ALTERATIONS OF THE SEROTONERGIC SYSTEM IN THE DOPAMINE DEFICIENT STRIATUM OF THE WEAVER MUTANT MOUSE

Elizabeth H. Stotz

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Doctoral Committee

B. Ghetti, M.D.
(Chairman)

J.A. Richter, Ph.D.

J.R. Simon, Ph.D.

L.C. Triarhou, M.D., Ph.D.

F.C. Zhou, Ph.D.

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Elizabeth H. Stotz

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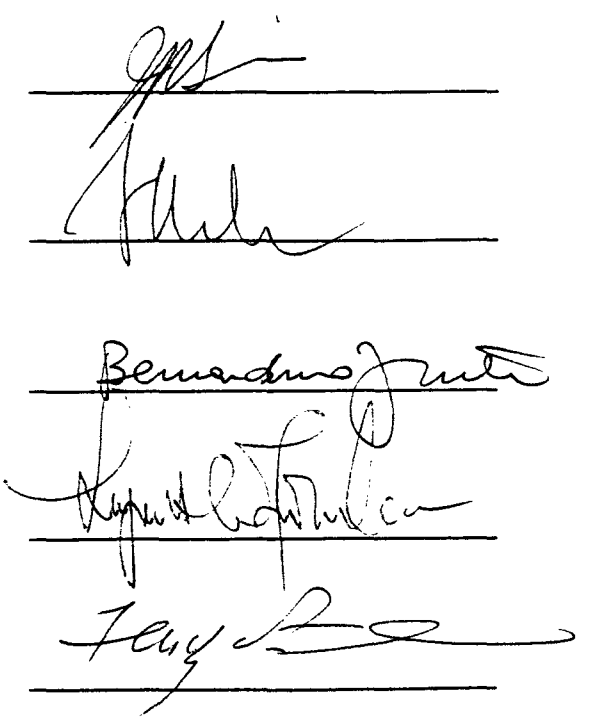
Mice homozygous for the weaver mutation have been shown to have a major deficit in the nigrostriatal dopaminergic system. In the weaver mutant mouse, there is a decrease in the number of dopaminergic cells in the substantia nigra. Striatal dopamine content, tyrosine hydroxylase activity and dopamine uptake are decreased in weaver mice compared to wild-type mice. This dissertation reports on the original finding that the serotonergic system is also altered in the striatum of this mutant. The topographical distribution of serotonin content in the weaver and wild-type striatum was determined using HPLC-EC. Striatal serotonin uptake was measured in two ways; 1) [^{3}H] serotonin uptake was measured in synaptosomes from the dorsal portion of the striatum and 2) [^{3}H] citalopram binding to striatal serotonin uptake carriers was measured using autoradiographic methods. The release of endogenous serotonin was measured from striatal pieces in a superfusion release system. Serotonin release was stimulated by a 5 minute exposure to either 12 mM K^+ or to 10 μM fenfluramine. The

findings indicate that the only gradient seen for serotonin content in the wild-type striatum is along the dorsoventral axis which favors the ventral region. Overall, serotonin content is increased by 45% in the weaver striatum. The primary site of the serotonin increase is the dorsal portion of the weaver striatum. The two techniques used to study uptake reveal an increase in the number of serotonin uptake carriers in the dorsal portion of the weaver striatum. Basal and potassium stimulated serotonin release is decreased in the weaver. Serotonin release stimulated by fenfluramine, a selective serotonin releaser, is greater in the weaver striatum than in the wild-type striatum. Taken together, these data suggest that, in the weaver striatum, there is a hyperinneravation of serotonin fibers in the dorsal portion and that the release process for serotonin is altered.



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