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BRIEF COMMUNICATION

# Anticonvulsant Effect of Allopurinol on Hippocampal-Kindled Seizures

YUJI WADA,[1] HIDEHIRO HASEGAWA,
MITSUHIKO NAKAMURA AND NARIYOSHI YAMAGUCHI

*Department of Neuropsychiatry, Kanazawa University School of Medicine, Kanazawa 920, Japan*

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WADA, Y., H. HASEGAWA, M. NAKAMURA AND N. YAMAGUCHI. *Anticonvulsant effect of allopurinol on hippocampal-kindled seizures.* PHARMACOL BIOCHEM BEHAV **42**(4) 899-901, 1992. – This study assessed the anticonvulsant effect of allopurinol (5 and 50 mg/kg, IP) on seizures kindled from the feline hippocampus. Allopurinol at a higher dose significantly reduced the behavioral seizure stage, but not afterdischarge duration, without producing any behavioral toxicity. The present results lend experimental support to the contention that allopurinol possesses anticonvulsant efficacy in the treatment of human epilepsy.

Epilepsy Allopurinol Kindling Hippocampus

SINCE the first report by Coleman et al. (3), allopurinol has been shown to be effective in the treatment of epilepsy (5, 6,15,22). Some studies have demonstrated, however, that allopurinol possesses no clinical efficacy (18,20). To our knowledge, there have been two experimental studies on the anticonvulsant effect of allopurinol, but the results are conflicting: Makhailov and Gusel (14) showed that allopurinol suppressed penicillin-induced epileptic activity of the rat hippocampus (HIP), whereas Hoppe et al. (9) reported no inhibitory effects on oxygen-induced seizures in mice.

Kindling is a phenomenon in which repeated administration of an initially subconvulsive electrical stimulation results in progressive intensification of seizure activity, culminating in a generalized convulsion (8). The kindling model has been validated as a useful test of anticonvulsant action and offers several advantages in the screening of potential anticonvulsant drugs (1). The present study was conducted to examine the effect of allopurinol on seizures kindled from the feline HIP.

## METHOD

Experiments were performed on six adult cats of either sex weighing 2.6–3.5 kg. Under pentobarbital anesthesia (30 mg/kg, IP), bipolar stimulating-recording electrodes were inserted into the dorsal HIP, according to the coordinates of the atlas of Jasper and Ajmone-Marsan (10). Stainless steel screws were placed bilaterally in the skull over the motor, auditory, and visual cortices. A reference electrode was placed on the bone over the anterior part of the frontal sinus.

Following 1 week of postoperative recovery, we determined the threshold intensity of stimulation sufficient to elicit an afterdischarge (AD). Electrical stimulation was performed once daily with a 2-s train of biphasic constant-current, 60-Hz, sine-wave pulses. The stimulus intensity was initially set at 100 $\mu$A peak-to-peak and was subsequently increased by 50-$\mu$A steps each day until AD was elicited. The intensity that first produced AD was designated as the AD threshold (420 ± 99 $\mu$A, mean ± SEM) and was continued until generalized convulsions were provoked on 5 consecutive days. The generalized seizure-triggering threshold (GST) was then determined in each cat by application of trains that were decreased in intensity at 50-$\mu$A steps once daily. Cats were placed in an observation chamber with a one-way window through which behavioral observation was made. Kindling seizure development of the HIP was rated according to the following six-point scale (19): stage 1, attention response; stage 2, immobility; stage 3, autonomic manifestation; stage 4, facial twitching; stage 5, tonic extension of the contralateral forepaw; stage 6, generalized convulsion. Cats had a 1-week rest after elicitation of the final generalized convulsion, after which the following experiments were conducted.

[1] Requests for reprints should be addressed to Yuji Wada, M.D., Department of Neuropsychiatry, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa 920, Japan.

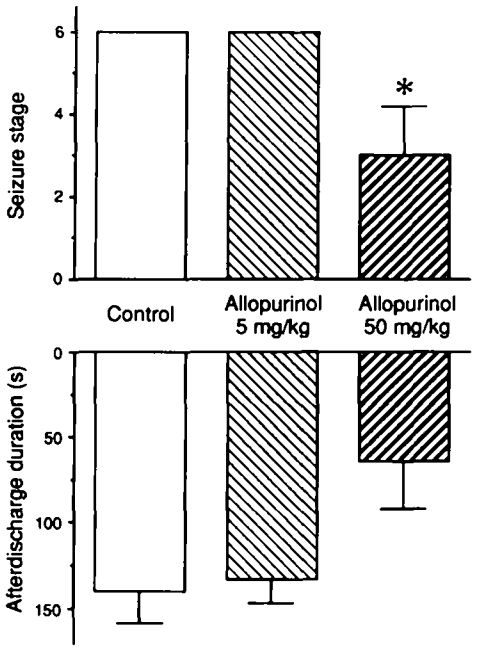


FIG. 1. Effects of allopurinol (5 and 50 mg/kg, IP) on the seizure stage and afterdischarge duration of fully kindled seizures from the hippocampus. Data represent mean ± SEM ($n$ = 6). Seizure stages graded as in the Method section. *$p < 0.05$, compared with DMSO control (Dunnett's test).

Allopurinol was dissolved in dimethyl sulfoxide (DMSO). Cats received IP injection of either DMSO or allopurinol (5 or 50 mg/kg) in random order. Electrical stimulation at GST (300 ± 86 μA) was delivered 1 h after drug administration. Each drug or DMSO trial was separated by at least 72 h. The background electroencephalographic (EEG) activity and behavior were continuously monitored for at least 1 h following drug administration. The anticonvulsant effect of allopurinol was assessed by behavioral seizure stage as outlined above and by AD duration. Following the experiment, cats were killed under deep anesthesia, and histological examination showed that all electrode tips were in the intended structures.

The data were evaluated by Friedman's analysis of variance (ANOVA), followed by Dunnett's multiple-comparisons procedure. A value of $p < 0.05$ was considered significant.

## RESULTS

The results of the present experiment are shown in Fig. 1. Allopurinol significantly affected the behavioral stage in the HIP-kindled seizures ($p$ = 0.018, Friedman's test). Posthoc analysis by Dunnett's test showed that allopurinol at 50 mg/kg, but not 5 mg/kg, produced a significant reduction in the behavioral seizure stage ($p < 0.05$) when compared with the DMSO control. The AD duration was not significantly affected by allopurinol ($p$ = 0.22, Friedman's test). Since stimulation at GST failed to elicit seizure activity in two cats after the injection of 50 mg/kg, the intensity was then increased in steps of 50 μA at intervals of 5 min until an AD was provoked. In response to the stimulation at the intensity of 100 μA above GST, these cats showed stage 6 generalized convulsions.

There were no appreciable changes in background EEG activity or behavior after the injection of allopurinol at two doses.

## DISCUSSION

Allopurinol is an inhibitor of xanthine oxidase that has been used clinically to treat primary or secondary hyperuricemia (16). This drug has also been reported to ameliorate ischemic tissue damage (4,17). Clinical trials have shown that allopurinol is effective in patients with medically refractory partial and generalized tonic-clonic seizures (3,5,6,15,22). In addition, Kramer et al. (11) reported a case of convulsive status epilepticus occurring after allopurinol withdrawal. The present experiment shows that allopurinol administered acutely can suppress HIP-kindled seizures in the cat. Our finding is consistent with that obtained in the rat with penicillin-induced epileptogenic foci of the HIP (14), and supports the view of Tada et al. (22) that allopurinol would be most effective in patients with localization-related epilepsy, especially temporal lobe epilepsy.

The mechanism of action of allopurinol is unknown. Since the plasma concentrations of conventional antiepileptic drugs remain virtually unchanged (5,6,22), the allopurinol effect is not due to pharmacokinetic interactions. Allopurinol inhibits tryptophan-2,3-dioxygenase, the key enzyme in the oxidation of tryptophan, and leads to a reduction in quinolinic acid (2). Stober and Jacobi (21) postulated the "quinolinic acid hypothesis" as a part of the mechanism because quinolinic acid is a potent endogenous neuroexcitatory substance known to exert a proconvulsant action (7,13). Mikhailov and Gusel (14) demonstrated that allopurinol increases the serotonin content and suggested that a shift in tryptophan metabolism toward elevated serotonin production results in suppression of penicillin-induced seizures. This serotonergic inhibition is likely because 5-hydroxytryptophan, an immediate precursor that elevates brain serotonin, has an inhibitory action against HIP-kindled seizures (23). It is of interest that long-term antiepileptic medication results in lower concentrations of uric acid in epileptic patients than in normal controls (12), suggesting that antiepileptic drugs may be of value in the treatment of hyperuricemia.

Although the precise mechanism remains to be clarified, the present experiment shows that allopurinol can suppress HIP-kindled seizures in the absence of behavioral toxicity and background EEG changes. Our data lend experimental support to the contention that allopurinol possesses anticonvulsant efficacy in human epilepsy.

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