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Hypothesis

The mechanism of neuronal resistance and adaptation to hypoxia

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In this work we provide a theoretical explanation for the observations that: (i) young animals are more resistant to hypoxia than adult ones and (ii) repeated exposure to a hypoxic insult increases the tolerance of young animals and isolated brain tissue to that insult. Considered here is the role of taurine, a putative Ca^{2+} transport modulator, in attenuating Ca^{2+} influx and overload in brain tissue upon hypoxia. It is proposed that the higher resistance of young animals to hypoxia stems from their higher brain content of taurine as compared with adults. The increased resistance to lack of oxygen upon re-exposure to hypoxia may occur as a result of protein and coenzyme A (CoA) breakdown which leads to the accumulation of products like cystine, cysteine, cysteamine and other sulfur-containing compounds. Upon reoxygenation, these compounds are oxidized to form taurine, which in turn attenuates neuronal Ca^{2+} accumulation. The sulfur-containing compounds are considered to be natural scavengers of oxygen-derived free radicals which are formed upon reoxygenation and have been implicated as a major component in the process leading to ischemic/hypoxic brain damage. Repeated hypoxic insults bring about the formation of higher levels of taurine and hence the observed adaptation to oxygen lack. The hypothesis presented here is supported by experimental observations in our laboratory and those of others.

Taurine; Hypoxia; Neuronal resistance; Adaptation; Ca^{2+} influx

1. INTRODUCTION

It is common knowledge that the tissue of mammalian central nervous system (CNS) is one of the most sensitive to any type of hypoxia. Oxygen lack can trigger biochemical as well as functional and structural changes, their intensity and localization depending on the phylogenic and ontogenic maturity of the CNS and the intensity of the hypoxic insult [1]. The higher resistance of immature animals than adults to hypoxia, anoxia, radial acceleration and bleeding [2–11] is yet to be explained. The better adaptability of young animals than mature ones to limited supplies of oxygen, especially where brain tissue is concerned [12–14], is also unexplained. Yet, as our knowledge of the mechanisms involved in hypoxic brain damage increases, a pharmacological treatment or prevention of such damage as part of future therapy appears to be feasible [15–17]. As a result of the rapid fall in ATP levels and energy charge (EC) upon hypoxia, Ca^{2+} homeostasis cannot be maintained, leading to Ca^{2+} overload and irreversible neuronal damage [18]. Oxygen-derived free radicals have been implicated in the causation of hypoxic brain damage, via lipid peroxidation, as

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they are formed upon reperfusion/reoxygenation [19–22]. Recently we have shown that the resistance of adult rat brain tissue to hypoxia in vitro increases by exposure to lack of oxygen [23]. Using the same preparation, we have also demonstrated taurine's ability to protect neuronal tissue against hypoxic damage [24]. The extracellular level of taurine has been shown to increase in the hippocampus of rabbits after ischemia [25]. Taurine is believed to modulate Ca^{2+} transport across biomembranes [26,27]. In situ, taurine is synthesized via sulfur-containing compounds like cystine, cysteine, cysteic acid, cysteamine and hypotaurine [28,29].

The following hypothesis is based on experimental data and biological knowledge. It provides an explanation for both the higher resistance and the better adaptability of young animals to hypoxia as compared to adults. We postulate the existence of an endogenous protective mechanism against hypoxic damage in brain and possibly in other tissues too. While active in young animals, this mechanism is dormant in adults, where it can be activated by repeated exposure to lack of oxygen.

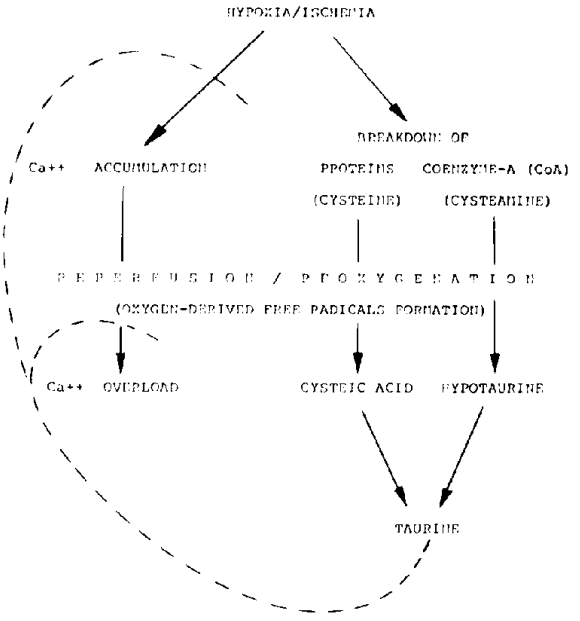

Fig.1. A hypothesis on the formation of taurine from sulfur-containing amino acids and amines upon hypoxia/ischemia and reoxygenation. See text for details.

2. HYPOTHESIS

While scanning the literature on the development of resistance to hypoxia in young animals and their adaptability to oxygen deprivation, on the one hand, and articles on the biosynthesis and functions of taurine, on the other, we noticed that the postnatal decrease in brain taurine levels [30,31] coincides with the postnatal decrease in resistance of animals to hypoxia [2–11]. Both resistance to hypoxia and taurine's brain levels are high in neonates and fall rapidly as animals mature. It therefore seems reasonable to hypothesize that the higher levels of taurine in young animals are the reason for the higher tolerance to hypoxia. Adaptation to hypoxia could be the result of an increase in the usually low levels of taurine, triggered by a hypoxic event. Fig.1 depicts our hypothesis on resistance and adaptation to hypoxia as follows: a hypoxic (or ischemic) insult halts the aerobic energy production and reduces ATP levels and EC to a minimum. Anaerobic glycolysis and low levels of ATP cannot support ion homeostasis and protein synthesis. This results in Ca^{2+} and Na^{+} influx, K^{+} efflux and protein breakdown which brings about the accumulation of cystine and cysteine. Also postulated is the breakdown of coenzyme A (CoA) or, alternatively, the halting of its production and the accumulation of some of its precursors, like *p*-pantothenyl cysteine, *p*-pantetheine and cysteamine. While at the initial stages of the hypoxic insult ion fluxes are reversible, extended periods of oxygen deprivation result in intracellular Ca^{2+} accumulation and irreversible damage. Reoxygenation, while supplying the most needed oxygen, increases tremendously the production of oxygen-derived free radicals which lead to membrane damage through lipid peroxidation and further increase in the accumulation of Ca^{2+} (overload). Concomitantly, the products of protein and CoA breakdown are oxidized to form taurine via intermediates like cysteine sulfinic acid, cysteic acid and hypotaurine. As they are being oxidized, these products act as scavengers of oxygen-derived free radicals, reducing the amount of, and the damage elicited by, the latter. Taurine, once formed, acts directly on the neuronal membrane to attenuate Ca^{2+} influx and/or overload.

3. DISCUSSION

The proposed hypothesis explains the higher resistance of young animals to hypoxia as compared with adults and the mechanism by which adaptation to lack of oxygen may occur. There are many published observations in the literature to support the above-mentioned hypothesis. Firstly, where the biosynthesis of taurine is concerned, it has been shown that hypotaurine can account for the metabolic origin of taurine [32]. Secondly, hypotaurine with its sulfinate moiety is an obvious oxidizable molecule, which is the basis of its antioxidant properties [32]. It has been proposed that hypotaurine plays a unique role as an oxygen-free radical trap in tissues; when oxygen free radicals are generated they may react with hypotaurine to extract an electron to form the resonance-stabilized hypotaurine radical and a hydroxide ion. Two hypotaurine radicals can next unite to form the intermediate disulfone which can rearrange in an internal oxidation-reduction to generate one molecule of taurine and one of hypotaurine [32]. The oxidation reaction is dependent on nicotinamide-adenine dinucleotides and divalent cations and can be stimulated, to a certain extent, by superoxide dismutase and inhibited by catalase [32,33]. Hypotaurine itself is formed via the cysteine sulfinic acid and the cysteic acid pathways [34]. In some organs, such as the kidney, taurine can be synthesized via the cysteamine pathway [28,34–36]. Hypotaurine and taurine have been shown to protect against light-induced damage to rod outer segments (ROS) of the frog eye in vitro [37]. Exposure of isolated ROS to continuous light of an intensity of about 5000 lux for 2 h resulted in marked ROS swelling, with extensive disruption of the architecture of lamellar discs in most of the segments. Addition of taurine provided a complete protection against the deleterious effect of light, preserving ROS structure in better condition than those kept in the dark [37]. Only hypotaurine exhibited an effect similar to that of taurine [37]. The involvement of lipid peroxidation processes in the light-induced damage to photoreceptors is well-documented [37–39]. Taurine protected membrane structure of illuminated ROS and at the same time prevented the increase in lipid peroxidation induced by light. Hypotaurine, the only other amino acid to exhibit an ability to reduce lipid peroxidation, was found to be even more effective than taurine [37]. Similar findings were reported for rabbit sperm motility which is impaired by oxidative reactions; both taurine and hypotaurine were efficacious in preserving cell motility and at the same time suppressing lipid peroxidation [40]. The capacity of hypotaurine to quench oxygen-derived free radicals generated by the xanthine oxidase system in the presence of EDTA-Fe^{2+} has also been shown [32]. Frog retinal taurine levels significantly decrease or increase following 3–6 weeks of light or dark adaptation, respectively [41].

Much evidence is available as to the role of taurine in the regulation of calcium homeostasis in excitable tissues, including our own studies using the hippocampal slice preparation (fig.2) [24]. The decline in the evoked population spike (synaptic function) amplitude upon Ca^{2+} depletion from the bathing medium was attenuated by pretreatment of the hippocampal slices with 1 mM taurine. In the myocardium taurine has been shown to slow the washout of calcium from isolated heart preparations exposed to buffers lacking calcium

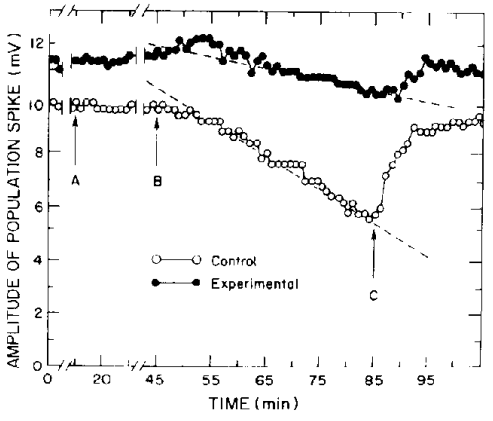

Fig.2. Changes in the amplitude of evoked population responses in rat hippocampal slices. Experimental slices (●) were perfused with 1 mM taurine (A) 30 min before perfusing both these slices and the control ones (○) with a medium containing 0 mM Ca^{2+} (B). 40 min later the perfusion medium was changed back to a Ca^{2+}-containing medium (C). Taurine attenuated the fall in the population spike amplitude by slowing the washout of Ca^{2+} from the experimental hippocampal slices as compared to control ones. For more details see [24].

[42,43] and to reverse the negative inotropic effects of reduced perfusate calcium and exposure to calcium antagonists [44]. Taurine also prevents myocardial necrotic lesions associated with calcium overload [45–47]. Accumulation of ^{45}Ca by retinal subcellular fractions isolated from the chick retina was decreased when taurine was present in the incubation medium [48]. Similar results were obtained using a sarcolemma preparation [49] and in synaptosomes [50]. With regard to the physiological role of taurine, stroke-prone spontaneously hypertensive rats (SHR) have been shown to have significantly reduced levels of taurine in their liver and serum [51]. Recently, a significant decrease in hypothalamic content of taurine in SHR was found [34]. Taurine shows a protective effect against a wide variety of convulsive states, with very different etiologies [52,53]. It has been shown that the anticonvulsant effect of taurine against metrazol requires the presence of free calcium [54]. Taurine also antagonizes 4-aminopyridine-induced seizures, which are probably caused by increased calcium entry into the nerve terminal [55].

The above mentioned observations are all in support of our proposed hypothesis on the role of taurine in the protection of neuronal tissue against hypoxic damage and adaptation to lack of oxygen. Lehmann and his colleagues [56] reported that the fall in extracellular Ca^{2+} upon decapitation ischemia is brought about by Ca^{2+} influx. This fall could be prevented by taurine. The same authors also measured a 25-fold increase in the initial levels of taurine following complete cerebral ischemia in the rabbit [25,56].

Thus, in both young and hypoxia-adapted animals, higher CNS taurine levels would provide the observed resistance to hypoxia by attenuating Ca^{2+} influx and/or overload which is triggered by lack of oxygen. Young animals should exhibit better adaptability to hypoxia than adults due to their initial higher CNS levels of taurine. In addition, the long time required for adaptation to hypoxia in vitro [24] and the slow decline (days) in the resistance to hypoxia in newborn rats [57] could be due to the slow turnover of taurine. Our hypothesis predicts that animals with inherently low levels of taurine or those in which taurine biosynthesis is defective, will be highly sensitive to hypoxia. Inversely, animals with high resistance to lack of oxygen might contain high brain levels of taurine.

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