Neurochemical Correlates of the Waltzing-Shaker Syndrome in the Varitint-Waddler Mouse

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Abstract. In the order to examine activity of the dopamine system in the Varitint-waddler (*Va*) mouse, behavioral effects of haloperidol and dexamphetamine on waltzing *Va*, non-waltzing *Va* and non-mutant mice were investigated. The dopamine system of these mice was studied by macro-autoradiography with ^{14}C-dihydroxyphenylalanine. High doses (5.0—10.0 μmol/kg) of haloperidol were similarly effective in both mutant and non-mutant mice: they induced a highly characteristic cataleptic effect in all types of mice. Low doses (0.10—3.16 μmol/kg) were significantly less effective in the waltzing *Va* mice: they induced a marked shift from a small increase of the sitting frequency in the waltzing mice to a large increase of this measure in the non-mutant mice. Several behavioral measures of the untreated waltzing mice mimicked those of control mice treated with amphetamine. Amphetamine reversed original strain differences and depressed several stereotyped *Va* activities. The autoradiograms of the waltzing *Va* mice, which showed a marked labelling of the Harderian gland, differed significantly from those of the non-waltzing *Va* mice and controls, which showed no labelling of this gland. It is suggested that a hyperactive dopaminergic mechanism is involved in the waltzing-shaker syndrome of the Varitint-waddler.

Key words: Waltzing-Shaker Syndrome — Amphetamine — Haloperidol — Mice.

Introduction

In the Varitint-waddler mouse the *Va* allele leads to a syndrome of circling, head-tossing, hyperactivity, extrapyramidal-like symptoms and deafness. These choreiform disturbances etc. are combined with a piebald spotted pattern, in which the pigment areas are reduced to non-fading spots on a fading background (Cloudman and Bunker, 1945; Cools, in press; Deol, 1954).

A hypothesis has been put forward that a striatal disorder based upon a disturbance of the dopamine-metabolism is involved in the waltzing-shaker syndrome of these mutants (Cools, in press). The striatal system fulfills an important function with respect to the integration and coordination of motor activity; *Va* disorders such as hyperactivity, disorientation, rotational behavior and presence of abnormal postures and locomotion point to a possible involvement of this system. In addition, it has been suggested by Deol (1954) that the shaking movements of the

head may be analogous to Huntington's chorea in man, in which similar head movements are held to be due to the involvement of the striatal system. Of importance in this context is the essential significance of dopamine (DA) for the function of the striatal system (Bloom *et al.*, 1965; Connor, 1968; Cools and van Rossum, 1970; Cools, 1971; Herz and Zieglgänsberger, 1966; Hornykiewicz, 1966; York, 1967).

In order to examine the above-mentioned hypothesis, behavioral effects of intraperitoneally injected compounds, which interfere with DA in the Corpus striatum, were measured. It has been shown that the DA activity of the striatal system is sensitive to specific blocking and stimulating agents. Investigations on the mechanism of action of the neuroleptic drugs of the butyrophenone-group have shown that they are particularly effective in blocking the DA activity of the Corpus striatum (Cools, 1971; Costall and Olley, 1971; Florio and Longo, 1971; Fog, 1967b; Fog *et al.*, 1968; Fog *et al.*, 1970; Randrup and Munkvad, 1968). Investigations on the mechanism of dexamphetamine-like substances have shown that their central action is mediated by direct and indirect DA receptor stimulaton at the level of the nigrostriatal system.(Cools, 1971; Fog *et al.*, 1967a; Fuxe and Ungerstedt, 1970; McKenzie and Szerb, 1968; Randrup and Mundvad, 1970). Haloperidol, a neuroleptic drug of the butyrophenone-group, and dexamphetamine were therefore used as experimental tools in order to examine the striatal system of the Varitint-waddler. In order to examine histochemical disturbances of the dopamine system, a study was made by means of macro-autoradiography.

The evidence presented in this paper strongly supports the hypothesis that a disorder of the dopamine system is involved in the waltzing-shaker syndrome of the Varitint-waddler.

Experimental Animals

Male mice ranging in weight from 18—26 g, sixty to hundred and twenty days of age, were used routinely in this study. The animals came from the F_1 of two stocks, one heterozygous for Va and the other homozygous for dilute (dd): C57BL/6J. The details of the segregation of the gene Va are described by Cools (in press). Each F_1 littersize was reduced to 7—8 animals in order to ensure some uniformity in nutrition and growth rate. Littermates were kept together in large perspex cages ($32 \times 21 \times 16$ cm) until the 30th postnatal day; from this day on each animal was isolated in a small perspex cage ($13 \times 21 \times 16$ cm) with beddings of peat dust and metal covers. Since it was noted in a previous study that one group of the Va, which had no spots, did not turn at all (Cools, in press) waltzing (w $Va/+$) and non-waltzing (nw $Va/+$) mutants were tested separately; non-mutant littermates ($+/+$) were used as controls.

The temperature (22°C), day/night periodicity and light intensity were standardized. Food and water were supplied ad libitum; during the experiments only food was available.

Methods

For each experiment three groups, each including 12 animals, were tested: A. wild-type mice $(+/+)$; B. non-waltzing mutants (nw $Va/+$); C. waltzing mutants (w $Va/+$). In order to test the effect of haloperidol, frequency counts of sitting displayed by the mice in their own home-cages were made every 30 sec according to the time-sample method for a period of 30 min; each period included six successive sessions of 5 min. Twelve min prior to testing the animals received the haloperidol injection. In order to test the effects of dexamphetamine frequency counts of ten behavioral components displayed by the mice in their own home-cages were made every 30 sec for a period of 30 min: sitting, cleaning, eating, sniffing at the ground, reconnoitering, digging, circling, tail-raising, head-tossing and ' miscellaneous"; miscellaneous comprised jumping, waddling, forward and backward locomotion. For a description of the first mentioned items reference is made to Abeelen (1966); postures and acts such as leaning against a wall, climbing wire mesh etc. were not registered in view of the low scores obtained in preliminary experiments. Six min prior to testing the animals were injected. Haloperidol and dexamphetamine-sulphate were administered intraperitoneally in 0.9% saline. All solutions of chemical agents were prepared freshly prior to injection (0.1 ml/kg). In an initial test for each substance mice received a single injection of the agents at 5 geometrically spaced concentration levels ranging from 1.0 to 20.0 µmol/kg in order to determine the effective dosage. Since haloperidol induced continuous sitting at the concentration level of 5 µmol/kg, supplementary experiments were conducted at more closely spaced dosage increments. As haloperidol induced qualitatively similar, but quantitatively different effects in both mutants and non-mutants, five different concentrations (see Fig. 1) were chosen for the definite test. Dexamphetamine at a concentration of 10 µmol/kg induced clearly observable changes in the behavior of both $Va/+$ and $+/+$ mice and this dose was chosen for the dexamphetamine test.

In order to study the aminergic system, the autoradiographic technique of Ullberg (1954) was used. Male mice, $+/+$, nw $Va/+$ and w $Va/+$ ranging in weight from 18—22 g, sixty days of age, were given 20 mg (200 µC)/kg ^{14}C-dihydroxyphenylalanine (DOPA) intraperitoneally; twenty min prior to the DOPA injection Ro-4-4602 (N^1-DL-seryl-N^2-(2,3,4-trihydroxybenzyl)-hydrazine was given in order to block extra-cerebral decarboxylase without inhibition of cerebral decarboxylase (Bartholini et al., 1967; Constantinides et al., 1968). The mice received

0.1 ml/kg of saline solution, in which the compounds were dissolved. After a survival period of 2 h, the animals were decapitated and frozen according to the mentioned method. Frontal sections of the head and sagittal sections of the body, 20 μ thick, were made; sections were stuck to Scotch Tape, freeze-dried and pressed on to Structurix (Gevaert) D 7 X-ray films and exposed for 20 to 30 days at − 12°C.

Results

In general, haloperidol at dose levels higher than 5 μmol/kg induced catalepsy in all types of mice. However, lower concentrations resulted only in a reduction of normal activities: no abnormal postures or movement were elicited. Since the reduction of the behavioral activities started at about 25 min after the injection, only the data of the third session (22 to 27 min after the injection) were analyzed. The values found for the responses of the three types of mice on different doses of haloperidol were arranged in the cumulative concentration curves of Fig. 1, in which the percentages of the maximum scores of sitting frequency (S/Sm) of 12 animals were plotted against the logarithmic dose concentration. Differences in responses on the same dose of the different types were evaluated nonparametrically by means of the two-tailed Wilcoxon test (Siegel, 1956). The values obtained for $+/+$ and nw $Va/+$ mice showed that the effects of the same dose of haloperidol in both groups were very similar, although the significant difference ($p \leqslant 0.05$) at the dose 0.10 μmol/kg suggested that haloperidol was somewhat less effective in the nw $Va/+$ (Table 1). However, significant differences were found for the w $Va/+$ mice on all ocasions (Table 1). Moreover, calculations of differences in responses of successive dosage increments gave significant differences ($p \leqslant 0.05$ in the two-tailed Mann-Whitney test) for the nw $Va/+$ at dosage steps 0.316−0.750, 0.750−2.32 and 2.32−3.16 μmol/kg, but only significant differences for the $+/+$ mice and the nw $Va/+$ mice at the dosage steps 0.00−0.10 and 0.10−0.316 μmol/kg. Thus, the haloperidol effect was significantly less effective in the w $Va/+$.

All data of the saline-amphetamine test are arranged in Tables 2−4. Differences in responses of the $+/+$ and $Va/+$ mice on the two drugs were evaluated by means of the nonparametric two-tailed Mann-Whitney test (Siegel, 1956), while differences in responses to the same drug of the different types of mice were evaluated by means of the two-tailed Wilcoxon test or the Fisher exact test (Siegel, 1956). As shown in Table 2, the scores of several behavioral activities in the $+/+$ mice differed originally from those of the mutants: for instance, $+/+$ scored significantly lower than the nw $Va/+$ for sitting, but significantly higher for cleaning, sniffing and reconnoitering; in contrast, $+/+$ scored significantly lower than w $Va/+$ for reconnoitering, but significantly higher
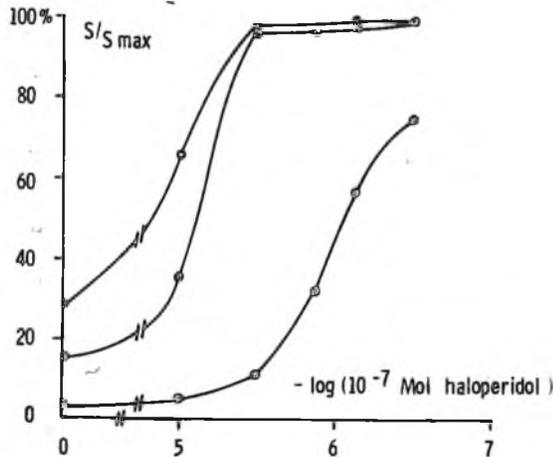
Fig. 1. Sitting-scores of $^+/+$ (o), non-waltzing $Va/+$ (ⓓ), and waltzing $Va/+$ (o),
following i.p. injections of haloperidol. S/S max is the percentage of the maximum-
score of sitting-frequency of 12 mice during the third session

Table 1. *Differences in responses to increasing doses of haloperidol in wild-type*
(+/+), non-waltzing (nw Va/+) and waltzing mice (w Va/+)

Haloperidol (μmol/kg)	+/+ vs nw Va/+	+/+ vs w Va/+	nwVa/+ vs W Va/+
0.00	ns	*	*
0.10	*	*	*
0.316	ns	*	*
0.750	ns	*	*
2.32	ns	*	*
3.16	ns	*	*

* significant at $p \leqslant 0.05$ (Wilcoxon test).

for cleaning, sitting and sniffing. Thus, marked differences were observed
not only between the non-mutant and mutant mice, but also between the
nw $Va/+$ and w $Va/+$ mice. In fact, the pleiotropic effects of the Va-
allele on behavioral activities were drastic and appeared to influence the
whole behavior pattern.

As shown in Tables 2—4 the effects of amphetamine were characteris-
tic for each group of mice. For instance, the abnormally low sitting scores
of the w $Va/+$ were significantly increased and appeared to be similar to
the scores of the untreated $+/+$ mice, while the sitting scores of the $+/+$
mice were significantly lowered and appeared to be similar to the scores
of the untreated w $Va/+$ animals; in contrast, the very high reconnoiter-

Table 2. *C57 BL/6J (+/+) versus non-waltzing (nw Va/+) versus waltzing (w Va/+) Varitint-waddlers: mean and median frequencies of behavioral components, elicited by saline.*

Components	+/+		nw Va/+		w Va/+		+/+ vs nw Va/+	+/+ vs w Va/+	nw Va/+ vs w Va/+
	$\bar{X}$	$\bar{M}$	$\bar{X}$	$\bar{M}$	$\bar{X}$	$\bar{M}$			
Sitting	21.4	20	34.4	35.5	0.8	0	lower*	higher**	higher**
Cleaning	15.6	15.5	7.3	8	9.8	8.5	higher**	higher*	—
Sniffing at ground	14.6	15	3.9	2.5	1.3	0	higher**	higher**	higher**
Reconnoitering	6.3	6	2.3	2	15.6	15.5	higher**	lower**	lower**
Eating	2.4	2	1.3	0	6.1	5.5	—	lower**	lower**
Head-tossing	0	0	9.6	9.5	6.4	7	lower**	lower**	higher**
Digging	2.8	1.5	0	0	0	0	higher**	higher*	—
Circling	0	0	0	0	40.9	36	—	lower**	lower**
Miscellaneous	4.5	4	1.6	1	5.3	4	—	—	lower*
Tail-raising	0	0	0	0	27.7	25	—	lower**	lower**

* $p \leqslant 0.05$ and ** $p \leqslant 0.01$ according to the Fisher exact test or Wilcoxon test.

Table 3. *C57BL/6J (+/+) versus non-waltzing (nw Va/+) versus waltzing (w Va/+) Variitnt-waddlers: mean and median frequencies of behavioral components, elicited by amphetamine*

Components	+/+		nw Va/+		w Va/+		+/+ vs nw Va/+	+/+ vs w Va/+	nw Va/+ vs w Va/+
	$\bar{X}$	M	$\bar{X}$	M	$\bar{X}$	M			
Sitting	1	0	17.2	16.5	26.6	27.5	lower**	lower**	lower*
Cleaning	16.6	16.5	8.6	8	10.0	10	higher**	higher**	—
Sniffing at ground	34.3	34	14.4	14	3.8	2	higher**	higher**	higher**
Reconnoitering	24.8	26.5	1.6	2	11.7	13.5	higher**	higher*	lower**
Eating	0	0	0	0	0	0	—	—	—
Head-tossing	0	0	26.6	25.5	29.8	29.5	lower**	lower**	—
Digging	0	0	0	0	0	0	—	—	—
Circling	0	0	0	0	7.4	4.5	—	lower**	lower**
Miscellaneous	36.8	37.5	3.8	4	9.7	11.5	higher**	higher**	lower*
Tail-raising	0	0	0	0	4.8	4	—	lower**	lower**

* $p \leqslant 0.05$ and ** $p \leqslant 0.01$ according the Fisher' exact test or Wilcoxon test

Table 4. *C57 BL/6 J(+/+), non-waltzing (nw Va/+) and waltzing (w Va/+) Varitint-waddlers: statistical differences between the saline and amphetamine effects upon behavioral components*

Components	+/+	nw Va/+	w Va/+
Sitting	decrease**	decrease**	increase**
Cleaning	—	—	—
Sniffing at ground	increase**	increase**	increase*
Reconnoitering	increase**	—	decrease*
Eating	decrease*	—	decrease**
Head-tossing	—	increase**	increase**
Digging	decrease*	—	—
Circling	—	—	decrease**
Miscellaneous	increase**	increase*	increase**
Tail-raising	—	—	decrease**

    * $p \leqslant 0.05$ and ** $p \leqslant 0.01$ according the Mann-Whitney test.

ing scores of the w $Va/+$ mice were reduced, while those of the $+/+$ mice were just significantly increased. Apart from these opposite effects, the effects upon sniffing, cleaning and miscellaneous were similar in all types of mice: amphetamine had no influence upon the cleaning scores and increased the scores of sniffing and miscellaneous, although in both cases a marked shift was observed from a large increase of these activities in the $+/+$ mice to a very small increase in the w $Va/+$. From the stereotyped activities of the w $Va/+$ circling and tail raising were decreased, while head tossing was increased. Digging activity was totally absent in both untreated and treated $Va/+$ mice and although originally present in the $+/+$ mice, was suppressed by the amphetamine injection. A marked decrease of the eating scores in the $+/+$ and w $Va/+$ mice was induced by amphetamine. Circling and tail-raising were not seen in $+/+$ and nw $Va/+$ mice and the head-tossing scores of the nw $Va/+$ mice had the same tendency as those of the w $Va/+$ mice: a significant increase after the amphetamine injection.

Finally, examinations of the body autoradiograms revealed that the labelled tissues were essentially similar for the three types of mice. However, examinations of the head sections resulted in the appearance of a significant difference between the w $Va/+$ mice and the other phenotypes as shown in Fig. 2: the Harderian gland of the w $Va/+$ mice was strongly labelled, while the glands of the other ones were unlabelled.

Discussion

Neuroleptic drugs like haloperidol have been shown to elicit a highly characteristic cataleptic effect in several species by blocking the
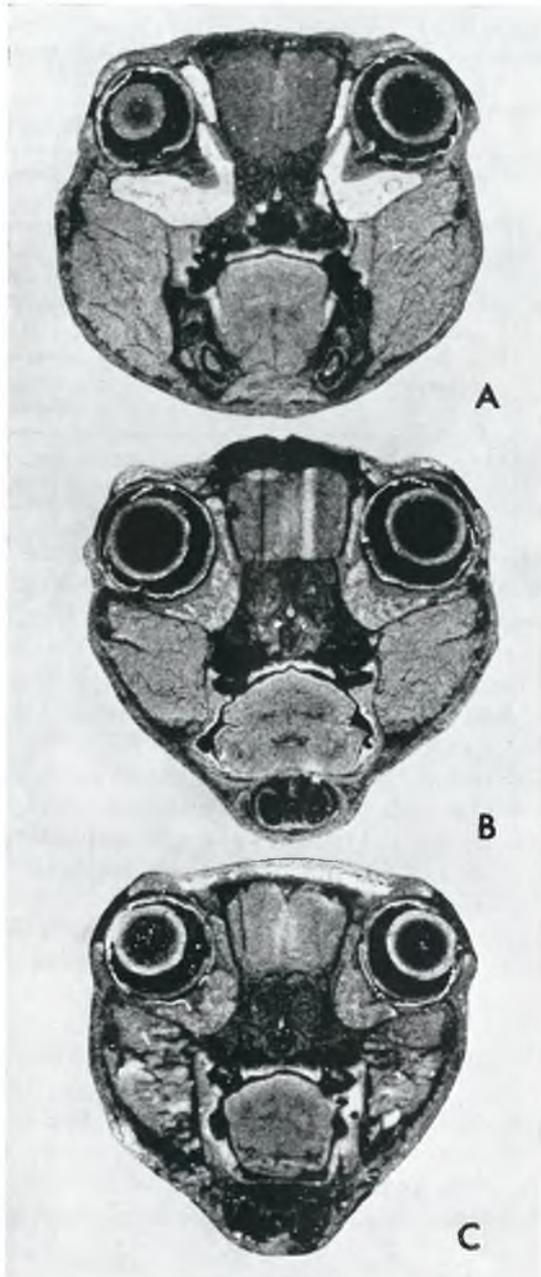
Fig. 2A—C. (^{14}C)DOPA-autoradiograms of waltzing (A); non-waltzing (B); Varitint-waddlers and C57BL/6J (C): frontal sections of the mouse head. Note the labelled Harderian gland in (A)

dopaminergic activity of the striatal system (Costall and Olley, 1971);
Florio and Longo, 1971; Fog, 1967b; Fog et al., 1968; Fog et al., 1970).
The finding that high concentrations of haloperidol induced catalepsy in
the Varitint-waddler indicates that the striatal system of the $Va/+$ is
sensitive to the blocking action of haloperidol; in fact, the cataleptic
effect points to a functional integrity of the striatal system, since lesions
of this system abolishes the effect (Fog et al., 1970). The experiments
with low doses of haloperidol showed that reduction of nearly all behavio-
ral activities, except for sitting, occurred in all types of mice. However
the results of Fig. 1 showed a marked shift from a more rapid and large
increase of sitting frequency in the $+/+$ mice to a slower and intermediate
increase of sitting frequency in the w $Va/+$. It would, therefore, seem
that the blocking activity of haloperidol in the striatal system is reduced.
Since high doses of haloperidol induced essentially similar effects in the
non-mutants, the differences in the dose-dependent effect of haloperidol
may be most simply explained by assigning a dopaminergic hyperactivity
to the striatal system of the Varitints. This is further supported by the
results of the dexamphetamine tests.

It has been shown that amphetamine gives rise in several species to
characteristic stereotyped behavior by activating the dopaminergic
mechanism of the nigrostriatal system (Fog et al., 1967a; Fog, 1967b;
Fog et al., 1970; Fuxe and Ungerstedt, 1970; Randrup and Scheel-
Krüger, 1966; Randrup and Munkvad, 1970). From the comparison of the
hyperactive mutants with the $+/+$ mice, clear differences emerged:
several characteristic activities of the untreated Va did not differ from
the stereotyped activities induced by amphetamine in the $+/+$ mice.
For instance, amphetamine induced sitting scores in the $+/+$ mice,
which were essentially similar to the scores of the untreated w $Va/+$
mice. In contrast, amphetamine reversed the originally low sitting
scores of the untreated Va to those of the untreated $+/+$ mice; in view of
this data, it may be mentioned that the amphetamine effect in hyper-
active children is also reversed in comparison with the drug effect in
normal children (Lasagna and Epstein, 1970). The same holds for several
activities as shown in Tables 3 and 4. In addition, the high miscellaneous
scores of the $+/+$ mice treated with amphetamine consisted mostly of
scores of retropulsive movements; movements which were normally
present in the untreated w $Va/+$ mice.

From these data, it may be concluded that the behavior of the Varitint-
waddler mimics in several aspects the behavior of normal mice treated
with the dopamine stimulating agent, amphetamine. Furthermore, it
may be concluded from the observed differences between nw $Va/+$ and
w $Va/+$ mice that the Va genotype has an incomplete penetrance and a
variable expressivity; it is noteworthy that the genotype of Huntington's

chorea in man, which may be partially analogous to the *Va* syndrome as mentioned in the introduction, has the same phenotypic effect with respect to its penetrance and expressivity (Dobzansky, 1958). Both the mimicking action of amphetamine and the ineffectiveness of low doses of the dopamine blocking agent haloperidol suggest that the *Va* allele exerts its effects by an increased dopamine activity, particularly in the striatal system. In view of the suggestion that a hypersensitive-dop-aminergic mechanism of the Corpus striatum is involved in Huntington's chorea (Klawan, 1970), the increase in the head-tossing scores of the Varitint-waddler, following amphetamine-injection, strengthens this assumption.

However, when examining carefully the isotopically labelled sections of the dopamine-rich areas of the brain, i.e. the Corpus striatum, no gross histochemical differences were found between $+/+$ and $Va/+$ mice. Since it has been shown that inhibition of the extracerebral and brain capillary L-DOPA decarboxylase resulted in an increased penetration of L-DOPA into the brain parenchyma and enhanced the amount of DA in the dopaminergic brain areas (Constantinides *et al.*, 1968) quantitative differences could have been masked by the DA increase induced by the Ro-4-4602 pretreatment in the brain of all mice.

In contrast, the penetration of L-DOPA or its metabolites into the Harderian gland of the waltzing Varitint-waddler supports the assumption that the *Va* allele exerts its effects by interference with the dopamine mechanism: the Harderian gland, which may be functioning as an extraretinal photosensitive organ (Wetterberg *et al.*, 1970) contains melanocytes, which have a melanin-synthesizing mechanism (Searle, 1968). In the melanocytes, melanin is formed through the oxidation of L-DOPA, the precursor of dopamine. The abnormal piebald spotting pattern of the fur points into the same direction, since a similar melanin-synthesizing system is involved in the determination of the pigment areas.

In addition, the correation between the localisation of the non-fading spots and the dominant direction of circling movements (Cools, in press) suggest that the pigment disorder and the dyskinesia are based upon one common mechanism of action: the dopamine synthesizing system, which has an essential significance both in the striatal nuclei and in the process of skin pigmentation. As a final remark, it is interesting to note that an inner-ear defect resembling that of the Varitint-waddler is associated with the absence of melanin in the membraneous labyrinth of the coat-color mutants, pallid and muted (Erway *et al.*, 1966); however, the involvement of the dopamine-synthesizing mechanism in this defect awaits confirmation from other studies.

In conclusion, our results indicate that a hyperactive dopaminergic mechanism is involved in the waltzing-shaker syndrome of the Varitint-waddler. With respect to the regularly occurring association of one or more of the triad psychosis, dyskinesia and hypopigmentation or hyper-pigmentation in man (Proctor, 1971), it may be relevant to consider the Varitint-waddler as a tool for therapeutic investigations because of its potential analogy to striatal disorders in man such as schizophrenic-like psychosis, Huntington's chorea etc.

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