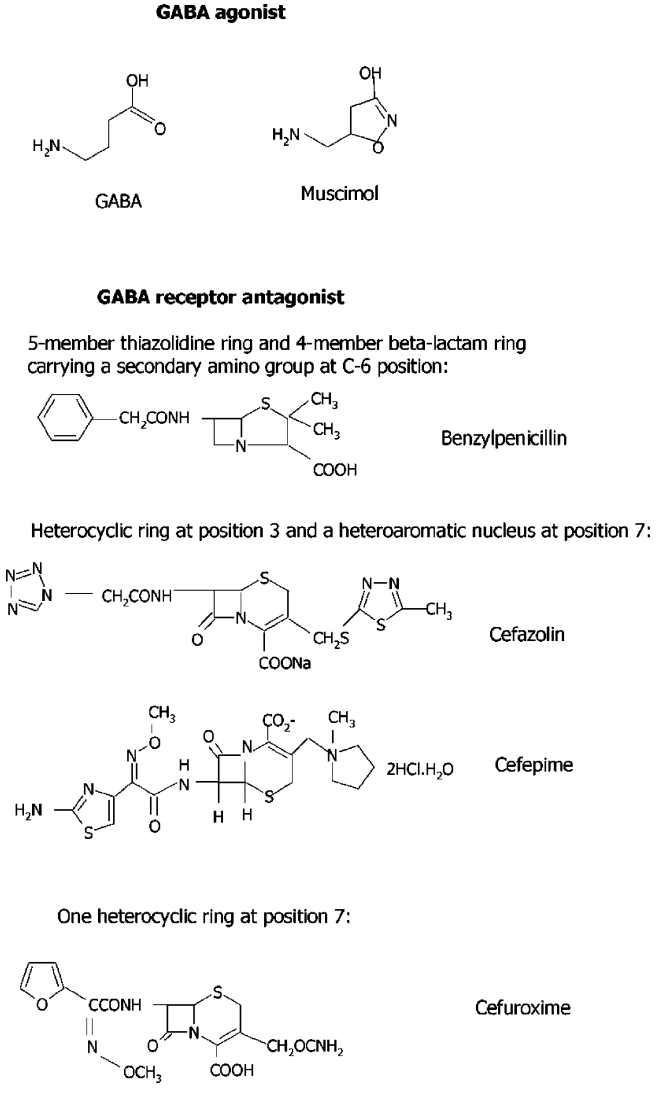

Fig. 2 Diagrammatic illustration of benzylpenicillins and beta-lactam antibiotics

Table 1 Likelihood of neurotoxicity caused by beta-lactam antibiotics

Risk of neurotoxocity due to beta-lactam antibiotics[a]	Structural characteristics (see Fig. 2 for details)
High-risk agents	
Benzylpenicillin	
Cefazolin	Tetrazole derivatives and marked similarity with pentylenetetrazole
Cefoperazone	
Cefoselis	
Ceftazidime	Heterocyclic ring at position 3 and position 7 of 7-aminocephalosporanic acid
Cefepime[b]	
Medium-risk agent	
Ceftriaxone	Heterocyclic ring at position 3 and position 7
Low-risk agents	
Cefotaxime	One heterocyclic ring at position 7
Cefuroxime	
Cephalexin	Substitution of a heterocyclic ring at position 3 (R2) with small groups
Cephradine	

[a]This table is subject to the limitations of the medical literature, and this column reflects the authors' assessment of the likelihood of antibiotic-related neurotoxicity, based on all the available sources of information as presented in the text

[b]Despite the lack of laboratory evidence, the risk of cefepime-related neurotoxicity exists, given the proximity of cefepime to another fourth-generation cephalosporin, cefoselis, as well as recent clinical data [8, 30]

compared to that in meropenem) and hence has higher binding avidity to $GABA_A$ receptors [32, 33].

Patient factors

Irrespective of the aforementioned pathogenesis, neurotoxicity following administration of beta-lactam antibiotics was believed to result from accumulation of the compounds in the central nervous system, particularly in the setting of excessive dosage and impaired renal clearance.

Previous clinical observations of beta-lactam antibiotic-related neurotoxicity suggested several at-risk populations, including infants and elderly patients, patients with meningitis, and those who have undergone cardiopulmonary bypass [7, 11, 12, 29, 34]. Nevertheless, little doubt now exists that renal insufficiency is the most important patient-related factor predisposing to neurotoxicity caused by beta-lactam antibiotics [8, 11, 30, 31, 35–37]. The association between renal failure and the potential for beta-lactam antibiotic-related neurotoxicity was initially based on the tacit assumption of increased drug levels in serum and cerebrospinal fluid [35, 38, 39]. The weight of current evidence, largely from animal studies, suggests that the concentrations of antibiotic in brain tissue, rather than the concentrations in cerebrospinal fluid, were predictive of neurotoxicity [31, 40, 41]. In the rabbit models of benzylpenicillin neurotoxicity [40, 41], drug concentrations in serum, cerebrospinal fluid, and brain tissue fluid were determined at the onset of epileptogenic electroencephalographic activity or convulsions. The concentrations of benzylpenicillin in brain tissue fluid, rather than the concentrations in cerebrospinal fluid, were found to correlate consistently with neurotoxicity. These experimental data, as derived from animals, have contributed to unravel the myriad mechanisms underlying neurotoxicity in renal failure, although the precise pathophysiology remains poorly understood. It is possible that increased permeability of the blood-brain barrier and decreased albumin binding of antibiotics in the presence of uremia, as well as the presence of endogenous uremic toxins such as potentially neurotoxic guanidino compounds, might increase a patient's vulnerability to antibiotic-associated neurotoxicity [29, 42].

Last, but not the least, the involvement of patient-related factors in neurotoxicity caused by beta-lactam antibiotics is best illustrated by the example of imipenem-cilastatin. Seizures, mostly observed 7 days after the commencement of therapy, are particularly common when imipenem-cilastatin is administered to patients with central nervous system lesions, a history of seizures, renal insufficiency, and an excessive dose relative to renal function. For unclear reasons, patients with *Pseudomonas aeruginosa* infection are more predisposed to develop seizures after receiving imipenem-cilastatin [43].

Conclusion

Not until recently have we begun to understand the mechanisms that govern the diverse clinical manifestations of neurotoxicity caused by beta-lactam antibiotics. Obviously, understanding which cellular and molecular mechanisms are at work in patients predisposed to antibiotic-related neurotoxicity is of considerable clinical interest. Deciphering the convulsive action of beta-lactam antibiotics is also important for a better understanding of epilepsy. Equally important, we envisage the potential clinical impact of better designed antimicrobial therapy, resulting in a lower likelihood of neurotoxicity.

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