DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
~~[illegible]~~ committees
Hardin Jones papers reprints speeches
BANCROFT/LARC DIN
Banc Mss 79/112c
COPY
CARTON NO
5
FOLDER NAME
UC Berkeley
Human Use Committee 1966-74
NOTES
pg 1/7
FOUND BY/DATE FOUND
K. Holmes 4/9/94

Copied from originals in Nor-Bancroft Library for reference [illegible] not be deposited in other [illegible] address per [illegible] Bancroft Library [illegible] Permission [illegible] brary of [illegible] to reproduce [illegible] must be obtained in writing from [illegible] Director, The Bancroft Library, University of California, Berkeley, California, 94720.

BERKELEY: DONNER LABORATORY AND DONNER PAVILION

April 30, 1968

Dr. Hardin Jones
45[illegible] Donner Laboratory

Dear Dr. Jones:

Enclosed is a research proposal for consideration before the Donner Laboratory Committee for Clinical Research. I have reviewed it and found it to be acceptable and would like it reviewed by the members of our "human use committee".

Sincerely yours,

H. S. Winchell

HSWinch

UNIVERSITY OF CALIFORNIA (Letterhead for interdepartmental use)

dopamine and noradrenaline from controls, and oral or intravenous DOPA administration appeared to improve symptoms of the disease while administration of phenylalanine worsened them. The normal pathway is: phenylalanine-tyrosine-DOPA-dopamine-noradrenaline-adrenaline. The rate limiting step in noradrenaline production is conversion of tyrosine to DOPA by tyrosine hydroxylase. Abnormally large amounts of tyrosine and abnormally low levels of dopamine are found in the urine of Parkinson patients, but there is no deficiency of noradrenaline or adrenaline. When [illegible] pixen radioactive DOPA intraventricularly, labelled dopamine appears in the caudate nucleus but is not converted to noradrenaline in this brain region, while it is rapidly converted to noradrenaline in other brain areas. This suggests that there is some independence, perhaps due to selective uptake, in the synthesis

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE Committees, papers, Hardin Jones reprints, speeches
BANCROFT/LARC ID Banc MSS 79/112c
COPY
CARTON NO. 5
FOLDER NAME UC Berkeley Human Use Committee 1966-74
NOTES Pg. 2/7
FOUND BY/DATE FOUND K. Holmes 11/9/94

Copied from originals in The Bancroft Library for [illegible] Permission [illegible] obtained in writing from the Director, The Bancroft Library, University of California, Berkeley, California, 94720.

Protocol for Berkeley U.C.L.R.S. Committee for Safegards

in Research in Human Subjects

TYROSINE AND DOPA METABOLISM IN PARKINSONISM

Responsible Investigators: Thornton Sargent, Ph.D.
Stephen A. Landaw, M.D.
Sean O'Reilly, M.D., M.R.C.P.E.,
San Francisco General Hospital
Martin E. Glasser, M.D.
San Francisco General Hospital

(1) It had been known for [illegible] time that reserpine could produce a Parkinson [illegible], and it was then shown that dopamine, a precursor [illegible] and [illegible] had a characteristic distribution in the basal ganglia and could be depleted by reserpine. Noradrenaline is now accepted as a neurotransmitter in the CNS, and dopamine has also met almost all of the criteria for such a substance; reference is made to "dopamine-pre" pathways, and it seems possible that a defect in some or all of these pathways could be involved in Parkinsonism. It was then shown that the brains of Parkinson patients contained less dopamine and noradrenaline than controls, and oral or intravenous DOPA administration appears to improve symptoms of the disease while administration of phenylalanine worsened them. The normal pathway is: phenylalanine-tyrosine-DOPA-dopamine-noradrenaline-adrenaline. The rate limiting step in noradrenaline production is conversion of tyrosine to DOPA by tyrosine hydroxylase. Abnormally large amounts of tyrosine and abnormally low levels of dopamine are found in the urine of Parkinson patients, but there is no deficiency of noradrenaline or adrenaline. When rats are given radioactive DOPA intraventricularly, labelled dopamine appears in the caudate nucleus but is not converted to noradrenaline in this brain region, while it is rapidly converted to noradrenaline in other brain areas. This suggests that there is some independence, perhaps due to selective uptake, in the synthesis

1161839

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE committees, papers, reprints, speeches
Harden Jones
BANCROFT/CARC ID NO. Banc MSS 79/112c
COPY
CARTON NO. 5
FOLDER NAME UC Berkeley Human Use Committee 1966-74
NOTES pg. 3/7
COMPLETED BY/DATE COPIED K. Holmes 11/9/94

of dopamine and of norepinephrine in the brain; this might be due to a specific requirement for dopamine in the dopaminergic pathways. Indeed, the very specific enzyme for conversion of L-tyrosine to L-DOPA, tyrosine hydroxylase, is associated with specific particles in the caudate nucleus and in sympathetically innervated tissues but not with particles in the adrenal medulla. The primary neuropathology in Parkinsonism is the present deterioration of melanin-containing cells of the substantia nigra, and tyrosine and DOPA are the precursors of melanin. All of the above evidence seems to point to the possibility of an enzymatic defect in tyrosine hydroxylase leading to: i) a deficiency in the supply of dopamine (which is correctable by feeding DOPA), a dumping of tyramine as a metabolite of surplus tyrosine, ii) exacerbation by feeding phenylalanine presumably increasing toxic products of tyrosine, iii) inhibition in the production of brain melanin by presence of too much tyrosine and too little DOPA (both precursors of melanin) leading to deterioration of pigmented cells in the substantia nigra and failure of the neural functioning of these cells. Function of these nerve cells may also depend on dopamine as a neurotransmitter and thus fail for lack of the transmitter.

Administration of ^{14}C carboxyl labelled tyrosine to patients with rank bacillus is expected to show an altered pattern of $^{14}CO_2$ expiration if there is an inhibition of tyrosine hydroxylase, since the supply of DOPA for aromatic L-amino acid decarboxylase would be reduced. However, the picture may be complicated by the fact that tyrosine is also decarboxylated by aromatic L-amino acid decarboxylase, so that whether the tissue would appear as an increase or a decrease in $^{14}CO_2$ production, or whether it would be apparent at all, is far from certain.

1111453

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
Harden Jones committees, papers, reprints, speeches
BANCROFT/ARCHIVES NO.
Banc Mss 79/112c
COPY
CARTON NO.
(5)
FOLDER NAME
UC Berkeley Human Use Committee 1966-74
NOTES
pg. 4/7
FOUND BY DATE FOUND
K. Holmes 11/9/94

Copied from the Bancroft Library for reference use only. Copyright not the deposited in other Bancroft Library or without express permission. Please contact the Bancroft Library to request permission to reproduce or distribute any copy of this document. Permission to reproduce or distribute any copy of this document is prohibited. Bancroft Library, University of California, Berkeley, CA 94720.

[illegible] (COOH DOPA will also be administered, and if there is a [illegible] in the [illegible] an increased decarboxylation might [illegible] the [illegible] metabolic error may of course be at some [illegible] within the DOPA system, but may [illegible] reflected in the decarboxylation reaction rates.

According to [illegible] text books of Neurology, Parkinsonism is of [illegible]. Most authorities accept the existence of at least four groups of cases:

1. Idiopathic (paralysis agitans, Parkinson's disease)
2. Postencephalitic
3. Arteriosclerotic (senile Parkinsonism)
4. Toxic (e.g. reserpine poisoning, drugs such as reserpine, phenothiazines)

Of these groups, a subgroup of the idiopathic variety would appear to be reasonably well-documented i.e. familial Parkinsonism. This sub-group might be the best one in which to look for a biochemical defect in tyrosine and/or dopamine metabolism. The present study will begin, therefore, with three patients from two families with a family history of Parkinsonism, who have already volunteered for the study. If any significant abnormality is found an attempt to study all other available family members will be made. Similar studies will be carried out on at least six other patients with non-familial Parkinsonism, of varying degrees of clinical severity. The patients will be matched for age and sex with an equal number of normal volunteer control subjects who will have the same studies carried out.

One of the responsible investigators (Sean O'Reilly) has F.D.A. approval of an I.N.D. application for the [illegible] investigation of the

DOCUMENT SOURCE
University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
RECORDS SERIES TITLE
Hardin Jones committees, papers, reprints, speeches
BANCROFT CARD NO.
Banc MSS 79/112c
CARTON NO.
5
COPY
COLLECTION NAME
UC Berkeley Human Use Committee 1966-74
NOTE
pg. 5/7
COMPLETION DATE
K. Holman 11/9/94

[illegible] and metabolic effects of L-dopa. If significant abnormality in the pattern of $^{14}CO_2$ expiration after the tracer doses above described is found in these patients, the effect of a loading dose (0.5 gm) of L-dopa on such abnormality will be investigated. The breath-study [illegible] in a month or three patients who elect a long-term [illegible] of L-dopa and who show significant clinical improvement.

The patients will be informed that the study is one directly related to a [illegible] understanding of their disease but that it is not otherwise likely to be of direct benefit to them. The radiation will be stated in terms of the dose relative to a chest X-ray and other radiological procedures, and a standard consent form obtained. It will be explained that the compounds to be injected are trace amounts of normal metabolites and are not hazardous. Normal subjects will not have been previous subjects in radioisotope studies.

d) The compounds L-tyrosine and DL-dihydroxy phenylalanine (DOPA) will be labelled with ^{14}C in the carboxyl position, with specific activities of [illegible] mCi/mM and [illegible] mCi/mM respectively, obtained from New England Nuclear. ^{14}C has a physical half-life of 5568 years with a maximum beta energy [illegible] mev. and average beta energy [illegible] mev. L-tyrosine has been given to normal human volunteers at San Francisco General Hospital and the $^{14}CO_2$ expiration curve had three components with biological half-times of three minutes, five minutes, and 100 minutes. The large yield of $^{14}CO_2$ per injected dose suggests that a large fraction of the ^{14}C is eliminated by this route. DL-DOPA injected into a rat showed one very fast component ([illegible] min.) and a second

University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley CA
Hardin Jones — Committees, papers, reprints, speeches
Bank Mss 79/112c
COPY
(5)
U Berkeley Human Use Committee 1966-74
Pg 6/7
R. Hallas 11/9/96

[illegible] of 20 minutes [illegible] which was a single exponential until the [illegible] returned to background level of three hours. The turnover of the product dopamine in the brain is about two hours. (Iversen, [illegible] The Uptake and Storage of Noradrenaline, p. 531.)

(c) Brain dopamine is found in the highest concentration in the basal [illegible] the corpus striatum containing 5 μgm/gm compared to 0.07 μgm/gm [illegible]. Above the [illegible], the corpus striatum contains less than [illegible] the total body [illegible]. It is the only known physiologic [illegible] of noradrenaline and adrenaline, but as found in relatively low concentration in the adrenal medulla, suggesting rapid turnover [illegible] in the pathway to noradrenaline. The turnover of dopamine however is very rapid, [illegible] of [illegible] min. in rats. Tyrosine, as a precursor of DOPA, would be expected to concentrate to some degree in the same [illegible] and also to have a more general distribution in amino acid pools in the body. [illegible] precursor of various iodinated thyroid hormones, but since the turnover of these is very slow (on the order of [illegible] days) and tyrosine is fairly abundant, uptake of tyrosine by the thyroid is probably quite low. In summary, I expect some concentration in relatively small areas of the brain, with very rapid uptake and release from these areas.

(d) The maximum [illegible] will be [illegible] each compound to each patient and each volunteer possibly less can be used as experience dictates. Assuming [illegible] uniform distribution in the body:

(1) R_{max} = [illegible] × [illegible] × [illegible] × [illegible] × 10^{-3} rad/day

(2) For DOPA, integral excretion of ^{24}Na from rats was 100% of the injected dose within 5 hours, with $T_{1/2}$ = [illegible] min.

University of California at Berkeley
The Bancroft Library/The University Archives, Berkeley, CA
Hardin Jones Committees, papers, reprints, speeches
Bank Ass 79/112c
COPY
(5)
Berkeley
Human Use Committee 1966-74
pg 7/7
K. Holmes 11/9/94

$$D_p = 6 \times \frac{[illegible]}{[illegible]} \times \frac{[illegible]}{[illegible]} = [illegible] \times 10^{-[illegible]} \text{ rad}$$

[illegible] in 100 gm of tissue, $D_p = [illegible] \times 10^{-[illegible]}$ rad. [illegible], the integral excretion of [illegible] in bounds, using a three [illegible] [illegible], was [illegible]% of the injected dose. Assuming 90% of [illegible] [illegible] with $T_{1/2} = 30$ days as typical for amino acids, and [illegible] the major part of the dose:

$$[illegible] \times \frac{[illegible]}{[illegible]} \times 30 = [illegible] \times 10^{-[illegible]} \text{ rad}$$

[illegible] of the wide distribution of tyrosine in the body, it is considered very unlikely that it will concentrate in any small mass of tissue.

[illegible] The tyrosine is supplied by New England Nuclear sterile for injection. The [illegible] was dissolved in saline, sterilized by passage through [illegible] millipore, and injected into two rats without evidence of pyrogenicity.

[illegible] 11/30/68
[illegible]