Life Sciences, Vol. 32, pp. 421-432

DUAL ACTION ON CENTRAL DOPAMINE FUNCTION OF TRANSDIHYDROLISURIDE, A 9, 10-DIHYDROGENATED ANALOGUE OF THE ERGOT DOPAMINE AGONIST LISURIDE

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(Received in final form October 11, 1982)

Summary

Transdihydrolisuride (TDHL), a 9,10-dihydrogenated analogue of the ergot dopamine (DA) agonist lisuride (LIS), was investigated for its influence on central dopaminergic functions in rats and mice after single i.p. administration. TDHL (0.39-25 mg/kg) unexpectedly induced catalepsy and antagonized apomorphine-induced stereotypies in rats; it was approx. 3-5 times less potent than the DA antagonist haloperidol. TDHL (0.025-6.25 mg/kg) caused hypokinesia and antagonized the apomorphine-induced hyperactivity in rats. Pretreatment with TDHL (0.78-12.5 mg/kg) which per se did not alter thermoregulation at room temperature, antagonized the hypothermia induced by the DA agonist apomorphine (5 mg/kg i.p.) in mice. These DA antagonistic properties contrasted with the prolactin (PRL) lowering effect of TDHL (0.01-10 mg/kg p.o.) in reserpinized female rats thus indicating DA agonist function. PRL inhibition tended to be longer lasting (>8h) than after LIS (0.01-1 mg/kg p.o.) with comparable potency. In healthy volunteers TDHL (0.2-1 mg p.o.) effectively lowered PRL levels with similar potency but with a markedly longer duration of action than LIS (>24h after 0.5 mg TDHL). In contrast to the side effects after acute LIS treatment, no comparable adverse reactions such as nausea, emesis or postural hypotension typical for DA agonists could be observed with effective PRL lowering doses of TDHL. The unique profile of TDHL on DA functions suggests its usefulness as a potent, long-lasting PRL inhibitor with less unwanted effects. The behavioural findings indicate the potential usefulness of TDHL as a neuroleptic, which due to its partial DA agonistic action, should lack typical extrapyramidal or neuroendocrine side effects of classic DA receptor blocking agents. Possible implications of the dual function of TDHL upon central DA receptors are discussed with regard to the incidence of side effects or selectivity of action for other conceivable therapeutic indications.

In the search for long-acting structural analogues of the central dopaminergic ergot compound lisuride (LIS) (1,2) the behavioural effects of the 9,10-dihydrogenated LIS analogue transdihydrolisuride (TDHL) were investigated. TDHL was first synthesized by Semonsky and coworkers (3) in 1972 and has been shown to inhibit lactation and nidation in rats (4) as well as to induce contralateral rotations in animals with unilateral nigrostriatal lesions (5). Preliminary investigations revealed that the saturation of the 9,10-double bond of the LIS molecule (Fig. 1) did not change the prolactin (PRL) lowering properties, but surprisingly caused a complete reversal of the behavioural pattern in rodents. In contrast to the typical signs of central dopamine (DA) receptor stimulation induced by the ergot DA agonists bromocriptine (6), pergolide (7,8) and LIS (1) such as stereotypies and locomotor stimulation, TDHL produced symptoms reminiscent of functional disruption of central dopaminergic transmission such as catalepsy (9) and locomotor depression (10). The present investigation was performed to establish the cataleptogenic, motor inhibitory, hypothermic and apomorphine-antagonistic actions of TDHL in rodents. In addition the effect of TDHL on PRL secretion was studied in human volunteers and rats.

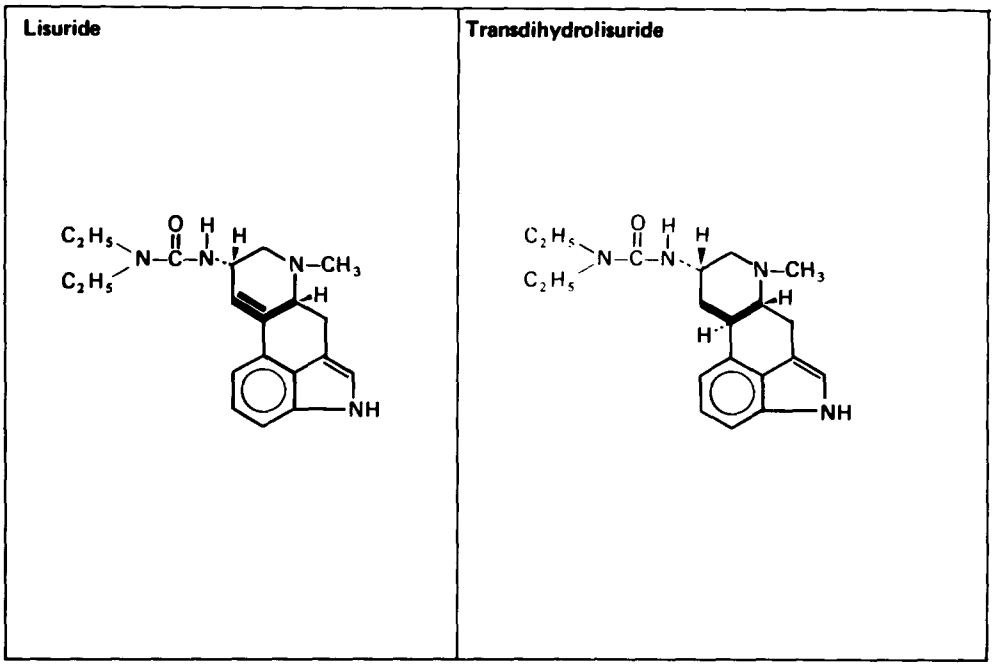

FIG. 1

Materials and Methods

A. Drugs and Solutions

The following drugs were used: transdihydrolisuride (1,1-diethyl-3-(6-methyl-8α-ergolinyl)-urea dihydrogen phosphate, prepared by Dr. Rahtz, Department of Medicinal Chemistry,

Schering AG, Berlin, Germany); lisuride (3-(9,10-didehydro-6-methyl-8α-ergolinyl)-1,1-diethyl urea hydrogen maleate, Spofa, Prague, Czechoslovakia); fluphenazine dihydrochloride (Squibb Inc., Princeton, USA); haloperidol (Janssen, Beerse, Belgium); apomorphine hydrochloride (Sandoz AG, Basle, Switzerland). All drugs were dissolved in isotonic saline solution except for haloperidol which was suspended in isotonic saline solution containing 10% w/v Cremophor EL® (polyethoxylated castor oil, BASF, Ludwigshafen, Germany). Ascorbic acid (0.1% w/v) was added to the apomorphine solutions. Reserpine was used in commercially available ampoule formulations (Serpasil®, 1 mg/ml, Ciba, Basle, Switzerland). For the studies in human volunteers TDHL and identical placebo tablets were kindly prepared by J. Hilmann (Department of Pharmaceutical Research, Schering AG, Berlin, Germany).

B. Animals and Treatment Schedules

Male NMRI mice weighing 20-25 g and Wistar rats (male for behavioural and female for PRL studies) weighing 80-120 g (Department Tierzucht und -haltung, Schering AG, Berlin, Germany) were used. The animals were kept in a temperature-controlled room (22 ± 1 °C) with a 12 h light/dark cycle. The room was illuminated between 6 a.m. and 6 p.m. The animals received a standard diet (Altromin®, Altromin Spezialfutterwerke GmbH, Lage, Germany) and water ad libitum. For behavioural investigations drugs were administered i.p. except for apomorphine which as given s.c. or i.p. For PRL studies TDHL and LIS were given p.o. All doses were calculated as base and administered in a volume of 0.1 ml per 10 g body weight (mice) or 0.05 ml per 10 g body weight (rats) with randomized allocation of treatments. Control animals received the corresponding volume of the vehicle.

C. Test Methods

Catalepsy: In rats pretreated with TDHL or haloperidol i.p., catalepsy was measured at 60 minutes by gently placing the animal's hind limbs on the upper plateau of a plastic step (height 6 cm, width 18 cm) and recording the time before the animal put both paws on the floor. Animals remaining in this imposed posture for ≥ 5 seconds were considered cataleptic.

Antagonism of stereotyped behaviour: Stereotypies induced by apomorphine 1.56 mg/kg s.c. were determined according to the method described earlier (1). One hour before experimentation individual rats were placed into transparent plastic cages (25 x 19 x 13.5 cm). Animals were given TDHL or haloperidol i.p. 30 minutes prior to apomorphine. Thirty minutes after apomorphine the animals were observed for 2 minutes for the presence of stereotyped behaviour (continuous sniffing, licking or gnawing movements for more than 30 seconds within this time) by an experienced observer unaware of the previous treatment.

Locomotor activity: Locomotor activity of rats was measured using circular photocell activity cages similar to those described by Wright et al. (11). Immediately following the i.p. administration of TDHL or saline, individual animals were placed into the motility cages and the number of light beam interruptions accumulated at 10 minutes intervals was recorded for 60 minutes.

Body temperature: Mice were individually placed into acrylic glass cages (9 x 10 x 8.5 cm) one hour prior to experimentation. Body temperature was measured with an electric thermometer (ELLAB TE 3) for 20 seconds after the introduction of a rectal probe (RM 6). Dose-response relationships were determined at 60 minutes after the i.p. administration of TDHL. The involvement of DA receptors in the temperature effects of TDHL was examined in comparison with fluphenazine as follows: mice were given saline or various doses of TDHL or fluphenazine i.p. 30 minutes prior to a hypothermic dosage of apomorphine (5 mg/kg i.p.) and rectal temperature was measured 30 minutes after administration.

Prolactin: Female rats were injected with reserpine 2 mg/kg i.p. before oral treatment with TDHL, LIS or vehicle. Rats were killed by decapitation 2 hours or 8 hours after drug administration, blood from the trunk was collected in centrifuge tubes, allowed to clot at 4 °C and centrifuged at 3000 x g for 10 minutes. The serum was removed and stored at -20 °C until assayed. PRL was determined using the radioimmunoassay kit for rat PRL kindly supplied by NIAMDD. Results were expressed in ng/ml of the reference.

D. Subjects and Study Design

Fifteen healthy male volunteers (age 20-40 years) were included in a double blind, placebo controlled randomized study, in which 0.2, 0.5 and 1 mg TDHL or placebo were given orally on a cross-over basis. Before the beginning of the trial written informed consent was obtained from all volunteers. Routine chemical analysis of blood and urine was performed before and one week after completion of the trial. In addition physical examinations were carried out at regular intervals. Incidence of side effects, psychic state and well being was investigated by questionnaires (TWIS and DOTES (12)) and subjective observation made by a physician, who was unaware of the medication. Human PRL was measured by radioimmunoassay kindly provided by the NIAMDD program. Results were expressed as ng/ml serum.

Results

A. Animal Studies

Catalepsy: The cataleptogenic effect in rats of TDHL compared to the DA antagonist haloperidol is shown in Table I. TDHL was approximately 5 times less potent than haloperidol in producing catalepsy.

Antagonism of stereotyped behaviour: The antagonistic effect of TDHL and haloperidol upon apomorphine-induced stereotyped behaviour of rats is shown in Table I. TDHL was 3 times less potent than haloperidol in antagonizing apomorphine-induced stereotypies. The relative potency of TDHL compared to haloperidol regarding the antistereotypic action is in accordance with that obtained for the cataleptogenic effect.

TABLE I

Cataleptogenic and Antistereotypic Efficacy of Transdihydrolisuride (TDHL) in Rats in Comparison with Haloperidol (HAL)

effect	compound	ED_{50} (mg/kg)	relative potency
cataleptogenic effect	TDHL	9.0 (3.9-21.9)	4.5 (1.4-12.3)
	HAL	2.0 (0.8- 4.3)	
antistereotypic effect	TDHL	2.4 (1.8- 3.3)	3.0 (1.9- 5.0)
	HAL	0.8 (0.5- 1.9)	

Median effective doses (ED_{50}), relative potencies and 95 % confidence limits (indicated in brackets) were calculated by probit analysis. The various treatment groups comprised 8 animals. For methodological details cf. Materials and Methods.

TABLE II

Effect of Transdihydrolisuride (TDHL) upon Locomotor Activity of Rats (A) Alone and (B) in Combination with Apomorphine

treatment	locomotor activity (counts per 60 min) (A)	(B)
saline	569 ± 139	4043 ± 1159
TDHL 0.025 mg/kg	350 ± 66 xx	3250 ± 624
TDHL 0.1 mg/kg	289 ± 47 xx	2402 ± 388
TDHL 0.39 mg/kg	164 ± 28 xx	3139 ± 513
TDHL 1.56 mg/kg	62 ± 16 xx	939 ± 274 x
TDHL 6.25 mg/kg	19 ± 5 xx	248 ± 80 x

Rats were treated i.p. with various doses of TDHL or with saline, either (A) alone or (B) together with apomorphine 0.39 mg/kg s.c. Immediately following the injections individual animals were placed into photocell motility cages and the counts accumulated during 60 minutes were recorded. The values are means ± S.E.M. of 12 experiments. Statistical significances of the differences between the various TDHL dosages and the saline control are shown (xx: $p \leq 0.01$, x: $p \leq 0.05$; one-way analysis of variance followed by Dunnett test).

TABLE III

Effect of Transdihydrolisuride (TDHL) upon Body Temperature of Mice

treatment	rectal temperature (°C)
saline	36.0 ± 0.3
TDHL 3.13 mg/kg	36.5 ± 0.3
TDHL 6.25 mg/kg	36.4 ± 0.3
TDHL 12.5 mg/kg	35.7 ± 0.2
TDHL 25.0 mg/kg	35.1 ± 0.2
TDHL 50.0 mg/kg	34.5 ± 0.3 xx

Rectal temperature of individually-housed mice was measured by means of an electric thermometer 60 minutes following i.p. administration of various drug dosages or of saline. The values are means ± S.E.M. of 8 experiments. Statistical analysis was as in legend to Table II.

TABLE IV

Antagonism of Apomorphine-induced Hypothermia in Mice by Pretreatment with Transdihydrolisuride (TDHL) or Fluphenazine (FLU)

treatment	rectal temperature (°C)	treatment	rectal temperature (°C)
saline	32.5 ± 0.4	saline	32.9 ± 0.3
TDHL 0.78 mg/kg	33.9 ± 0.5	FLU 0.025 mg/kg	34.9 ± 0.3 xx
TDHL 1.56 mg/kg	33.8 ± 0.4	FLU 0.05 mg/kg	34.7 ± 0.3 xx
TDHL 3.13 mg/kg	35.1 ± 0.5 xx	FLU 0.1 mg/kg	36.6 ± 0.4 xx
TDHL 6.25 mg/kg	35.5 ± 0.5 xx	FLU 0.2 mg/kg	36.4 ± 0.4 xx
TDHL 12.5 mg/kg	36.0 ± 0.4 xx	FLU 0.39 mg/kg	36.4 ± 0.4 xx

Individually-housed mice were given saline, various doses of TDHL or FLU i.p. 30 minutes prior to apomorphine (5 mg/kg i.p.). Thirty minutes following the administration of apomorphine the rectal temperature was measured by means of an electric thermometer. The values are means ± S.E.M. of 8 experiments. Statistical analysis was as in legend to Table II.

Locomotor activity: TDHL, 0.025 to 6.25 mg/kg i.p., caused a dose-related decrease in spontaneous locomotor activity of rats as is shown in Table II. A dosage of TDHL as low as 0.025 mg/kg induced a statistically significant hypokinesia. The hyperactivity of rats induced by the DA agonist apomorphine 0.39 mg/kg s.c. was dose-dependently antagonized by TDHL (Table II).

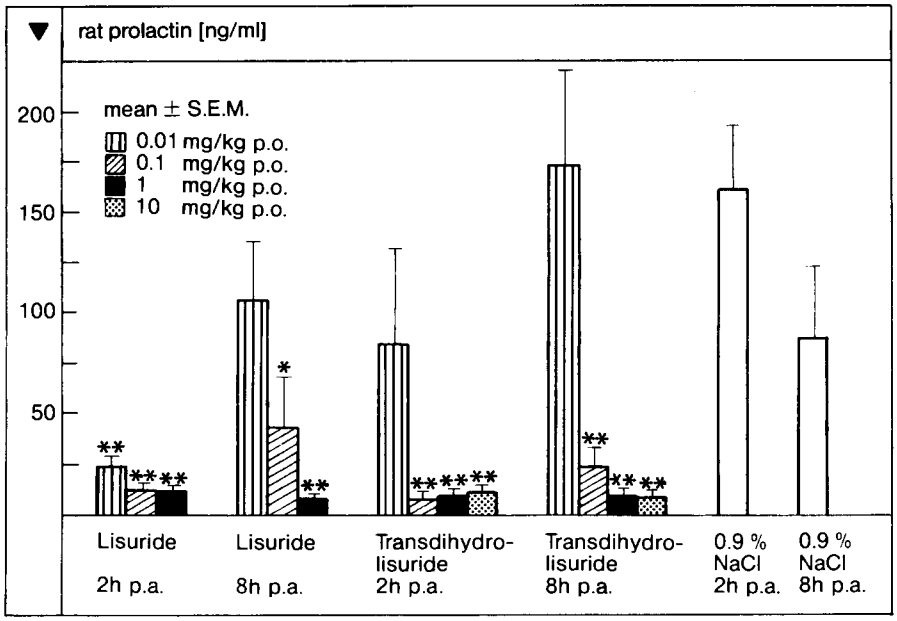

FIG. 2

Serum prolactin (PRL) of female rats treated with reserpine (2 mg/kg i.p.) 24 hours prior to oral administration of lisuride (LIS), transdihydrolisuride (TDHL) or saline. Animals were decapitated 2 hours and 8 hours respectively after oral treatment. The values are means ± S.E.M. of 5 experiments. Statistical analysis was as in legend to Table II.

Body temperature: The effect of TDHL, 3.13 to 50 mg/kg, on rectal temperature of mice 60 minutes after i.p. administration is shown in Table III. TDHL had no effect on body temperature except at the highest dosage (50 mg/kg) which caused a statistically significant hypothermia.
Pretreatment of mice with TDHL at dosages which per se did not influence thermoregulation antagonized in a dose-related manner the hypothermic action of apomorphine 5 mg/kg i.p. (Table IV). Statistically significant antagonism was obtained with 3.13 mg/kg TDHL. A similar effect, although at much lower dosages (0.025 mg/kg i.p.), was obtained with the DA antagonist fluphenazine.

Prolactin: TDHL, 0.1 to 10 mg/kg p.o., inhibited PRL secretion in reserpinized female rats for more than 8 hours. LIS was ef-

fective at lower dosages (0.01 to 1 mg/kg p.o.), yet, the duration of its PRL lowering effect was less pronounced (Fig. 2). At 8 hours LIS 0.1 mg/kg p.o. was clearly less effective than the same dose of TDHL. Similar results were obtained after i.p. administration of TDHL, 0.01 to 10 mg/kg, or LIS, 0.01 to 1 mg/kg (data not shown).

B. Studies in Man

Prolactin: In human volunteers TDHL effectively lowered PRL levels in all subjects and at all dosages tested (Fig. 3). Lowest levels were measured 3 hours after drug intake and single doses of 0.5 to 1.0 mg TDHL clearly inhibited PRL secretion for more than 24 hours. TDHL 0.2 mg effectively lowered PRL levels up to 8 hours but was ineffective at 24 hours.

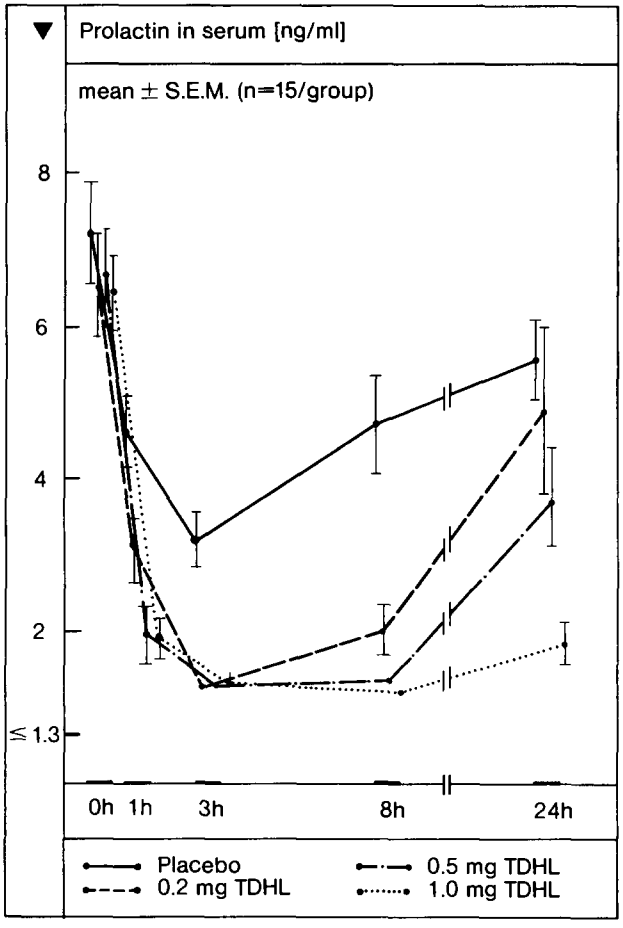

FIG. 3

Serum prolactin levels of 15 healthy male subjects (mean ± S.E.M.) after oral treatment with various doses of transdihydrolisuride (TDHL) or placebo.

Side effects: Most side effects occurred after 1 mg TDHL one to two hours after drug intake, whereas 0.2 mg TDHL, which was very effective in lowering PRL levels, did not differ from placebo treatment (Table V).

Discussion

The present data confirm previous findings indicating a DA agonistic action of TDHL (5). The PRL lowering effect in rats is in agreement with the inhibition of lactation and nidation by TDHL described earlier (4). The longer lasting action in both humans and rats as compared with LIS (13) might be due to pharmacokinetic reasons, since both ergot derivatives differ only slightly in their affinities towards striatal DA receptors as was evaluated by ^{3}H-spiroperidol binding (14). On the other hand, the present results also confirm and extend recent findings in mice on the cataleptogenic, locomotor inhibitory and apomorphine-antagonistic effects of TDHL (8). They demonstrate that TDHL has similar behavioural properties to those of classical neuroleptics e.g. haloperidol and fluphenazine suggesting functional antagonism upon central DA receptors. Therefore, it is conceivable that TDHL combines both antagonistic and agonistic properties within its molecule and acts as a DA partial agonist. Neurobiochemical in-vivo investigations upon the synthesis and turnover of DA in the central nervous system of rats support this assumption. Thus, the enhancement of striatal DOPA accumulation as well as the increased 3-methoxytyramine formation in rat brain indicate a DA receptor blocking action of TDHL (14). These effects are in contrast to LIS or other DA agonists (2), but are typical of neuroleptics. On the other hand, TDHL like LIS inhibited the striatal DOPA accumulation in gammabutyrolactone-pretreated rats presumably via stimulation of presynaptic DA receptors (14). Antagonistic effects on the synthesis and turnover of DA in rat striatum in vivo have recently been published for CU 32-085 (15), another 9,10-dihydrogenated ergot compound with PRL lowering properties (16). However, the initial antagonistic effect of CU 32-085 was followed by an agonistic phase on DA turnover probably indicating the formation of an active dopaminergic metabolite (15). A time-dependent biphasic action was not evident from the behavioural or neurobiochemical investigations of TDHL.

There is evidence of multiple DA receptors in the mammalian brain. Two types of DA receptors are discernible with regard to their influence on neuronal cAMP formation (17, 18, 19). Stimulation of the D-1 receptor increases, whereas D-2 receptor blockade does not seem to influence cAMP accumulation (17). LIS stimulates D-1 receptors (20, 21, 22, 23) just as D-2 receptors (24), but also exerts antidopaminergic effects in vitro as judged from the inhibition of DA-stimulated cAMP formation in striatal homogenates (25). Saturation of the 9,10-double bond of the LIS molecule may change the affinity towards the different DA receptors with the effect that TDHL may preferentially stimulate D-2 receptors. As the inhibition of PRL secretion is mediated via D-2 receptors (17), the pronounced and long-lasting PRL lowering effect of TDHL in rats and human volunteers would support this assumption. The failure of TDHL to stimulate growth

TABLE V

Side Effects after Transdihydrolisuride (TDHL) in Human Volunteers

symptoms	treatment			
	placebo	TDHL 0.2	0.5	1.0 mg
tiredness	5	4	6	6
headache	1	1	1	4
nasal congestion	0	0	4	2
nausea	0	0	1	7
emesis	0	0	0	1
postural hypotension	0	0	0	2

Incidence of side effects in 15 male volunteers during 24 hours after various oral doses of TDHL in comparison with placebo.

hormone secretion in normal subjects at effective PRL lowering doses, which is in contrast to the effect of classical DA agonists (26) also suggests an unique profile of dopaminergic functions. The presumed preferential action of TDHL on such a subpopulation of DA receptors would imply that stimulation of D-2 receptors exerts functional DA antagonistic effects. In fact, this concept would be compatible with the hypothesis of Cools and van Rossum (27) that postulates excitation- and inhibition-mediating DA receptors. The absence of DA agonist-induced supersensitivity following subchronic administration of TDHL gives further support to this concept (H. Wachtel, to be published). Differences in the affinity towards particular DA receptors rather than differences in the accessibility of TDHL to cerebral structures seem to be of some importance since nausea and emesis in humans emerged at higher doses than necessary for lowering PRL. Due to their localization outside the blood brain barrier, both the chemoreceptor trigger zone and the pituitary should be within reach for TDHL to about the same extent. In human volunteers, acute oral administration of 0.3 mg TDHL and LIS, respectively, lowered PRL levels to about the same extent (13, 27). However, the incidence of side effects like nausea, emesis or postural hypotension was markedly less frequent after TDHL (28). Similarly, TDHL was one order of magnitude less potent than LIS in inducing vomitus in dogs (5).

In summary, the present data provide evidence of an unique profile of agonistic as well as antagonistic actions of TDHL upon central DA receptor mediated functions. Apparently the agonistic action prevails at the level of the pituitary and the chemoreceptor trigger zone, whereas the antagonistic action predominates within the nigrostriatal and mesolimbic DA system as judged from the present data and the neurobiochemical findings of Kehr et al. (14). This is strengthened by the finding that

in rats depleted from endogenous DA stores by pretreatment with reserpine, TDHL was effective in antagonizing hyperprolactinaemia (present data), but was inactive in producing stereotypies or motor stimulation (H. Wachtel, unpublished results). The observation that TDHL induces contralateral rotations in rats with unilateral 6-hydroxydopamine-induced nigrostriatal lesions (5) could indicate that the weak agonistic action of TDHL at the striatal level is unmasked only at supersensitive postsynaptic DA receptors.

Two assumptions with respect to the potential therapeutic usefulness of TDHL may be made from the data presented. As judged from the PRL lowering effect, TDHL represents a feasible alternative in the treatment of hyperprolactinaemic states combining a long lasting action with a low incidence of side effects compared to DA agonists in clinical use. On the other hand, the DA antagonistic properties of TDHL at the level of the nigrostriatal and mesolimbic DA pathway as judged from the behavioural and neurobiochemical findings in animals, would suggest the potential usefulness of TDHL as a neuroleptic. Assuming an antipsychotic efficacy of TDHL in humans, the partial DA agonistic property could oppose the development of unwanted effects typical of classic neurolepties e.g. Parkinsonism, tardive dyskinesia, amenorrhea, galactorrhea or loss of libido. Concomitant pharmaco-EEG evaluations in the volunteers revealed a pattern clearly different from that of the reference neuroleptic chlorpromazine (R. Dorow, unpublished results). Ongoing trials in schizophrenic patients will shed light on the validity of this concept. On the other hand, if one assumes that TDHL does induce a preferential stimulation of a subpopulation of central DA receptors, then its potential usefulness in particular forms of Parkinson's disease or in tardive dyskinesia and also in Huntington's chorea ought to be investigated.

Acknowledgement

We are grateful to Dr. Dieter Rahtz for supplying us with transdihydrolisuride, to Dr. K.J. Gräf and Dr. S.A. Hasan for PRL determinations, to Peter Böttcher, Cornelia Riedel, Monika Schlangen, Petra Zehleke and Renate Zimmermann for technical assistance and to Heide Hölbüng for typing the manuscript. We are indebted to the NIAMDD pituitary hormone distribution program for kindly supplying the materials used in the rat and human PRL radioimmunoassay.

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