Minimal Brain Dysfunction: Dopamine Depletion?

Shaywitz, Yager, and Klopper (1) propose that the hyperkinetic, or minimal-brain-dysfunction, syndrome in children may be due to a deficiency in the neural transmitter dopamine. As evidence, they demonstrate that rats selectively depleted of dopamine during infancy are significantly more active than normals during the 10-25-day range, and that they show learning deficits later in life. However, there are several difficulties with this analysis:

First, normal 10- to 25-day-old rats are “hyperactive” compared to older rats, apparently because certain adrenergic “activity” systems mature around age 10 days, while the cholinergic “inhibitory” systems, particularly the hippocampus and frontal cortex, approach maturity between ages 15 and 25 days (2). The hyperactivity produced by dopamine depletion was merely a moderate increase in the already-hyperactive behavior which is normal for this age. It disappeared at the same time that normal hyperactivity disappears, around age 25 days, presumably because of the maturation at this time of the cholinergic and perhaps also serotoninergic systems.

Second, Shaywitz et al. interpret the disappearance of hyperactivity in their rats at age 25 days as analogous to the amelioration of the hyperkinetic syndrome in children at age 10 to 12 years. However, age 25 days in a rat is merely the age of weaning. Puberty, corresponding to human age 10 to 12 years, occurs at about age 80 to 100 days in rats.

A more general hypothesis for hyperkinesis, which includes dopamine deplle as a special case, is that this syndrome is caused by a predominance of norepinephrine (NE) relative to other transmitters. Activity level and reward seem to depend on NE (3), and seem to be inhibited by acetylcholine (4), serotonin (5), and to a lesser extent dopamine (6). Rats with increased NE, or depletion of acetylcholine or serotonin, or damage to predominantly cholinergic structures, show high activity (3-6), deficits in habituation (7), difficulty with selective attention (8), and impaired punishment avoidance (4, 9). Adult human manics also show these four symptoms, plus euphoria (which is hard to demonstrate in rats); this parallel led to the now widely accepted theory that mania is due to an excessive level of NE relative to the other three transmitters (8, 10). The commonly reported characteristics of hyperkinetic children are, again, high activity, difficulty with selective attention, impaired punishment avoidance, and euphoria (11). One would suspect, therefore, that hyperkinetics, like manics, suffer from an excess of NE relative to the activity-inhibiting transmitters. (Curiously, mania is reportedly extremely rare in children, and hyperkinesis is unheard-of in adults.) Since the NE activating systems seem to mature before the cholinergic suppressive systems (2), any process which retarded the later periods of brain maturation would be expected to produce temporary dominance of the adrenergic systems, and therefore a hyperkinetic syndrome.

There are several other points about the hyperkinetic syndrome which make sense if we attribute it to delayed maturation of the later-maturing parts of the brain. First, the syndrome is three or four times more common in boys than in girls (11), which correlates with the fact that girls mature faster than boys. Second, the amelioration of the condition with age may be attributed to the continued, though belated, maturation.

Hyperkinesis, therefore, could be caused by anything which produced NE dominance with delayed maturation of cholinergic systems being perhaps the most common mechanism. One otherwise paradoxical phenomenon of hyperkinetic children makes sense on the basis of NE dominance: the activity-reducing effect of amphetamine. As Shaywitz et al. insightfully suggested, this result can best be explained by assuming that amphetamine stimulates the activity-suppressing transmitters dopamine and 5-hydroxytryptamine (5-HT) (6, 12) as well as NE. The question, of course, is why amphetamine effects on dopamine and 5-HT should dominate in hyperkinesics, although the effect on NE is greatly predominant in normals. An attractive possibility is that amphetamine’s effects on dopamine and 5-HT become evident only when NE levels are so high that further increases would be ineffective. Indeed, analogous phenomena have already been demonstrated in rats: After NE has been highly potentiated by high doses of imipramine or amitriptyline, amphetamine has less activity-facilitating effect than usual. Also, when operant response rates are very high (analogous to hyperkinesis), amphetamine decreases the response rate (13).

References
3. L. Stein, in Nebraska Symposium on Motivation (Univ. of Nebraska Press, Lincoln, 1974), vol. 22, p. 113.
Shaywitz, Yager, and Klower (1) reported that rats treated neonatally with 6-hydroxydopamine (6-OHDA) intracisternally exhibit learning deficits as well as transitory activity increases. Shaywitz et al. attributed these behavioral characteristics to the depletion of brain dopamine that resulted from the neonatal injections. They then took a giant step to generalize their results to children who are diagnosed as having minimal brain dysfunction (MBD). These children are characterized by learning disabilities and hyperactivity, with activity levels subsiding as adolescence is approached. While treatment of rat pups with 6-OHDA may ultimately prove to be an invaluable animal model for MBD, we feel this extrapolation is unwarranted for several reasons.

First, our research which preferentially depletes central norepinephrine (NE) to the exclusion of other neurotransmitters, also reports activity increases (2). It should be pointed out that we obtained activity increases without concomitant dopamine alterations.

Second, previous work with 6-OHDA administered neonatally or in adulthood, usually reports hypophagia to some degree and a parallel weight loss (3, 4). Body weight was not reported by Shaywitz et al., but if the experimental animals were indeed lighter than controls, then the observer was not really “blind” as to which rats were treated or untreated. Further, reduced food intake in the experimental group would imply that these animals received too little nourishment during the critical developmental period and therefore there is no appropriately matched control. A “weight matched” control group could be produced by restricting intake to an amount equivalent to that eaten by the experimental group.

Third, previous studies in which 6-OHDA is administered to neonatal rats typically find severe and apparently permanent depletions of NE in peripheral structures (4, 5). Treated rats are effectively partially sympathetically blocked. Shaywitz et al. fail to mention NE content in peripheral structures; however, if peripheral NE depletions did indeed occur, one could hardly attribute behavioral changes to central nervous system effects.

Fourth, the volume of the intracisternal injection appears extremely large for newborn rat pups. The 25-μl injection, in fact, is equivalent to that used for intracisternal injections of adult rats (6). One might expect an intracranial injection of this magnitude to raise intra-cerebral pressure significantly. This suggests that in addition to the vehicle group, a second, noninjected control group should have been employed.

Finally, we question the statistical analysis of the activity data of Shaywitz et al. It is inappropriate to use the t-test to compare the experimental group to the control group on each trial or observation. Instead, a two-factor analysis of variance with repeated measures on one factor is required. Then, if the group-by-trials interaction was significant, one would be justified in comparing the two groups at each individual observation or trial with tests of simple effects. Further, one should note that systematic application of the t-test between groups at each observation greatly increases the probability of finding statistically significant differences.

In conclusion, we feel that the experimental model of neonatal injections with various neurotoxins provides valuable information about the functional significance of different neurotransmitter systems. However, it is only an experimental, not a clinical model. We feel it is a bit premature and perhaps ambitious to equate human behavioral disorders with the behaviors of rats that receive neonatal 6-OHDA.

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Shaywitz et al. (1) presented a rat model of the minimal brain dysfunction syndrome (MBD). They injected 5-day-old rat pups intraperitoneally with des-methylimipramine (DMI) and then intracisternally with 6-hydroxydopamine (6-OHDA), producing permanent reduction of whole brain dopamine with no significant reduction in whole brain norepinephrine. In comparison to vehicle controls, these rats were significantly hyperactive from 15 to 22 days of age. The hyperactivity abated by 26 days of age, but a deficit in avoidance learning was observed at 27 days. Shaywitz et al. considered this profile to be analogous to the child with MBD who is hyperactive until 10 to 12 years of age. This hyperactivity subsides but is followed by other behavioral difficulties.

This proposed animal model is interesting because of the general utility of such models in deciphering the possible neurochemical bases of this and other syndromes such as Parkinson's disease. However, Shaywitz et al. failed to use the appropriate control groups which would permit them to relate their behavioral alterations only to the proposed critical pharmacological manipulation, the depletion of brain dopamine. No groups that had received only DMI or 6-OHDA were behaviorally tested. Thus Shaywitz et al. can only conclude that pharmacological manipulation, regardless of its specific nature, leads to the behavioral changes that they observed.

Behavioral alterations similar to those observed by Shaywitz et al. can in fact be observed after peripheral injections of 6-OHDA in the newborn rat. This treatment permanently destroys forebrain norepinephrine projections apparently originating in the locus coeruleus, while elevating pontine norepinephrine levels, but does not alter brain dopamine levels (2). These rats are hyperactive during infancy until about 25 days of age, and they also show a persisting behavioral deficit (3). Furthermore, neonatal injections of guanethidine induce hyperactivity during infancy but do not have a toxic effect upon brain catecholamine.
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