Quebec Cooperative Study of
Friedreich's Ataxia

Emerging Treatments: Replacement Therapy with Choline or Lecithin in Neurological Diseases

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SUMMARY: *This review evaluates the theoretical background and experimental data behind a new development: the replacement therapy of deficient central cholinergic systems with the dietary precursors choline or lecithin. Cholinergic deficiency states are possibly present in five neurological entities: Huntington's chorea, Tardive Dyskinesia, Gilles de la Tourette's disease, Friedreich's ataxia and pre-senile dementia. Preliminary data from various laboratories, including our own, in each of these disorders indicate that some clinical improvement can occasionally be seen, and that this approach deserves further investigation.*

RÉSUMÉ: *La présente revue a pour but d'évaluer l'arrière-plan théorique ainsi que les données expérimentales appuyant une nouvelle observation d'importance: la thérapie de remplacement dans les déficiences cholinergiques centrales avec les précurseurs diététiques choline ou lécithine. De telles déficiences dans le système cholinergique peuvent être postulées pour cinq entités neurologiques: la chorée de Huntington, la Dyskinésie Tardive, la maladie de Gilles de la Tourette, l'ataxie de Friedreich et la démence pré-sénile. Les données préliminaires provenant de plusieurs laboratoires, dont le nôtre, indiquent que dans chacune de ces maladies une amélioration clinique a peut-être observée chez quelques patients et que, par conséquent, cette approche mérite une investigation plus poussée.*

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The last 15 years have witnessed the rapid developments surrounding the replacement therapy with Levodopa alone or in combination with a DOPA-decarboxylase inhibitor in Parkinson's disease (Barbeau, 1969, 1976a; Barbeau and Roy, 1976). It has now been proven that, when a putative neurotransmitter such as dopamine is deficient, specific neurological symptoms can be related to this defect, and these symptoms can be successfully modified by giving metabolic precursors (Barbeau, 1976b). Although Levodopa is the best known of these compounds, much has been learned lately from the use of tryptophan, 5-hydroxytryptophan, taurine and gama-aminobutyric acid (GABA). The concentration of the essential amino acid tryptophan can be manipulated in the diet to elevate brain tryptophan and serotonin levels. Although not yet clearly demonstrated, it is probable that such manipulations result in increased synthesis and release of serotonin (Fernstrom and Wurtman, 1971, 1972). Use of this knowledge has resulted in clinical benefits to patients with myoclonus (De Lean and Richardson, 1975; Van Woert and Sethy, 1974) and depression (Growdon et al., 1977). A similar reasoning in the presence of low taurine levels in epilepsy (van Gelder et al., 1972) and retinitis pigmentosa (Pasantes-Morales et al., 1973) has led to the utilization of this amino acid in both disorders with encouraging results (Barbeau et al., 1975; Huxtable and Barbeau, 1976). In Huntington's chorea, the demonstration of a low brain concentration of GABA (Perry et al., 1973) and glutamic acid decarboxylast (GAD). (Bird and Iversen, 1974) led to a large number of therapeutic trials with GABA and drugs known to modify its metabolism with variable and still uninterpretable results (Barbeau, 1976d). However, in all this activity the oldest known of the putative neurotransmitters, acetyl choline, appeared to be consistently left out. Fortunately, recent developments have contributed to modify this situation.

The uneven distribution of acetyl choline in the brain, with particular concentrations in the striatum, cortex and cerebellum and in certain pathways, has been recognized since the availability of methods to determine and identify the cholinesterases and cholineacetylase (Shute and Lewis, 1963; Olivier et al., 1970; Fonnum, 1973) and the use of poisons to modify the metabolism of the transmitter or to identify specific receptors (Simpson, 1974; Snyder et al., 1975). Pharmacologic studies in animals and man with anticholinergic drugs have permitted the delineation of a number of central behavioral manifestations such as confusion, ataxia, hallucinations, tachycardia and even seizures (Albanus, 1970; Safer and Allen, 1971; Greenblatt and Shader, 1973), which can be completely reversed with cholinergic drugs like physostigmine (Duvoisin and Katz, 1968; Flynn, 1972; Snyder, 1975). It was evident that acetyl choline was present in certain areas of the brain and it had specific functions.

The study of the pathophysiology of extrapyramidal disorders led to the elaboration of the so-called "balance hypothesis" between the functions of catecholamines, particularly dopamine, and those of

acetyl choline (McGeer et al., 1961; Barbeau, 1962). The main tenets of this hypothesis have been confirmed by drug manipulations in animals and man, which have permitted an understanding of the pharmacology of symptoms of extrapyramidal disorders such as akinesia, rigidity, tremor and chorea (Duvoisin, 1967; Barbeau, 1973, 1974, 1976c; Klawans, 1969; Jurna, 1976). Unfortunately, the biochemistry and physiology of this interrelationship is not simple and is still under intensive study (Barbeau, 1973b; McGeer et al., 1974; Cools et al., 1975; Agid et al., 1975). It now appears that, anatomically, dopamine and acetyl choline in the striatum act in series rather than in parallel. Variations in the concentration of acetyl choline may be present in a number of disease states and pharmacological modifications of acetyl choline may be warranted in an attempt to correct such imbalances.

The best known probable acetyl choline deficiency state is Huntington's chorea (Klawans and Rubovits, 1972; Barbeau, 1973a). In this disease low levels of choline acetyl transferase, the enzyme that catalyzes the combination of choline and acetyl coenzyme A to form acetyl choline, have been clearly demonstrated (McGeer et al., 1973; Bird & Iversen, 1974; Stahl and Swanson, 1974). Muscarinic cholinergic receptor binding was also found to be decreased in brain of patients with Huntington's chorea (Enna et al., 1976). Similar evidence indicates that there may also be a cholinergic deficit in tardive dyskinesia, the syndrome-complex observed after long term treatment with phenothiazines (Crane, 1973; Crane and Smeets, 1974). In both these entities the hyperkinesis is attributed to the combination of dopamine receptor hypersensitivity and cholinergic deficiencies (Barbeau, 1973a). Following a similar reasoning it is possible that the biochemical substratum of Gilles de la Tourette's disease ("Maladie des Tics") is closely related to the above diseases (Gonce and Barbeau, 1977) and that again an acetyl choline deficit could be expected. Data obtained from studies with septal-lesioned rats are consistent with the proposition that hyper-reactive, aggressive behavior (frequent in that illness) is suppressed by a centrally acting cholinergic system (Stark and Henderson, 1972). In presenile dementia (Alzheimer type) a decrease in cortical choline acetyl transferase has been demonstrated (Bowen et al., 1976; Davies and Maloney, 1976; Perry et al., 1977; anonymous editorial, 1977). Finally, there is recent evidence that a defect may exist in the pyruvate dehydrogenase complex in Friedreich's ataxia (Barbeau, 1975; Blass et al., 1976; Barbeau et al., 1976). Such a defect has been shown to result in a decreased synthesis of acetyl choline (Dreyfus & Hauser, 1965; Gibson et al., 1975). Thus, five disorders of the nervous system are candidates for replacement therapy of acetyl choline, if this could be accomplished.

Such an approach has been proposed recently. Brain acetyl choline is synthesized from choline and acetyl coenzyme A by choline acetyl transferase. It is metabolized by acetyl cholinesterase. The metabolism of acetyl choline could be blocked to increase its concentration. Physostigmine has been shown to function in this way (Duvoisin and Kata, 1968) and we recently demonstrated that thiamine and choline can also inhibit acetyl cholinesterase (Ngo et al., 1977). It is of interest that physostigmine was found to be useful, for short periods in choreiform and dyskinetic movements (Klawans and Rubovits, 1972; Tarsy et al., 1974), and recently in familial ataxias (Kark et al., 1977). In tardive dyskinesia, Deanol (dimethylaminoethanol), thought to be slowly converted to acetyl choline, was claimed to be useful (Miller, 1974), but this has not been our experience. Physostigmine, however, was occasionally useful (Aquilonius and Sjostrom, 1971) while benztropine increased the symptoms.

The precursor choline cannot be made in the brain and must come from synthesis in the liver or from the diet. An adequate supply of choline is critical for cholinergic nerve function. This necessitates functional transport mechanisms for choline into the brain. Both a low affinity and a high affinity transport systems were demonstrated in brain synaptosomes by Yamamura and Snyder (1973) and regional differences were identified (Carroll and Buterbaugh, 1975). Uptake is not saturated even at very high concentrations of choline in plasma (Barker and Mittag, 1975). There is also good evidence that the concentration of free choline in tissues may be important in regulation of the rate of synthesis of acetyl choline and possibly also of tyrosine hydroxylase in dopaminergic neurons (Ulus and Wurtman, 1976). The brain contains fair concentrations of free choline (Stavinoha and Weintraub, 1974; Mann and Hebb, 1977) and these can be increased after the administration of choline by systemic injection or orally in rats (Cohen and Wurtman, 1975, 1976; Haubrich et al., 1976). The administration of choline chloride causes a sequential increase in serum-choline, brain-choline, and brain-acetyl choline levels. The increase in acetyl choline occurs within presynaptic terminals (Hirsch et al., 1977) and is followed by biochemical changes within postsynaptic cells that have a cholinergic innervation (Ulus and Wurtman, 1976). Choline probably increases the release of acetyl choline into synapses. Such experimental background was sufficient to justify the use of choline in man. It was shown that choline consumption caused dose related increases in the choline levels of serum and cerebrospinal fluid (Aquilonius and Eckernas, 1975; Growdon et al., 1977).

Choline, given orally in doses up to 20 g per day, was found to be active against the choreiform and dyskinetic movements of some patients with Huntington's chorea and tardive dyskinesia (Aquilonius and Eckernas, 1975; Davis et al., 1975, 1976; Growdon et al., 1977). Our own experience (Barbeau, 1977, unpublished with choline chloride given orally in daily doses up to 10 grams is limited to observations in 15 patients for periods up to four months (4 with Huntington's chorea, 3 with

Gilles de la Tourette, 2 with tardive dyskinesia and 6 with Friedreich's ataxia). The results are preliminary, but there has been objective improvement in the dyskinesias in 2 choreics, 1 Gilles de la Tourette and 1 patient with tardive dyskinesia. All 6 patients with Friedreich's ataxia have some subjective improvement in strength with an apparent decrease in the ataxia. This diet supplementation is not easy to prepare, conserve or absorb. Nausea and mental depression have been seen. Recently, Wurtman and his collaborators (1977) have shown that oral lecithin (phosphatidyl choline, the bound form of choline) is more effective in raising human serum-choline levels than an equivalent quantity of choline chloride (265% to 86% above control levels respectively). This rise persists far longer after lecithin (4 hours to 12 hours respectively). We have initiated trials with lecithin in the five diseases mentioned above, where we have reasons to suspect that brain acetyl choline may be deficient. We have used phosphatidylcholine (lecithin) in daily doses up to 24 g/day in 8 cases of typical Friedreich's ataxia, 1 of Marie's ataxia and 3 of olivo-ponto-cerebellar atrophy. The improvement noted in speech, balance and movement disorders averaged 30% after two months of treatment.

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