RECENT PROGRESS

Progress in Understanding Huntington's Chorea

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This report is based on presentations and discussions during three recent meetings on Huntington's Chorea: a meeting of the Research Group on Huntington's Chorea of the World Federation of Neurology (Leuven, Belgium, 8-12 September, 1974); a Symposium on Huntington's Chorea of the Huntington Society of Canada (Toronto, Canada, 8-9 November, 1974); and a Workshop of the Huntington's Disease Foundation (Los Angeles, U.S.A., January 10-12, 1975). To the lecturers and discussors of these meetings belong many of the new ideas expressed herein, even if they are not acknowledged by name.

SUMMARY: *The present paper analyses the new data accumulated since 1972 concerning the etiology and pathogenesis of Huntington's chorea. Particular attention is paid to the respective roles of the dopaminergic and GABA-ergic systems.*

RÉSUMÉ: *Le présent article analyse les nouveaux développements survenus depuis 1972 concernant l'étiologie et le traitement de la chorée de Huntington. En particulier, il est fait mention du rôle respectif des systèmes dopaminergiques et GABA-ergiques.*

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INTRODUCTION

Hungtington's chorea is a degenerative neurological disease with a dominant mode of inheritance. The accumulated data about this illness was recently summarized in a Centennial volume(Barbeau et al., 1973) coupled with an extensive bibliographical survey (Bruyn et al., 1974). However, new ideas have recently been proposed during three meetings on Huntington's chorea which have further advanced our knowledge. The present summary will attempt to convey the excitement of these recent conferences.

Pharmacological research

The impetus for most of the new research programs came from the elucidation of the role of dopamine in the central nervous system and from the introduction of L-DOPA into the therapy of Parkinson's disease. However, it was soon recognized that the physiology of most of the extrapyramidal symptoms was related more to a cholinergic/catecholaminergic imbalance in the CNS than to dopamine alone. The true situation is even more complex:

a) Role of the cholinergic system

A few clinical observations are of importance: the long-term use of anticholinergic drugs has recently been recognized as a cause of variable dyskinesias of the choreic type. Physostigmine, by increasing the concentration of acetylcholine in the brain and particularly within the basal ganglia, was known to worsen the symptoms of Parkinson's disease considerably and rapidly. Klawans (1970) has recently demonstrated that physostigmine, which crosses the blood brain barrier, will significantly diminish chorea for 20 to 30 minutes. This effect can be reversed by the addition of Benztropine. Neostigmine, which does not cross the blood-brain barrier, is ineffective in modifying chorea.

Acetylcholine is undoubtedly an important neurotransmitter within the basal ganglia, but its proper function and connections are still largely unknown. Cholinesterase staining methods have demonstrated the existence of a striato-pallidal and possibly striato-nigral cholinergic pathway serving as a sort of feed-back loop to the nigro-striatal dopaminergic fibers (Olivier et al., 1970). However, more recent studies, reviewed by Cools and Van Rossum (1970), tend to favor the hypothesis that striatal cholinergic fibers are short, possibly belonging to intra-striatal interneurons. Others postulate the existence of two types of cholinergic systems within the basal ganglia. Whatever the final resolution of this

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problem, it is now clear that the cholinergic neurons work in series with the dopaminergic input, rather than in parallel. It is even probable that the dopamine receptors are situated on such cholinergic neurons, thus modulating their output. This conclusion is compatible with the decrease in striatal acetylcholine concentration seen after reserpine, a decrease corrected by the addition of L-DOPA (Orzeck and Barbeau, 1970). It is also compatible with recent electrophysiological data indicating that dopamine is mainly excitatory in the basal ganglia. In this scheme, it is the cholinergic chain thus stimulated that would be responsible for the inhibition produced by nigro-striatal activation.

Determinations of striatal acetylcholine, of cholinesterase or of the synthetising enzymes in Huntington's chorea are technically difficult. However, two recent studies (Bird and Iversen, 1974; Stahl and Swanson, 1974) have shown decreased values of choline-acetylase but normal concentrations of acetyl-cholinesterase in Huntington's chorea brain. The conclusion is that the amount of effective acetylcholine at specific (muscarinic) receptor sites is decreased in that illness. There is even a suggestion that the receptor sites themselves could be reduced in number or in sensitivity. Thus the efficacy of the cholinergic system would seem to be lowered in Huntington's thorea.

b) Role of the catecholaminergic system

Much more information is available concerning this side of the postulated balance system, but it is unclear whether dopamine is involved alone, or in association with noradrenaline. Clinical evidence indicating a role for the catecholamines in the production of chorea is too extensive to be reviewed again. Suffice it to recall that drugs lowering, (reserpine, tetrabenazine) displacing (alpha-methyl-dopa) or blocking (phenothiazines, butyrophenones) the action of catecholamines have all been reported to be of some use, albeit limited, in Huntington's chorea. On the other hand, L-DOPA has generally been shown to worsen chorea, except in the simultaneous presence of akinesia (such as is occasionally found in the juvenile form). This observation has even been used as the basis for a provocative test in the symptomatic, at risk, descendants of choreic patients (Klawans et al., 1972).

The early evidence gathered from biochemical studies of a few Huntington's chorea brains (Ehringer and Hornykiewicz, 1960) indicated normal striatal dopamine levels, although on the low side of control limits. This was confirmed by low or near normal cerebrospinal fluid homovanillic acid (HVA), depending on the stage of the illness (Curzon and Wald, 1963) and apparently normal urinary excretion of Dopa and its metabolites (Sourkes et al., 1964). Because of this situation, it became difficult to explain how chorea could result from overstimulation of striatal dopamine receptors. Klawans (1970) proposed that these dopamine receptors were supersensitive, but this hypothesis was difficult to accept in view of the fact that such supersensitivity usually results from presynaptic denervation which had not been demonstrated in the nigrostriatal pathway of choreic patients. However, the fact that choreic movements can appear in hyperthyroidism, where the reactivity of the dopaminergic receptors is modified, is a further positive argument in favor of the theory.

New data obtained from two sources now permit a clearer understanding of the mechanism involved. Studies with selective and localized intracerebral injections of apomorphine (Butterworth et al., 1975), a specific dopamine agonist, raise some doubts about the predominantly striatal site of production of these dyskinesias. Apomorphine itself tends to be taken up along the mesolimbic system at least as much as within the striatum (Butterworth et al., 1975). Ablation of the olfactory bulb abolishes the stereotypes produced by apomorphine (Costall and Naylor, 1974). Thus, the mesolimbic system is more likely to be the important site of the aminergic damage involved in the denervation supersensitivity. This catecholaminergic system was shown to innervate, among other areas, the hypothalamus, nucleus accumbens and stria terminalis. There is some evidence that the corresponding area in humans is the head of the caudate nucleus.

A recent paper by Berheimer et al. (1973) clearly demonstrates that there is a dopamine and HVA deficit in Huntington's chorea and that this involves specifically the caudate nucleus and not, as in Parkinson's disease, the putamen. Some investigators (Barbeau, 1975; Mattson, 1974) have confirmed this finding and further demonstrated that the head of the caudate nucleus shows the greatest dopamine loss and that there is a decrease in the concentration of noradrenaline in the rostro ventral part of that nucleus. The hypothalamus is the second area where both dopamine and noradrenaline were found decreased in our cases. Mattson (1974) has found low serotonin in the hippocampus. In all these cases, as well as in the rigid patients studied by Bird and Iversen (1974), the concentration of dopamine within the putamen appeared to be above normal limits. Anatomical, histochemical and physiological confirmation of such fiber damage in the mesolimbic system in Huntington's chorea is still lacking, but it is now permissible, on the basis of the pharmacological studies, to propose that the postulated supersensitive receptors are indeed situated within that pathway and that their stimulation contributes, along with the striatal localized interneuronal cholinergic and GABA-ergic hypofunction, to the production of chorea. This symptom, previously considered to be of pure striatal origin, should now be thought of as resulting from a functional imbalance between the striatal and the mesolimbic areas.

c) Role of the GABA-ergic system

The output of the striatem is through the pallidum to the substantia nigra, other brainstem nuclei and the reticular formation. The nature of the neurotransmitter involved in the mainly inhibitory output from

the striatum to the pallidum is still uncertain, but the most likely candidate appears to be gamma-aminobutyric acid (GABA) (Anonymous editorial, 1974; Crow, 1974; Anonymous editorial, 1974). GABA-ergic pathways to the pallidum and through it to the substantia nigra have been demonstrated (Fahn and Coté, 1968; McGeer et al., 1971). It was thus of great interest when Perry and his collaborators (Perry et al., 1973) found a deficit in GABA concentrations in the basal ganglia of patients with Huntington's chorea. This finding received confirmation from the demonstration of decreased levels of glutamic acid decarboxylase (GAD) in the brain of choreic patients (Bird and Iversen, 1974; Stahl and Swanson, 1974; McGeer et al., 1973). Unfortunately, GAD deficits, even in the basal ganglia, are not specific to Huntington's chorea, having been found also in Parkinson's disease (Lloyd and Hornykiewicz, 1973; Laaksonen et al., 1974) and in ageing (Bowen et al., 1974). Preliminary (unpublished) data by Hare and collaborators would indicate that CSF GABA levels are also low in Huntington's chorea.

It is thus evident that the pathogenetic process in this disease results in an imbalance in the dopamine-acetylcholine coupling mechanism which may be one trigger to the symptom, chorea. Abnormal input from serotonin, and noradrenaline pathways involved in sleep and awareness mechanisms to the large GABA-ergic efferents, could also play a role. This abnormal activity cannot be checked by the predominantly inhibitory GABA-ergic output system, also deficient. Many more basic studies will be required to delineate the relative importance of these pathways in normal and abnormal functions of the basal ganglia, but this new knowledge is sufficient to permit the development of novel therapeutic approaches and strategies.

Therapeutic research

The above considerations have led to new therapeutic approaches, as well as to a reevaluation of existing ones. It is well known that drugs which interfere with dopaminergic stimulation (reserpine, alpha-methyl-DOPA, phenothiazines and butyrophenones) diminish the choreic movements (Barbeau et al., 1973). Following the suggestion of Dalén (1973), lithium carbonate was added to these drugs (mainly haloperidol), in the hopes of favorably modifying receptor sensitivity. Most results, including double-blind studies, show no distinct advantage (Leonard et al., 1974). Tetrabenazine, which had proved of some use against tardive dyskinesia, was also carefully evaluated. European authors, who have had more experience with this drug, are convinced it has earned the right to be used as the drug of first choice for the suppression of chorea (McLellan et al., 1974). Tetrabenazine apparently acts by reducing the concentration of dopamine in the striatum, substantia nigra and pallidum. It definitely increases dopamine turnover, as indicated by large increments in HVA concentrations in the CSF (McLellan et al., 1974).

We have mentioned the beneficial effects upon chorea of parenteral physostigmine (Klawans, 1970). However this observation has not yet been followed up, neither alone, nor in combination with tetrabenazine or other dopamine blockers. On the other hand, many studies have been initiated following Perry's observations of low GABA. Various strategies have been employed to attack this problem: GABA itself, unfortunately, either does not cross the intact blood-brain barrier (BBB), or does so in very limited quantities. Nevertheless, it has been tried in variable doses. Most authors (Barbeau, 1973; Carman et al., 1974) are unable to demonstrate any clinical effect, except possibly upon rigidity when it is present. However Fisher and collaborators (Fisher et al., 1974), using doses of GABA as high as 32 g. daily, claim to observe clear-cut benefits. The possible dangers of such high doses have been emphasized by Perry et al. (1974). In the absence of direct passage of GABA across the BBB, it was logical to attempt raising brain concentrations of the amino acid with accepted pharmacological tricks: blocking catabolism with Depakin^R, blocking GABA-T (GABA-aminotransferase) with amino-oxyacetic acid (AOAA), using the combination of isoniconinic acid hydrazide (INH) plus Vit. B_6, as suggested by Wood and Peesker (1973). Both Dr. T. Chase in Bethesda, and our own group (Barbeau, 1973), have tried these approaches, to date without success. Another possibility for accomplishing the same result, would be to use GABA analogues. A variety of these drugs, such as β-p-chlorophenyl γ-amino-butyric acid (Lioresal^R, or Baclophen^R) or γ-(4-methylpiperidino)-p-fluoro-butyrophenone (Buronil^R), a neuroleptic agent derived from GABA, have been used (Barbeau, 1973; Mattson and Boman, 1974), again without much success. It is likely that neither substance effectively crosses the BBB. For this reason, it was suggested by members of the Los Angeles workshop that paraglutamyl-GABA or γ-glytamyl-GABA be synthesized and tested for possible central GABA-like effects after parenteral injection. Unfortunately, such research is hampered by the lack of a suitable behavioral animal model of GABA actions. To this effect, I would like to propose the use of the ouabain-induced seizure model, where GABA possesses clear-cut antiepileptic activity (Izumi et al., 1973). If such centrally active and non toxic drugs can be prepared and analyzed, a test of the GABA-hypothesis in Huntington's chorea could be made.

Early detection

One of the aims of biochemical research in Huntington's chorea is the development of a test to permit detection of the disease long before the appearance of symptoms and, if possible, before child-bearing days. Unfortunately, such a goal has not yet been achieved. Meanwhile the Research Group on Huntington's Chorea is in the process of evaluating a battery of physiological tests, each of which shows some promise: accelerometer readings, eye move-

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ment recordings and H-reflex responses. The L-DOPA load test (Klawans et al., 1972) is not used any more, but the original group of at risk subjects is still being followed while some modifications in the test are being worked out. It now appears that dopamine receptor changes in the hypothalamus can be tested through variations in growth hormone or prolactin secretion. Preliminary studies in my laboratory indicate that Huntington's chorea subjects have a delayed and dampened growth hormone response to L-DOPA. At risk subjects appear to segregate into two groups, but it is too early to conclusively evaluate this test. Other abnormalities in growth hormone responses to hyperglycemia have been reported by Podolsky and Leopold (1973). At this time we must conclude that no proven predictive test of the disease exists.

Etiological research

It is evident that a GABA deficit is not the cause of Huntington's chorea, any more than a dopamine lack is that of Parkinson's disease. Because Huntington's chorea is not recessive, it is probably not due to a single enzymatic defect. If an enzyme is involved, it will be in some regulatory mechanism basic to membrane or protein chemistry. Many hypotheses are now being explored in various laboratories:

1) Huntington's chorea could be an ageing (biogenic necrosis) phenomenon superimposed upon a specific system deficiency of neuronal anlage (hyponeurogenesis) of the lateral ganglion hill (Van Wolferen et al., 1974).
2) The disease could be the result of some autoimmune reaction against caudate cells.
3) Cell death in the caudate could result from increased levels and stimulation of cAMP, since this substance has been implicated as a regulator of cell growth in many systems (N. Krieger, unpublished).
4) Cell death could be due to the accumulation of somatic mutations in repair DNA polymerases with a slightly increased error frequency (D. S. Barkley, unpublished).
5) The role of slow viruses similar to those in Kuru and in Jakob-Creutzfeldt disease is still being investigated, although the evidence to date is meager. However, new data on the relationship between viruses and autoimmune disease should be closely followed.
6) Protein abnormalities have recently been isolated in Huntington's chorea brains (Stahl and Swanson, 1974; Iqbal et al., 1974), but are still being characterized.
7) There is no convincing explanation for the increased content of lipofuscin found in the brain of Huntington's chorea patients.
8) A search is being carried out (Barbeau) to find a possible derangement in trace metals in this disease, despite the failure of previous such investigations (Courville et al., 1963).
9) Finally some authors agree with our suggestion (Barbeau et al., 1973) that the defect in Huntington's chorea could be manifested in other tissues outside the brain. Recently Barbeau et al. (1975) have demonstrated a decreased uptake of ^{14}C-dopamine into platelets in Parkinson's disease, and the opposite situation in Huntington's chorea (Barbeau, 1975). Aminoff and co-workers (1974) independently found a significant increased uptake of dopamine in Huntingtonian platelets. If this peripheral defect is confirmed, easier means of study will exist for both these extrapyramidal diseases.

In conclusion, we feel that the explosion of knowledge about Huntington's chorea which has occurred within the last few years deserves attention, for it is one of the promising, albeit little known, fields of neurology.

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