Altered Metabolism of Serotonin in the Brain of the Rat after Chronic Ingestion of d-Amphetamine*

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Abstract. Dextro-amphetamine at doses of 1 mg/kg/day was administered intragastrically to rats for one month. At 18 h after the final dose, a small (16%) increase of brain serotonin concentration was found as well as an increase (30%) of the synthesis and degradation of [3H] serotonin formed from intracisternally injected exogenous [3H]-L-tryptophan.

Key words: Chronic d-Amphetamine -- Brain Serotonin Metabolism -- Tryptophan -- 5-Hydroxy-3-Indoleacetic Acid.

Acute psychotic episodes may develop in individuals who have ingested d-amphetamine over a long period of time (Young and Scoville, 1938; Herman and Nagler, 1954; Connell, 1958; Breitner, 1963; Griffith, Cavanaugh, Held, and Oates, 1970). Amphetamine psychoses have been compared to acute paranoid schizophrenia (Hampton, 1961; Bell, 1965; Díaz, 1966; Kalant, 1966) and theoretical implications of this resemblance have been discussed (Kety, 1959; Nieto, 1960; Bell, 1965). This type of reaction to amphetamine is said to be the psychosis of known origin most similar to idiopathic schizophrenia (Slater and Roth, 1969). In spite of these facts relatively few studies of the chronic effects of d-amphetamine have been done and most studies have been directed to the analysis of behavior patterns (Randrup and Munkvad, 1967) and their relations to changes in catecholamine metabolism in the brains of animals (Hanson, 1967).

Less work has been done with serotonin metabolism even though this indoleamine has been implicated theoretically in abnormal mentation repeatedly since 1954 (Woolley and Shaw, 1954; Airaksinen and McIsaac, 1968; Curzon, 1969). Reports of the effects of d-amphetamine on the metabolism of serotonin in the brain are inconsistent. Endogenous levels

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of serotonin have been reported to be decreased (Paasonen and Vogt, 1956; Lal and Chessick, 1964; Pletscher, Partholini, Brudere, Burkhard, and Gey, 1964; Laverty and Sharman, 1965; Henig and Seifer, 1968) and increased (McCLean and McCartney, 1961; Garatini and Valzelli, 1965; Kostowski and Giacalone, 1969; Welch and Welch, 1970). Gaddum and Vogt (1956) showed that d-amphetamine antagonized the behavioral effects of serotonin administered intraventricularly. Levels of both serotonin and 5-hydroxindole acetic acid (5HIAA) in the brain of the chicken were increased by d-amphetamine (Schrold and Squired, 1971). Fuxe (1970) reported qualitative histochemical evidence of the disappearance of serotonin from central neurons after large, but not after small doses of d-amphetamine. The turnover of the indoleamine has been reported to increase after two doses of 5 mg/kg of d-amphetamine (Reid, 1970). Furthermore, the formation of (14C)-serotonin and (14C)-5HIAA from radioactive tryptophan was increased after a single dose of d-amphetamine (Hitzemann, Loh, and Domino, 1970). After chronic intoxication with methamphetamine (3 mg/kg), Utena (1966) found an increase of serotonin in most areas of the brain. The doses used in both acute and chronic experiments have generally been several times greater than those taken by the chronic abusers of the drug on the basis of mg per kg body weight. It was therefore, of interest to study effects of small chronic doses of d-amphetamine upon the metabolism of brain serotonin.

Material and Methods

Young male Sprague-Dawley rats weighing 150—170 g at the start of the experiment were used. Dextro-amphetamine (1 mg/kg) was given to the animals in 1 ml of water through an oro-gastric tube once a day between 5:00 and 7:00 P.M. for one month. The dose was increased daily according to changes in weight. Control animals received 1 ml of water only.

Sixteen to twenty hours after the last dose of d-amphetamine, 10 μCi of uniformly labelled (3H)-L-tryptophan (New England Nuclear Co., 5 Ci/mMole) in 25 μl of a physiological solution were injected intracisternally (Shanberg, Schildkraut, and Kopin, 1967) under light ether anesthesia. Fifteen minutes later the rats were decapitated. The brains were removed, weighed and homogenized in 6 ml of 1 N HCl in 0.5% (w/v) ascorbic acid. After centrifugation of the homogenates at 30000 g for 10 min the resulting pellets were resuspended in 3 ml of the homogenization medium and recentrifuged and the pellets were discarded. The metabolites of tryptophan and serotonin were separated by the method of Macon and Diaz (in preparation). Thus, after the addition of a drop of 2% (w/v) EDTA the pH of the combined supernatants was