J Neural Transm [GenSect] (1991) 83: 127–137

Journal of Neural Transmission

Decreased susceptibility to seizures induced by bicuculline after transient bilateral clamping of the carotid arteries in rats*

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Accepted June 26, 1990

Summary. Rats were exposed for 24 min to bilateral clamping of the common carotid arteries (BCCA) in pentobarbital anaesthesia. 14 days later the animals were subjected to subcutaneous injection of (+)-bicuculline (3 or 4 mg/kg). A significantly decreased susceptibility to bicuculline-induced seizures could be observed in BCCA treated rats compared with sham operated controls. It is suggested that BCCA treatment protects animals against status epilepticus and lethal toxicity produced by bicuculline. Electrographic recordings of the BCCA animals revealed no ictal activity within 1 h after bicuculline injection. An analysis of the GABA content showed a significant increase in the hippocampus (HPC), frontal cortex (FCX), parietal cortex and substantia nigra in BCCA animals compared with controls. It is therefore possible that an increase in GABA content postsynaptically counteracts the $GABA_A$ antagonistic effect of bicuculline in BCCA animals thus preventing the normal seizure inducing effect of this substance.

Keywords: Seizure, status epilepticus, bicuculline, GABA, cerebral protection, carotid occlusion.

Introduction

Recently it has been reported that **b**ilateral **c**lamping of the common **c**arotid **a**rteries (BCCA) in normotensive rats for 24 min leads to a marked decrease in the susceptibility to pilocarpine induced seizures 14 days after surgery (Heim et al., 1987). After BCCA rats showed a significant increase in the GABA content

* Supported by Deutsche Forschungsgemeinschaft, SFB 330, Organprotektion

in hippocampus (18%) and frontal cortex (20%) 14 days after surgery (Heim et al., 1987). The inhibitory neurotransmitter γ-aminobutyric acid (GABA) has been implicated in both the generation (Le Gal la Salle et al., 1988; Meldrum, 1975; Tower, 1976) and blockade (Gale and Iadarola, 1980; Meldrum, 1982) of seizure processes. It was found that protection from seizures was due to an elevation of GABA or a direct stimulation of GABA receptors within a defined area (Iadarola and Gale, 1982). It was therefore suggested (Heim et al., 1987) that the decreased susceptibility for pilocarpine in BCCA animals might be related to the elevation of GABA in structures (Fukuda et al., 1987; Kamphuis et al., 1989; Cavalheiro et al., 1982) generating seizures.

An aim of our study therefore was to establish whether an elevation of GABA in selected regions of the brain confers protection from generalized motor seizures induced by the $GABA_A$ antagonist bicuculline. If the increased GABA content observed in BCCA rats reflects an increased postsynaptic function it may be postulated that the normal bicuculline-induced seizure response would be nullified.

BCCA treated and sham operated male and female rats were subjected to subcutaneous injection of bicuculline 14 days after surgery and the induced behavioural changes were observed and the seizure latency measured. In a seperate group, electrographic recordings were registered from the cortex and hippocampus. The GABA content was measured in the hippocampus, frontal and parietal cortex, amygdala and piriform cortex, thalamus, striatum, substantia nigra, colliculus, septum, hypothalamus and cerebellum.

Material and methods

Male as well as female HAN-WIST (own breeding colony) rats weighing 220–240 g were used. The animals were given free access to food and water and were housed in groups of 8. They were exposed to a light/dark cycle of 12 and 12 h, in room temperature 21 °C, humidity 55%.

Surgical procedure

Rats were operated in pentobarbital anaesthesia (Nembutal, CEVA, France, 60 mg/kg i.p.). The common carotid arteries were exposed and clamped by using thread (**b**ilateral **c**lamping of the **c**arotid **a**rteries: BCCA). After an occlusion time of 24 min the threads were removed, free blood flow through the vessels was visually inspected and the surrounding skin sutured. The carotid arteries of the sham operated rats were exposed but not clamped. During anaesthesia and surgery the rectal temperature of all animals fell to values between 35.5 – 34.5 °C. Intracerebral temperature measured stereotaxically (in a seperate group of animals) in hippocampus and frontal cortex by means of digital laboratory thermometer probe (model: BAT-12 R; IT 23, Sensortec Inc., Clifton, New Jersey, USA) was lowered by 1.6 °C and 2.5 °C, respectively, immediately after occlusion of the carotid arteries reflecting a reduced cerebral blood flow. The temperature increased so as to approach control values within the first 10 min of the reperfusion phase. The local pO_2 values measured by microelectrodes decreased during BCCA by 71% in hippocampus and 32% in striatum (Block et al., 1989). But no neuronal damage was to be seen in vulnerable brain structures up to 14 days after surgery. Thus physiological and morphological parameters reflect no

severe generalized ischemia or anoxia but reflect a state of reduced cerebral blood flow. The mean arterial blood pressure of about 120–140 mmHg was not altered significantly by BCCA treatment. The evoked potentials did not flatten during occlusion of arteries (cf. Block et al., 1990).

Induction of bicuculline seizures

4 days after surgery BCCA treated and sham operated control rats were injected subcutaneously with 3 or 4 mg/kg of (+)-bicuculline (Sigma, Heidelberg, FRG) dissolved in 0.1 N HCl and adjusted to pH 6–6.5 with 1 N NaOH. The two weeks interval was choosen to be sure that no delayed neuronal death (cf. Kirino, 1982; Schmidt-Kastner and Hossmann, 1988) occurs as it was checked by light microscopy. After injection of bicuculline the animals' behaviour was observed for a period of 1 hour. Status epilepticus was defined as motor seizure activity for at least 20 min according to the stages IV/V of the kindling scale of Racine (1972). Lethal toxicity was defined as death occuring within 24 h following the aministration of the substance.

Electrographic recordings

For intrahippocampal recording a bipolar twisted electrode (tip diameter 100 µm, interelectrode distance 500 µm) was stereotaxically positioned (under pentobarbital anaesthesia; 50 mg/kg) in the right dorsal hippocampus according to the atlas of Pellegrino and Cushman (1967) (AP 4.0, L + 2.5, V + 3.5) and anchored to the skull with dental acrylic. Surface recordings were led from jeweler screws positioned bilaterally over the frontal cortex. An additional screw placed in the frontal sinus served as a reference (indifferent) electrode. Signals under investigation were amplified by a Beckman model RM polygraph (time constant 0.03 s, high cut off filter 15). EEG recordings and behavioural observations were carried out in a plexiglas compartment (30 × 30 × 45 cm) 14 days after BCCA treatment. Before the monitoring of EEG, animals were individually placed in the recording compartment and allowed 30 min for habituation to the recording set-up. The baseline EEG recordings were made for 60 min. Following injection of bicuculline, EEG recordings were continuously registered and the behaviour observed for 60 min.

Determination of regional GABA content

Rats were decapitated 14 days after surgery and the heads immediately placed in liquid nitrogen for 6 s (Wood et al., 1968). The frozen brains were rapidly removed and the different structures dissected on an ice plate. GABA content was measured according to the method of Lowe et al. (1958) modified by Sutton and Simmons (1974), as described by Kleinrok and Turski (1980). To examine a possible increase of GABA during dissection, 1 group of animals was killed under the same conditions 2.5 min after the injection of 3-mercaptopropionic acid (3-MP, 100 mg/kg i.p.) (Lindgren and Simmonds, 1987; Löscher and Vetter, 1984). GABA content was calculated in µmol/g of fresh tissue.

Statistics

χ^2-Test was used to calculate statistical differences in the susceptibility of rats to seizures. For calculation of the time differences in seizure latency and differences in GABA content Student's t-test was used.

Results

Behaviour

24 min of BCCA decreased the susceptibility to bicuculline induced seizures when tested 14 days after surgery. As can be seen in Fig. 1, bicuculline in a dose of 3 mg/kg s.c. did not produce seizures in BCCA treated animals to the

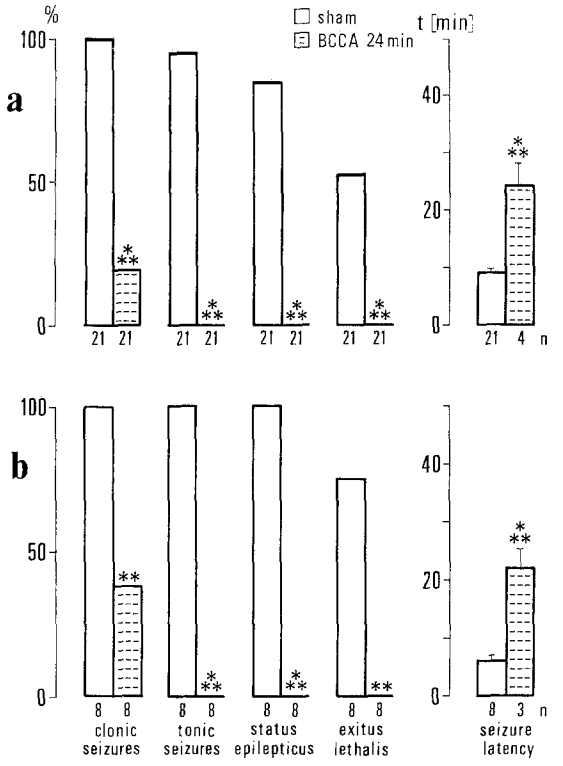

Fig. 1. Occurrence of motor seizures in % observed during the first hour after injection of bicuculline 3 mg/kg s.c. in female (**a**) and in male (**b**) rats 14 days after 24 min of BCCA treatment or sham operation. A marked decrease in seizure susceptibility can be observed in BCCA-treated rats, all of them are protected against tonic seizures, status and lethal toxicity. The latency of 1st seizure activity is significantly increased in n = 4 female and n = 3 male BCCA treated rats, which developed clonic motor seizures. Statistics: $^{**}p < 0.01$ vs sham; $^{***}p < 0.001$ vs sham; χ^2-test. Student's t-test was used for calculation of differences in seizure latency: $^{***}p < 0.001$ vs sham

same extent as in sham operated animals [females: 21 of 21 in sham but only 4 of 21 in BCCA animals, (a); males 8 of 8 in sham but only 3 of 8 in BCCA animals, (b)]. In BCCA animals where clonic seizures developed the seizure latency was significantly increased. Bicuculline (3 mg/kg) did not induce tonic seizures and status in BCCA treated animals (0 of 21 females or 0 of 8 males) while in the case of sham operated rats tonic seizures developed in 20 of 21 female (95%) and 8 of 8 male rats (100%) and status was observed in 18 of 21 female (86%) and 8 of 8 (100%) male rats. Furthermore, BCCA treated animals were protected against the lethal effects of the substance.

4 mg/kg of bicuculline elicited clonic seizures in both BCCA treated (55%) and sham operated (100%) animals (Fig. 2). Not only the clonic seizures but also the status epilepticus was significantly reduced in these female animals. Tonic seizures were only observed in sham operated animals. As for animals

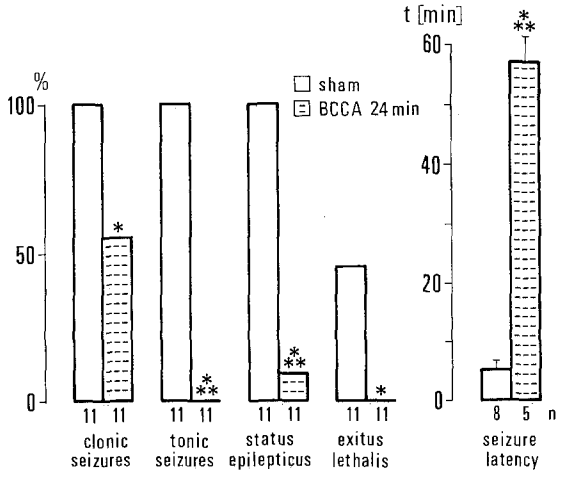

Fig. 2. Susceptibility to seizures induced by bicuculline 4 mg/kg s.c. 14 days after 24 min of BCCA. There is a significant decrease in clonic and tonic seizures as well as in status epilepticus in BCCA treated female rats. Even with this higher dose all BCCA treated animals are protected against the lethal effects of bicuculline. *$p < 0.05$ vs sham; ***$p < 0.001$ vs sham; χ^2-test. The seizure latency is markedly increased. ***$p < 0.001$ vs sham; Student's t-test

injected with 3 mg/kg the latency to first seizure activity after injection of 4 mg/kg of bicuculline was significantly increased. In addition the lethal toxicity was prevented in BCCA animals (Fig. 2).

Electrographic recordings

Alterations of elctrographic activity elicited by bicuculline in sham-operated rats are illustrated in Fig. 3 A. Within 1–2 min following the injection of 4 mg/kg of bicuculline, bursts of spikes, high voltage fast acitivity superseded pre-drug activity, mainly in the cortical EEG records. The electrographic alterations (high voltage and spiking) rapidly spread to hippocampal and cortical recording, within 3–6 min. The pattern of transient alterations prevailed for at least 20 min after the injection. Within 30 min–1 h these electrographic changes became progressively restricted to the cortical recording, then gradually normalized and returned to the background rhythms in 1–2 h.

As can be seen in Fig. 3 B, the nature of EEG produced by 4 mg/kg bicuculline, injected systemically in rats 14 days after BCCA treatment, produced no significant changes. Only some spiking activity was recorded in the cortical EEG, but hippocampal background activity remained unchanged.

GABA content

14 days after BCCA, GABA levels were increased in only four of the eleven brain areas analysed (Table 1). Significantly the frontal cortex (20%) and parietal cortex (19%), hippocampus (19%) and substantia nigra (20%) were the

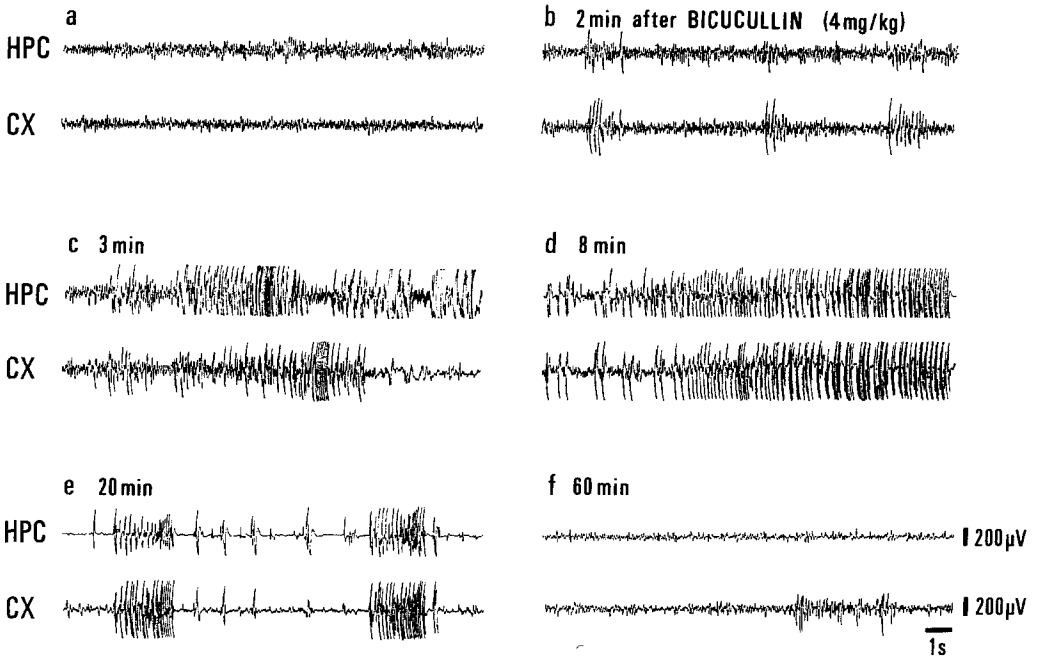

Fig. 3 A. Polygraphic recordings 14 days after sham operation illustrating the effect of systemic administration of bicuculline, 4 mg/kg. Pre-drug control recordings (**a**). Bursts of high-voltage spiking spreading from cortical to hippocampal recordings (**b**). Electrographic seizures recorded 3 and 8 min after injection (**c, d**). High-voltage fast activity and prominent spiking occurred in both recordings. Ictal periods progressively decreased in duration and complexity between 20 and 60 min. Normalization of the electrographic activity was observed 1–2 h after injection of bicuculline in female rats (not shown here). *HPC* hippocampus; *CX* frontal cortex

areas involved (see Table 1). The GABA content in control rats, which did or did not receive 3-MP 2.5 min prior to decapitation were the same (not shown here). The latter finding provides direct proof that the GABA content measured is not elevated artificiently (Baxter, 1976; Lindgren and Simmonds, 1987; Löscher and Vetter, 1984).

Discussion

The results of the present study showed that animals 14 days after 24 min occlusion of both common carotid arteries (BCCA treatment) were largely protected against the convulsant effect of 3 mg/kg of bicuculline. While 4 mg/kg of this GABA antagonist does induce seizures and status epilepticus in the BCCA animals it does so to a lesser extent with a prolonged latency compared with sham operated controls. Importantly, bicuculline at 4 mg/kg never proved lethal to the BCCA animals while controls did not survive such treatment. Electrographic studies support these observations as the hippocampus and frontal cortex of BCCA treated animals which did not elicit seizures also displayed an absence of ictal activity.

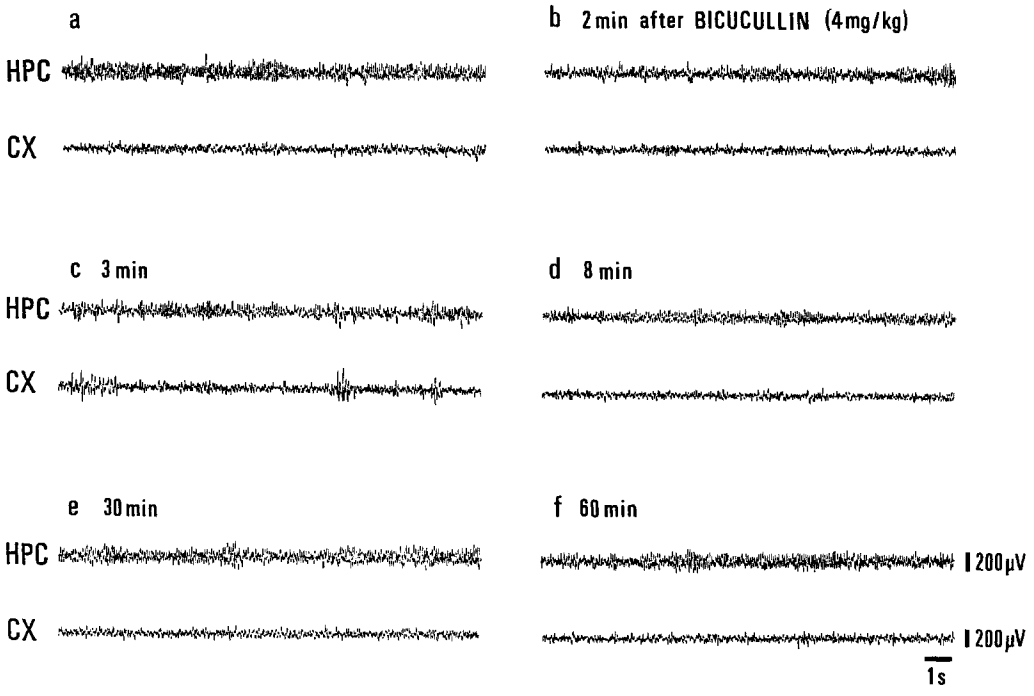

Fig. 3 B. Electrographic recordings illustrating the failure of the convulsant potency of 4 mg/kg bicuculline in female rats 14 days after 24 min of BCCA. Pre-drug control recordings (**a**). Theta rhythm and low-voltage activity are registered up to 60 min p.i. in the hippocampal recording while fast activity prevails in the cortical EEG (**b–f**). No difference to pre-drug control recordings is to be recognized with the exception of Fig. (**c**), where some small groups of spikes can be observed in the cortex 3 min after injection. *HPC* hippocampus; *CX* frontal cortex

Table 1. GABA content in µmol/g of wet tissue measured in different vulnerable brain structures 14 days after surgery

	HPC	FCX	PCX	SN	AMY	STRIA	COLL	HYPO	THAL	SEPT	CEREB
sham (n=11)	2.32 ±0.7	2.51 ±0.07	2.62 ±0.08	3.65 ±0.13	2.43 ±0.06	3.50 ±0.07	3.07 ±0.10	3.94 ±0.11	2.00 ±0.09	2.88 ±0.14	2.00 ±0.08
BCCA 24 min (n=9)	2.75 ±0.07 ***	3.00 ±0.10 ***	3.13 ±0.10 **	4.37 ±0.12 ***	2.54 ±0.06	3.56 ±0.09	3.36 ±0.12	4.34 ±0.19	2.19 ±0.13	2.96 ±0.15	2.03 ±0.08

A significant increase in GABA content is to be seen in hippocampus (HPC) (19%), frontal cortex (FCX) (20%), parietal cortex (PCX) (19%) and in substantia nigra (SN) (20%), of female rats, structures with important function for generating and gating seizure activity. Statistics: ** $p < 0.01$ vs sham, *** $p < 0.001$ vs sham, Student's t-test. Abbreviations: *STRIA* striatum; *COLL* collicullus; *HYPO* hypothalamus; *THAL* thalamus; *SEPT* septum; *CEREB* cerebellum; *AMY* amygdala

These results suggest that the observed elevated GABA content in structures such as the hippocampus or the substantia nigra reflects an increased action of GABA at postsynaptic receptor which in turn counteracts a decrease in the inhibitory function of GABA due to blockade of the $GABA_A$ receptor by bicuculline. This effect may prevent seizure generating and spreading (cf. Iadarola and Gale, 1982; Meldrum, 1975; Tower, 1976).

The present data are consistent with published reports. For example, it has been shown (Gale and Iadarola, 1980; Löscher, 1980; Schechter et al., 1977) that an elevated GABA level in selective brain regions elicits an anticonvulsive effect. The blockade of GABA transaminase by γ-vinyl GABA [which can elevate GABA levels severalfold (Gale, 1985)] reduces the susceptibility of seizures in a variety of experimental models (Gale, 1985).

The importance of GABAergic synaptic activity is highlighted in seizure controlling areas such as the hippocampus, prepiriform cortex and the striatum. When, for example, 1 pmol of bicuculline is injected into the caudate-putamen of the rat the normal pilocarpine and bicuculline-induced seizures are nullified (Turski et al., 1987, 1989). This could, however, be reversed by co-injection of 1 pmol of the GABA agonist muscimol (Diedrichs, 1987; Turski et al., 1987). On the other hand the substantia nigra blocks the spreading of seizure activity if the GABAergic activity is increased (Gale and Iadarola, 1980). This may be underlined by the presented data with the increased GABA content in substantia nigra of BCCA animals. These and other results show that a small change of the normal synaptic active GABA content can elicit a critical effect in specific structures (Piredda and Gale, 1985; Turski et al., 1985). The concentration changes of GABA in the whole brain would not necessary indicate this (Turski et al., 1989). It has been demonstrated furthermore that in vivo pyramidal cells isolated in CA_1 of the dorsal hippocampus are extremely sensitive to GABA (Burchfield et al., 1979). Typically, neuronal firing, spontaneously or glutamate induced, was depressed also when the retaining current for the iontophoretic application of GABA was turned off and only a diffusion of the drug was allowed (Burchfield et al., 1979).

The increased GABA levels in vulnerable structures and the blockade of GABA neurotransmission by the $GABA_A$ antagonist bicuculline which did not lead to typical bicuculline seizures as reported in this study therefore strongly support the idea that an elevated GABA content in brain structures was available for postsynaptic GABAergic activity.

An interesting parallel to our experiments exists in an earlier study by Blennow et al. (1978). Bicuculline induced seizure activity could be stopped for brief periods under hypoxic conditions (arterial PO_2 close to 50 mm Hg) followed by an absence of seizure activity (Blennow et al., 1978). These observations imply that hypoxia triggers a mechanism compensating the blockade of the postsynaptic $GABA_A$ receptor. We have also shown that hypoxic conditions exist in distinct brain structures of BCCA animals with decreased pO_2 values in the hippocampus, frontal cortex and striatum (Block et al., 1989).

The most surprising result of the experiments is the longlasting increase of GABA content in BCCA rats for which no explanation excists. Preliminary studies show that the GAD activity in these animals are unaltered while a significant decrease of the GABA-T activity exists (Heim et al., 1988). However, to provide a meaningful explanation of the mechanism involved it is necessary to follow transmitter changes at different stages following the BCCA procedure to find out whether a constant increase in GABA could be observed or whether the increase is a consequence of a new balance due to the plasticity of the nervous system.

Acknowledgements

The skillful technical assistance of R. Meseke†, H. Ropte and M. Schindler is gratefully acknowledged.

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Received April 24, 1990