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Haloperidol-Induced Hyperactivity in Neonatal Rats: Effect of Lithium and Stimulants

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SCHECHTER, M. D. AND J. T. CONCANNON. *Haloperidol-induced hyperactivity in neonatal rats: Effect of lithium and stimulants*. PHARMAC. BIOCHEM. BEHAV. **16**(1) 1–5, 1982.—The effect of chronic subcutaneous administration of haloperidol directly into neonatal rats was investigated as a possible model for the hyperkinetic syndrome in human children in terms of its onset, duration and offset of hyperactivity. In addition, the ability of chronically-administered lithium in the diet of nursing mothers to attenuate the haloperidol-induced hyperactivity was investigated. Experiments with acute administration of the clinically-effective stimulants, amphetamine and methylphenidate, to the pups were also conducted to determine the adequacy of this behavioral model vis-a-vis the human condition. The results indicate that, although chronic haloperidol (2.5 mg/kg) produces hyperactivity relative to controls on the 25th day of life, this hyperactive behavior does not return to control levels at 30 days of age. Moreover, neither the stimulants nor lithium attenuates this hyperactivity and, indeed, lithium, by itself, produces increased activity. Thus, chronic haloperidol administered directly into neonatal rat pups produces hyperactivity possibly by the production of dopaminergic supersensitivity, yet this effect does not model the temporal course seen in hyperkinetic humans. In addition, the administration of drugs that are clinically-useful in treating childhood hyperactivity were unable to decrease the hyperactivity produced by haloperidol in neonatal rats. Taken together, these observations cast doubt upon the usefulness of this animal model to mimic the human condition.

Hyperactivity Lithium Haloperidol Dopamine *d*-Amphetamine Supersensitivity Methylphenidate Developing rats

ALTHOUGH it is known that acute administration of neuroleptics in adult rodents initially produces a hypodopaminergic state by post-synaptic receptor blockade, chronic administration of neuroleptics eventually leads to a compensatory increase or hyper-dopaminergic state particularly after a short withdrawal period. Chronic neuroleptic treatment in adult rodents has been shown to produce behavioral hyperactivity and an augmented response to catecholamine agonists [6,12] and both of these phenomena are associated with an increase in the number of dopamine (DA) receptors in the brain [9,21]. Such behavioral and biochemical supersensitivity has been used to produce animal model(s) of tardive dyskinesia as may result from long-term neuroleptics administration in adult humans [6].

Recently, developmental neuropharmacologists have become interested in tardive-dyskinesia-like behavioral supersensitivity, resulting from chronic perinatal neuroleptic drug administration, as perhaps providing for a viable animal model of the childhood hyperkinetic syndrome ([2, 16, 18, 31] and see [14,31] for review of other biological and behavioral effects of pre- and post-natal neuroleptic administration). From this viewpoint, increased locomotor activity, altered habituation, and associative learning problems [16], which are among the cardinal features of the hyperkinetic syndrome, may simply be the developmental manifestation of an altered dopaminergic state resulting from chronic neonatal neuroleptic administration. Furthermore, biochemical receptor supersensitivity associated with this treatment [7] has been associated with the altered (or "paradoxical calming") response to psychostimulants in hyperkinetic vs normal organisms ([28,29] and see [14] for review of other biological and behavioral effects of pre- and post-natal psychostimulant administration) and may contribute to the production of one or more of the aforementioned behavioral problems [16].

A major problem in using chronic post-natal neuroleptic treatments to model the hyperkinetic syndrome is that few researchers have carefully investigated its similarity to the human situation. In order to replicate the human situation faithfully [27], the model should: (a) produce many of the cardinal features of the hyperkinetic syndrome (e.g., overactivity, learning problems, and short attention span); (b) bear some temporal relationship, in terms of onset, duration, and offset of overactivity, to the pathogenesis of hyperkinesis in humans; and most importantly, (c) respond well to psychostimulant medication or other therapeutic interventions (e.g., co-administration of lithium). The most thorough series of studies [16] concerned with these three issues has shown that the chronic administration of neuroleptics to nursing rat mothers post-natally produces hyperactivity in

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open-field behavior [1] and associative learning problems in their 4-week-old offspring and that this latter deficit can be reversed by the administration of *d*-amphetamine to the pups. However, problems of interpretation arise since psychostimulants were not tested in the open-field, and the dose of the neuroleptic drug is difficult to specify when administered through mother's milk. Nonetheless, the levels of activity in treated animals eventually reached control levels which seems to be a prerequisite for modeling the human situation. Spear *et al.* [31] have shown that chronic administration of haloperidol both pre- and post-natally to rat mothers produced hyperactivity and attentuated responsiveness (i.e., hyposensitivity) to *d,l*-amphetamine in weaning and pre-pubescent rat pups. Furthermore, hyperactive behavior temporarily returned to control levels. A major problem in interpretation of this study, however, is that it remains uncertain whether pre- or post-natal neuroleptic exposure was critical for altered behavior, since haloperidol was administered at both times (cf. [25]). In this regard, Rosengarten and Friedhoff [23] have shown that chronic pre-natal haloperidol administration to rat mothers produces a subsensitivity to apomorphine-induced stereotypy possibly due to interruption of DA terminal ingrowth, proliferation, or differentiation, while chronic post-natal administration of the neuroleptic produced a supersensitive response to apomorphine by chronic blockade of otherwise normally-developed, more mature receptors. In addition, none of the above-mentioned studies examined the role of co-administration of lithium with neuroleptics in an attempt to calm hyperactive behavior, although this treatment has been successful in abating behavioral and neuronal supersensitivity in adult rats [9, 21, 35]. In fact, little is known concerning the effects of chronic pre- or post-natal lithium administration in developing rats ([11] and see [13,26] for review of biological and behavioral effects of lithium in adult rodents).

Hence, the goal of the present study was to investigate the viability of an animal model of hyperkinesis resulting from chronic administration of the neuroleptic haloperidol directly into rat pups, by examining the temporal similarity of this hyperactivity to that observed in humans, in terms of onset, duration, and offset. Direct parenteral administration was used to more carefully specify the dosage of neuroleptic received by the offspring. In addition, the ability of psychostimulants (*d*-amphetamine and methylphenidate) and chronic lithium carbonate to decrease neuroleptic-induced hyperactivity was examined by employing a time-sampling technique suitable for detection of hyperactivity in developing rats [30].

METHOD

Animals

Sprague-Dawley-derived (Charles River) rats born and raised in the Department colony served as subjects. The parents were paired in plastic breeding cages and each breeding male was removed as soon as it was physically apparent that the paired female rat was pregnant. Within 2 days after birth, litters were culled to a maximum of 8 pups with an approximately equal number of males and females. On occasion, a litter with less than 8 pups was fortified by the addition of animals culled from other litters that were born on the same day. Throughout all phases of breeding and behavioral observation the animals were housed under controlled temperature and a 12-hr light/12-hr dark cycle. Food and water were provided ad lib.

Procedure

At 5 days of age, rat pups were toe-clipped for identification purposes and were randomly assigned to one of 3 drug treatments: (1) 2.5 mg/kg haloperidol, (2) 0.25 mg/kg haloperidol, or (3) saline (vehicle) control. These agents were administered subcutaneously (0.005 ml/g) from day 5 to day 14 of life. In addition, half of these animals were raised by mothers administered lithium carbonate in their diet, while the other half were raised by mothers fed a normal laboratory diet. The lithium diet consisted of 1500 g powdered laboratory chow and 2266 mg lithium carbonate mixed with 2000 ml of water. Maintenance of this diet for 14 days in adult male rats has been reported to produce and maintain serum and brain tissue levels of 0.8 mEq/l lithium which resembles therapeutically active plasma levels in humans [9,21]. Furthermore, it has been shown that lithium in the mother's drinking water can enter rat pups and alter neonatal biochemistry and behavior [11] strongly suggesting that lithium enters the suckling rat through the mother's milk. In the present study, the lithium diet started at the time of the first daily haloperidol injection and it was removed after the last injection.

Starting at 15 days of age, and at 5 day intervals through 30 days of age, activity of the rat pups was determined between the hours of 1300 and 1600 hours by using a time-sampling technique described in detail by Shaywitz *et al.* [30]. Thirty min prior to the activity test, rat pups were removed from the mother and were administered (intraperitoneally) either *d*-amphetamine (0.2 or 0.5 mg/kg), methylphenidate (0.2 mg/kg), or an equal volume of saline (0.9% sodium chloride). Thirty min after the injection, pups were again removed from the mother and individually placed in $33 \times 27 \times 17$ cm clear plastic cages for behavioral observation. Each cage was scanned every min for one hr and, thus, 60 measures for each animal on each observation day were generated. This activity was recorded by a single observer who was "blind" to the experimental treatments.

Drugs and Dosage Rationale

Haloperidol (Haldol®, McNeil Laboratories Inc. Fort Washington, PA) was obtained in vials of 2.0 mg/ml and was diluted in 0.9% saline. Lithium carbonate (Fisher Scientific, Fairlawn, NJ) was administered in the diet, as described. D-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO) and methylphenidate hydrochloride (Ciba-Geigy, Summit, NJ) were dissolved in saline and were administered in doses calculated as free base. All of these agents were administered within a dose range that had previously been reported to be effective in other paradigms including calming of 6-OHDA-induced hyperactive behavior [28,29] and production and alleviation of haloperidol-induced dopamine supersensitivity [9,21].

Statistical Methods

Measurements of each category of activity were calculated as percentage of occurrence of the 60 min observation period (i.e., number of times active divided by 60×100). For brevity of reporting, and to allow comparisons to the reports of Shaywitz *et al.* [28–30], only the category of total activity was analyzed. "Total activity" included ambulating, rearing, climbing, eating, drinking, sniffing, grooming, and scratching, as previously described [30]. Total activity data were analyzed in two separate ways. First, a 14 (Treatment)

TABLE 1

MEAN ABSOLUTE TOTAL ACTIVITY AND PERCENT TOTAL ACTIVITY FOR ALL TREATMENTS

Treatment Group*	Age (Days) 15	20	25	30
C/S/S	35.4 (59)†	43.8 (73)	28.8 (48)	30.6 (51)
C/S/A	57.0‡ (95)	59.4‡ (99)	58.8‡ (98)	58.2‡ (97)
C/h/S	40.2 (57)	47.4 (79)	28.2 (47)	40.2 (67)
C/h/A	50.4 (84)	60.0‡ (100)	60.0‡ (100)	58.8‡ (98)
C/H/S	39.0 (65)	49.8 (83)	42.6‡ (71)	43.8‡ (73)
C/H/M	29.4 (49)	51.0 (85)	43.8‡ (73)	46.2‡ (77)
C/H/a	48.0 (80)	60.0‡ (100)	55.8‡ (93)	49.8‡ (83)
C/H/A	57.6‡ (96)	60.0‡ (100)	60.0‡ (100)	58.8‡ (98)
L/S/S	28.8 (48)	39.6 (66)	46.8‡ (78)	48.0‡ (80)
L/S/A	49.8 (83)	60.0‡ (100)	60.0‡ (100)	51.6‡ (96)
L/h/S	26.4 (44)	45.0 (75)	48.6‡ (81)	40.2 (67)
L/h/A	45.6 (76)	60.0‡ (100)	57.6‡ (96)	57.6‡ (96)
L/H/S	37.8 (63)	54.6 (91)	46.2‡ (77)	52.8‡ (88)
L/H/A	53.4 (89)	60.0‡ (100)	57.0‡ (95)	57.6‡ (96)

*C=control diet; L=lithium diet; S=chronic saline administration; h=chronic 0.25 mg/kg haloperidol administration; H=chronic 2.5 mg/kg haloperidol administration; a=pre-treatment with 0.2 mg/kg *d*-amphetamine; A=pre-treatment with 0.50 mg/kg *d*-amphetamine; M=pre-treatment with 0.2 mg/kg methylphenidate.

†Indicates percent total activity (e.g., for C/S/S group on day 15: 35.4/60×100=59).

‡Significantly different from C/S/S group on same day (Dunnett's Test; $p \leq 0.05$).

× 4 (Age) mixed unweighted means analysis of variance (ANOVA) was conducted with Age representing the repeated measure. This somewhat conservative analysis was followed by the Dunnett's Test (for experimental groups vs a single control group) derived from the within-group error term, since we wanted to insure that all groups tested contributed to the error term, and since we were most interested in what experimental conditions returned activity to control levels [21]. Second, we eliminated the low dose amphetamine and methylphenidate groups from analysis and conducted a 2 (Diet) × 3 (Chronic Haloperidol Treatment) × 2 (Amphetamine vs Saline Treatment) × 4 (Age) mixed unweighted means ANOVA followed by Duncan's Multiple Range Test, derived from the appropriate within-group error term, in order to reveal possible Diet × Chronic Haloperidol Treatment interactions not accessible by the first means of analysis. Throughout the course of the experiment $p \leq 0.05$ was considered to be statistically significant.

RESULTS

The mean absolute, and percentage of, total activity as a function of age, diet and type of stimulant medication administered prior to behavioral observation is presented in Table 1. As seen in this table, most groups showed an increase in activity from moderate values at 15 days of age to high levels at 20 days of age. Thereafter, the decline in activity to adult levels in the control/saline/saline (C/S/S) group that has been repeatedly reported [2,30] was observed while most other groups, with the exception of the control/0.25 mg/kg haloperidol/saline (C/h/S) group, showed a continued rise or a plateau of activity.

At 15 days of age, only the control/saline/0.50 mg/kg amphetamine (C/S/A) and the control/2.5 mg/kg haloperidol/0.50 mg/kg amphetamine (C/H/A) groups differed from the control/saline/saline group (C/S/S). At 20 days of age, all of the stimulant-treated groups, with the exception of the control/2.5 mg/kg haloperidol/methylphenidate (C/H/M) group, showed higher activity than the C/S/S (control) group. At 25 and 30 days of age, hyperactivity was present in the control/2.5 mg/kg haloperidol/saline (C/H/S) group; the lower dose of haloperidol (C/h/S) was ineffective in this respect. Furthermore, all stimulant-treated groups displayed higher activity than the control (C/S/S) group at these ages. In addition to the stimulants, the lithium diet by itself produced overactivity at 25 and 30 days of age, and, unexpectedly, did not return the hyperactivity in animals chronically treated with the high dose of haloperidol (L/H/S) or the overactivity associated with stimulant administration to the control level. In fact, no combination of treatments, with the exception of the lithium/0.25 mg/kg haloperidol/saline (L/h/S) treatment at 30 days of age, returned activity to the control (C/S/S) level. Hence, although hyperactivity was clearly produced by 2.5 mg/kg haloperidol, there was no reversal of hyperactivity by either stimulant used or by the co-administration of lithium.

Statistical verification of these observations was achieved initially by the 14×4 ANOVA, which generated reliable simple main effects of Treatment, $F(13,115)=19.61$, $p<0.001$, and Age, $F(3,345)=22.34$, $p<0.001$ and a reliable effect re-

sulting from the Treatment × Age interaction, $F(39,345)=1.70$, $p<0.01$. Subsequent Dunnett's Tests revealed that the following groups differed statistically from the control/saline/saline (C/S/S) group at the following ages: (a) 15 days: control/saline/0.5 mg/kg amphetamine (C/S/A); control/2.5 mg/kg haloperidol/0.5 mg/kg amphetamine (C/H/A); (b) 20 days: all groups administered stimulants, except for the control/2.5 mg/kg haloperidol/0.2 mg/kg melthylphenidate (C/H/M) group; (c) 25 days: all groups except the control/0.25 mg/kg haloperidol/saline (C/h/S) group; and (d) 30 days: all groups, except control/0.25 mg/kg haloperidol/saline (C/h/S) and lithium/0.25 mg/kg haloperidol/saline (L/h/S) groups. Dunnett's *t*-tests of mean body weights showed that none of the experimental groups differed from the control group (C/S/S) at any age. Hence, differences in activity were not due to altered body weights associated with the various treatments.

Results using the factorial design were essentially the same, and they failed to reveal Diet × Chronic Treatment or Diet × Chronic Treatment × Drug Treatment interactions. In addition, post-hoc tests showed no combination of treatments decreased hyperactivity in the C/H groups either below the C/H/S baseline or to the C/S/S control baseline. Hence, no evidence was found for a "paradoxical calming" effect of stimulants. In fact, amphetamine actually increased hyperactivity in C/H animals in some cases.

DISCUSSION

The most important findings of the present investigation are that: (a) chronic administration of a high (2.5 mg/kg) dose of haloperidol directly into neonatal rats produced hyperactivity at 25 and 30 days of age, relative to control rats; (b) hyperactive behavior did not return to the control level at the last observation age; and, perhaps most impportantly, (c) there was no reduction in hyperactive behavior resulting from chronic co-administration of lithium or from acute psychostimulant (*d*-amphetamine and methylphenidate) administration. In addition, chronic administration of lithium by itself surprisingly produced overactivity [3,17] that was, likewise, not decreased by the administration of the stimulants. Furthermore, neither did chronic lithium decrease stimulant-increased activity [8,34].

These results are partially consistent with those studies reporting hyperactive, open-field behavior after the cessation of chronic neuroleptics pre- and/or post-natally [1,31]. That is, hyperactive behavior was clearly produced herein, but unlike the previously-mentioned studies, the level of hyperactive behavior never returned to control levels. This apparent inconsistency may well be related to either the dose, route of administration, duration of action of various anti-psychotics (i.e., penfluridol vs haloperidol), type of behavioral observation used (i.e., open-field vs time-sampling), or age at testing. Nonetheless, these results are formally similar to our previously published data, using the same time-sampling technique, that indicated that hyperactivity produced by neonatal 6-hydroxydopamine administration does not return to control levels at the last age of observation [4]. Hence, these combined observations cast some doubt upon the notion that the temporal course of hyperactive behavior produced in neonatal rats is closely modeling the timetable found in hyperactive children.

The inability to control hyperactive behavior by (co-administration of) lithium or by acute stimulant medication raises serious problems for the possibility that the hyperactive behavior is being produced through the mechanism of DA neuronal supersensitivity. That is, neuronal supersensitivity associated with chronic haloperidol treatment has been repeatedly shown to be reversible in adult rats, as is behavioral evidence for supersensitivity, such as heightened stereotypy and augmented apomorphine-induced increases in locomotor behavior [9, 21, 35]. The source of discrepancy in our present study remains unclear, although some speculations are evident. First, the dose of haloperidol that we used may not have altered the number of receptors [18], although this seems unlikely since we used the dose that others find increases the number of DA receptors when administered post-natally [23]. Second, the dosage of lithium may not have been sufficient, although it did produce hyperactivity by itself. Lastly, it remains possible that presynaptic impulse flow in haloperidol-treated rats was affected by lithium, and that this impulse flow is more important than post-synaptic receptor processes in mediating hyperactive behavior [16].

Failure to manage hyperkinesis by psychostimulants also seems perplexing since stimulants typically decrease overactivity in hyperkinetic children. This is not inevitably the case in animal models, however, since several recent reports have failed to clearly demonstrate decreased hyperactivity by stimulant drugs in rats administered either neonatal 6-hydroxydopamine or combined pre- and post-natal haloperidol [4, 5, 19, 31, 32]. These observations leave one to suspect that the "paradoxical" response to stimulants in these treated rats is the result of malnutrition or stunted weight gain, and not the direct result of DA denervation/supersensitivity or altered impulse flow.

To the best of our knowledge, there are no previous reports concerning the effects of chronic neonatal lithium treatment on either neonatal or adult activity behavior of haloperidol-treated pups. As previously mentioned, this treatment was completely ineffective in altering haloperidol-induced hyperactivity and amphetamine-induced activity increases, although it did, by itself, produce overactivity in developing rats. This latter finding is consistent with those of previous reports showing increased motility in adult mice [17] or rats [3] chronically treated with lithium. At present, it remains uncertain exactly by what mechanism lithium produced over-activity, since it apparently does not directly alter DA receptor binding in adults [9,21]. Nevertheless, effects of lithium upon other neurotransmitter(-related) systems (e.g., serotonin or adenylate cyclase) cannot be ruled out at this time [10, 20, 22, 24, 33]. In light of the above findings, it appears as though co-administration of lithium may not be helpful in managing hyperactivity per se, although other features of the hyperkinetic syndrome (i.e., heightened aggression) may be more sensitive to its effects [15].

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