RECENT PROGRESS

The Brain, The Heart and Taurine

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Based on a recent International Symposium on *Taurine* held in Tucson, Arizona, March 24-26, 1975.

SUMMARY: *This paper reviews some recent developments concerning the "non-essential" amino acid Taurine. It is shown that taurine is important in metabolic regulations within the heart, muscle and brain. Particular attention is paid to the neuropharmacology of taurine, such as its possible role in epilepsy.*

RÉSUMÉ: *Le présent article revoit les développements récents concernant la taurine, un acide aminé "non-essentiel". Il est conclu que la taurine est importante dans certaines régulations métaboliques au niveau du coeur, des muscles et du cerveau. Une attention particulière est portée à la neuropharmacologie de la taurine, tel son rôle possible dans l'épilepsie.*

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Taurine (2-aminoethanesulfonic acid) is a "non-essential" amino acid with a wide distribution in the body (Jacobsen and Smith, 1968). Although nearly 75% of taurine is situated within muscles, large concentrations can also be found in the brain. The relative metabolic inertness of this amino acid led to a neglect of its physiological role within these organs. However, recent discoveries have contributed towards a renewal of interest on the part of pharmacologists and biochemists.

The concentration of taurine was first examined in urine and tissues from patients with diseases of muscle. A specific increase in taurinuria was found in most patients with muscular dystrophy (Blahd et al., 1955; Berger, 1962), in contrast to the generalized amino aciduria of myotonic dystrophy (Steinert's disease). Baskin and Dagirmanjian (1973a) recently confirmed this finding, indicating that it most likely was an active marker of progressive muscle disease, since taurinuria decreased considerably in the amyotrophic stage. It was thus of great interest when Huxtable and Bressler (1974a, b) recently reported a marked increase in heart taurine in congestive heart failure. This finding led to a reevaluation of the metabolism and synthesis pathway of taurine which to that time had been incompletely understood. The immediate precursor was confirmed to be hypotaurine which, in turn, could originate from cysteine sulfinic acid or from cysteamine. Some of the early studies of Welty and Read (1964) on the role of taurine in the metabolic ionic balance of the heart were confirmed and extended. It would now appear that within this muscle, taurine is a modulator of membrane excitability and not a neurotransmitter (Huxtable and Bressler, 1974b).

Concentrations of taurine have been found high in the retina (Bonaventure et al., 1974), pineal gland (Guidotti et al., 1972), hypothalamus (Crabai et al., 1974) and cerebellum (Perry et al., 1971) in a variety of animal species from the rat to the human. It was thus natural that studies designed to investigate the possible role of taurine within these regions of the brain would be carried out. In the retina, Pasantes-Morales and her colleagues (1973a, b) were able to demonstrate that taurine can be specifically released by chemical as well as electrical stimulation. Moreover, they showed that the retinal concentration of taurine increased markedly when the animals were reared in darkness. This relationship between taurine and the light/darkness cycle may be carried further since, as mentioned before, this amino acid is found in high concentration within the pineal gland. Baskin and Dagirmanjian (1973b) even demonstrated that taurine can alter melatonin synthesis and/or release in the pineal gland. Taurine may also play a role in some endocrine functions. Injected intraventricularly in high doses it will produce hypophagia, a decreased water drive and a significant lowering of body temperature. There is some evidence that hypophysectomy will result in increased tissue concentrations of taurine (Awapara, 1956), while taurinuria and the urinary excretion of 17-hydroxycorticosteroids may be correlated in stress (burns, trauma) (Turner and Blum, 1964). Finally, the

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precursor hypotaurine has been shown to be in high concentration in the testes and epidydimis of many animal species and to be influenced by the testosterone content (Kochakian, 1973).

The most important recent findings concern the behavioural and neuropharmacological actions of taurine. It was shown that taurine can produce analgesia (Sugihara et al., 1936), hypothermia, slight arterial hypotension and a delay in recovery of the righting reflex with sedation (Scaragli and Pavan, 1972). A depression of habituated psychomotor activity is often coupled to loss of body balance and ataxic gait at higher doses (Baskin et al., 1974). Early studies in children with mental deficiency had demonstrated disturbances in taurine excretion, mainly in Down's syndrome (Goodman et al., 1964) and particularly when epilepsy was also present. Taurine was shown to raise the threshold of electrically or chemically induced seizures in the dog (Hayashi, 1959). In 1972, van Gelder, Sherwin and Rasmussen (1972) found modifications in the concentrations of many substances between the epileptic focus and surrounding areas of the temporal lobe in man. Of particular interest was a generalized lowering of GABA and aspartic acid levels throughout the cortex of patients with epilepsy while low levels of glutamic acid and taurine, in combination with high glycine concentrations, seemed to characterize the site of maximum seizure activity. Similar findings were soon reported in experimentally induced epileptic foci by Koyama (1972) and by Craig and Hartmann (1973), but challenged by Perry and his colleagues (1972). At this writing, the discrepancy appears to be methodological.

Van Gelder (van Gelder, 1972; van Gelder and Courtois, 1972) first reported that the administration of taurine exerted some anticonvulsant action in animals and that it modified towards normal the brain amino acid irregularities previously reported. These findings have since been confirmed by many authors in a variety of experimental epilepsy models from mice to rats, cats, dogs and even papio papio (Craig and Hartmann, 1973; Izumi et al., 1973; Tsukada et al., 1974; Izumi et al., 1974, Mutani et al., 1974a, b; Kaczmarek and Adey, 1974; Derouaux et al., 1973; Thursby, 1974; Adembri et al., 1974). There seems little doubt now that taurine possesses anti-epileptic activity in experimental animals. Whether this activity is specific or not is still conjectural (Izumi et al., 1974; Adembri et al., 1974), but taurine far surpasses in epileptic inhibitory activity GABA, hypotaurine, β -alanine and glycine (Izumi et al., 1973; Tsukada et al., 1974). The recent demonstration by McLardy (1974) that taurine blocks the zinc-rich dentato-hippocampal synapses, adds a further argument in favor of this specific action in epileptic brain. In man, only a few studies have been published, with variable results in relatively small numbers of patients (Barbeau and Donaldson, 1973 a, b; 1974; Bergamini et al., 1973, 1974; Borromei, 1975). It would appear, particularly when the blood brain barrier is damaged in the temporal lobe (Barbeau and Donaldson, 1974), that taurine can exert some anticonvulsant activity in man. Because only a minimal part of ingested taurine (less than 1%) reaches the brain, it is evident that better methods of administration will have to be designed and tested in larger series of patients before any firm conclusion can be drawn. However, such studies have served as a powerful incentive for a number of physiological investigations of the role and mode of action of taurine within the central nervous system.

As early as 1960, Curtis and his colleagues (Curtis and Watkins, 1960, 1965) had demonstrated that the iontophoretic injection of taurine exerts a depressor effect on most neurons. This was confirmed subsequently by Haas and Hosli (1973) and Honegger et al. (1973). What is not clear at this time is whether taurine acts as a true neurotransmitter or as a neuromodulator. Davison and Kaczmarek (Davison and Kaczmarek, 1971; Kaczmarek and Davison, 1972; Kaczmarek and Adey, 1974) have argued strongly in favor of a neurotransmitter role for this amino acid. Their arguments are based upon the demonstration: (1) that taurine can be released by electrical or chemical stimulation in vitro and in vivo (Pasantes-Morales et al., 1973 b; Kaczmarek and Adey 1974; Davison and Kaczmarek, 1971; Jasper and Koyama, 1969; Collins and Topiwala, 1974), (2) that there is a more or less specific uptake mechanism for taurine (Kaczmarek and Davison, 1972; Lähdesmäki and Oja, 1973), (3) that there is new biosynthesis of taurine after electrical stimulation, as if there were some sort of metabolic feedback control (Oja et al., 1973), and finally (4) that there is synaptosomal enrichment of taurine (De Belleroche and Bradford, 1973; Siegart and Karobath, 1974). However, some of the same arguments have been used to claim that taurine is a neuromodulator at certain brain synapses (van Gelder 1972; Honegger et al., 1973). There is also evidence that taurine uptake is not limited to neurons, but can occur within glial cells (Ehinger, 1973). Finally, it is known that taurine, through its sulfur group, can probably chelate or mobilize calcium. It has been shown to increase tissue affinity for, and retention of, calcium (Dolara et al., 1973) particularly after phospholipase -C (Huxtable and Bressler, 1973). From these studies it is our present position that taurine has a dual role to play within the brain. On most cells it is a modulator of membrane excitability (van Gelder, 1972; Barbeau and Donaldson, 1974; Huxtable and Bressler, 1973). In some specific regions, particularly in pathways responsible for the integration of specialized sensory modalities (visual, olfactory, proprioceptive), taurine may play a role as a specific neurotransmitter. In this, taurine would resemble GABA which also possesses general modulator functions and specific pathway transmitter roles. Much work remains to be done to clarify the actual role of taurine within the brain; but the studies reviewed above, and presented at a recent symposium (Huxtable and Barbeau, 1975) should point the way for further investigations.

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