Superoxide Production in Experimental Seizures in Cats

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Background and Purpose: Seizures cause cerebrovascular responses similar to those seen in conditions such as acute hypertension, ischemia/reperfusion, or fluid-percussion brain injury, which are associated with the generation of superoxide. Accordingly, we studied production of superoxide in experimental seizures.

Methods: Superoxide production was measured in anesthetized cats equipped with double cranial windows using the superoxide dismutase–inhibitable reduction of nitro blue tetrazolium as a measure of superoxide production. Seizures were induced by intravenous bicuculline. The contribution of hypertension associated with seizures was studied by maintaining arterial blood pressure constant by bleeding.

Results: Significant superoxide dismutase–inhibitable reduction of nitro blue tetrazolium indicative of superoxide production was found during seizures with or without control of arterial blood pressure (1.10±0.27 and 1.29±0.16 nmol/l/min, respectively).

Conclusions: The results show that experimental seizures are associated with superoxide generation that is independent of the rise in arterial blood pressure. It is likely that superoxide generation is due to the metabolic changes that occur during seizures. (Stroke 1992;23:1512–1514)

KEY WORDS • seizures • superoxide dismutase • cats
second group, mean arterial blood pressure was initially 102 ± 2.5 mm Hg and remained stable throughout the period of measurement of NBT reduction. In the first group, mean arterial blood pressure was initially 116 ± 18 mm Hg and increased to 161 ± 4 mm Hg. In the third group, mean arterial blood pressure was initially 97 ± 2 mm Hg and remained at that level during seizures.

**Discussion**

Our findings show that there is significant production of superoxide on the brain surface during experimental seizures. A second important finding was that superoxide production under these conditions did not depend on the increase in blood pressure. We found previously that acute elevations in arterial blood pressure in cats induce superoxide production in the brain.9,10 In those earlier experiments the increase in blood pressure was considerably higher than in the present experiments.9,10 Apparently, this accounted for the different effects of hypertension on superoxide production.

Because superoxide production during seizures was not due to the associated hypertension, it is likely that the increased metabolism and associated release of neurotransmitters might account for the increased superoxide production. During seizure activity, a number of systems that could lead to superoxide generation could be activated. Catecholamines released during seizures may undergo metal-catalyzed auto-oxidation, which produces superoxide as well as its derivatives hydrogen peroxide and hydroxyl radical.11-13 It is known that during seizures there is activation of phospholipases and a large increase in the concentration of free fatty acids including arachidonate.14,15 This fatty acid is metabolized via cyclooxygenase to produce eicosanoids. Cyclooxygenase also generates superoxide in the presence of suitable cofactors.16 Although the concentrations of glutamate and aspartate in brain can increase in certain types of seizures,17 the concentration of glutamate in the cortex actually decreases during bicuculline seizures18 while the concentration of aspartate does not change significantly.18 Therefore, the action of excitotoxic amino acids seems to be a less likely source of superoxide in seizures induced by bicuculline.

Because superoxide and its derivatives are very reactive and capable of causing tissue injury, the possibility might be profitably considered that they are the mediators of some of the vascular or neuronal abnormalities that occur during prolonged seizures.

**References**

8. Kontos HA, Wei EP, Jenkins LW, Povlishoch JT, Rowe GT, Hess ML: Appearance of superoxide anion radical in cerebral extracell-
In Dr. Kontos' continuing effort to elucidate the role of free radicals in the pathophysiologic responses of the cerebrovasculature, Dr. Bauknight has provided evidence for superoxide generation during bicuculline-induced seizures in cats, independent of the concomitant arterial hypertension. This may not be surprising because the known cerebrovascular and metabolic responses of the brain during seizures provide many reasons to suspect increased superoxide generation during seizures. Brain oxygen consumption and cerebral blood flow increase dramatically, tissue hyperoxia occurs, neurotransmitter (e.g., catecholamine) turnover increases, and free fatty acids increase, all of which contribute to accelerated superoxide generation. What is interesting is Dr. Kontos' view of these phenomena. He hypothesizes that because cerebral hyperemia, altered cerebrovascular reactivity, and blood-brain barrier breakdown occur in seizures as they do in other cerebral insults (e.g., brain injury, acute, severe, arterial hypertension) in which there is evidence of superoxide generation, increased superoxide generation occurs in seizures. Intended or not, this view tacitly implies that superoxide generation is the sole basis for these cerebrovascular effects and negates a multifactorial approach to the problem (see Figure).

**Editorial Comment**

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