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Interaction of Haloperidol and Risperidone (R 64 766) With Amphetamine-Induced Motility Changes in Rats

Anton A.H.P. Megens, Frans H.L. Awouters, and Carlos J.E. Niemegeers

Department of Pharmacology, Janssen Research Foundation, Beerse, Belgium

ABSTRACT

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The interaction of the new antipsychotic risperidone (RIS) and haloperidol (HAL) with amphetamine (AMP) was studied in rats using an activity meter which measured horizontal, vertical, and stationary components of motility. All three components increased markedly and progressively after AMP doses between 0.63 and 5.00 mg/kg (hyperactivity dose range). At still higher doses of 10.0 to 80.0 mg/kg, stationary movements (reflecting stereotypy) further increased, whereas horizontal activity was much reduced and vertical activity virtually abolished. Both HAL and RIS were potent AMP antagonists. Doses on the order of 0.02 to 0.04 mg/kg significantly reduced hyperactivity and reversed stereotypy to a motility pattern equivalent to that of a lower AMP dose. Both compounds were able to restore normal motility at any dose level of AMP stimulation. At the lowest dose of AMP (0.63 mg/kg), the required normalization doses were comparable for HAL (0.022–0.046 mg/kg) and RIS (0.034–0.16 mg/kg). In order to normalize motility induced by higher AMP doses up to 5.00 mg/kg, however, a relatively small dose increment of HAL (to 0.045–0.071 mg/kg), but a large dose increment of RIS (to 0.50–0.96 mg/kg) was required. In other words, the dose-normalization curves of RIS and HAL diverged at low doses of AMP (0.63–5.0 mg/kg). At higher doses of AMP (10–80 mg/kg), however, this difference disappeared, and the slopes of the dose-normalization curves became comparable for the two antagonists. It is suggested from these experiments that RIS and HAL are equipotent in controlling a low level of dopaminergic overactivity by partially occupying dopamine-D_2

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Address reprint requests to Dr. A.A.H.P. Megens, Department of Pharmacology, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium.

receptors. Higher levels of functional dopamine antagonism up to saturation of the D_2 receptors require a much higher dose of RIS than of HAL. Therefore, the risk of dopaminergic overblockade (and induction of EPS) is considered to be much smaller with RIS than with HAL.

Key words: antipsychotics, risperidone, amphetamine, stereotypes, hyperactivity

INTRODUCTION

The benzisoxazole derivative risperidone (RIS; R 64 766) is a new potent antipsychotic agent with mixed serotonin-dopamine antagonistic properties and a peculiar pharmacological activity profile [Janssen et al., 1988]. When compared with the classical neuroleptic haloperidol (HAL), RIS shows a much larger variation in the doses required to antagonize various drug-induced dopaminergic responses, and some effects such as catalepsy, inhibition of conditioned food intake, and inhibition of small motor movements are only observed following relatively high doses [Janssen et al., 1988; Megens et al., 1988]. To further delineate the behavioural profile and the nature of action of RIS, its interaction with amphetamine (AMP) was studied in detail and compared with that of HAL.

Behavioural changes induced by AMP in rats are dose-dependent: low doses produce hypermotility characterized by increased locomotion and rearing, higher doses induce stereotyped behaviour, consisting of sniffing, licking, chewing, head and body movements, and a concomitant reduction of locomotion and rearing [Niemegeers and Leysen, 1982; Randrup and Munkvad, 1975; Sharp et al., 1987; Taylor and Snyder, 1970]. As recently reported [Megens et al., 1987], both types of behaviour can be differentiated using an activity meter which quantifies separately horizontal, vertical and stationary components of motility and which is particularly sensitive to small, stationary movements. The present study reports on the interaction of RIS and HAL with AMP using this new motility meter.

MATERIALS AND METHODS

Animals

Male Wistar rats (240–260 g), used only once, were housed in groups of 5 per cage in the experimental room (T = 21 ± 2°C; RH = 65% ± 15%) the day before the test session. They were deprived of food, but tapwater was available ad libitum until the start of the experiments.

Activity Meter

The activity meter has been extensively described in previous reports [Megens et al., 1987, 1988] and consisted of 5 identical test cages (23.3 × 23 × 30 cm). Horizontal activity (HOR) was defined as each change in number or location of interrupted xy-beams, set up as 2 arrays of 12 infrared beams, perpendicular to each other in the horizontal plane, 3 cm above the cage floor. Vertical activity (VER) was defined as the number of 1/3 sec that at least one of the z-beams was interrupted (which were set up in a third array of 12 beams in a horizontal plane, 17 cm above the floor). Piezo activity (PIE) measured animal-induced vibrations of the flexible cage floor.

Procedure

Experiments were performed between 7.30 and 12.30 A.M. The rats were injected s.c. with either haloperidol (HAL), risperidone (RIS), or saline (SAL) and immediately placed in individual cages. Thirty minutes later, amphetamine (AMP) or SAL was injected s.c. and, again 30 min later, the rats were placed in the activity cages and motor activity was recorded

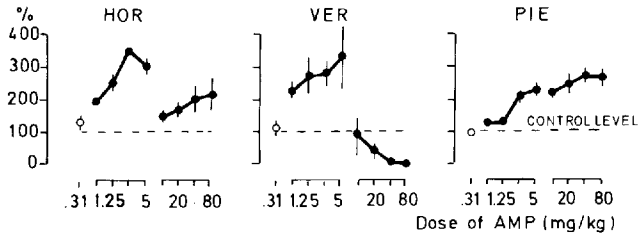

Fig. 1. Horizontal (HOR), vertical (VER), and piezo (PIE) activity (% of controls; mean ± S.E.M.) obtained with 9 different doses (x-scale: 0.31–0.63 . . . 40–80 mg/kg) of amphetamine (AMP) in rats. The S.E.M. values, if not too small, are represented by vertical bars. Dotted line: activity levels of normal control rats. Closed symbols indicate significant differences from saline treated control rats.

for a standard period of 27 min. Five experimental sessions, comprising five different test groups of five rats, were run daily. The variables (test cage, time of the day, day of the week, drug treatment) were randomized using a Latin square design. The averaged activity obtained in the saline-treated control group (n = 25) was considered to reflect normal activity. The activity obtained in the experimental groups (n = 5) was averaged and expressed as a percentage of this normal control activity. Probit analysis of the graduated data [Finney, 1962] was used to determine doses of the compounds that increased activity to 2 and 3 times the normal control level (ED_{200} and ED_{300} values, respectively), or that reversed drug-induced effects to normal control levels (ED_{100} values). Linear regression lines were obtained according to the method of Davies [1947].

Test Compounds

d,l-Amphetamine sulphate, haloperidol, and risperidone were obtained from Janssen Pharmaceutica (Beerse, Belgium). The compounds were dissolved in distilled water, haloperidol and risperidone under addition of two equivalents tartaric acid. The doses, referring to the base, were selected from the geometrical series: 0.01, 0.02, 0.04, . . . , 20.0, 40.0, 80.0 mg/kg and injected subcutaneously (1 ml/100 g).

RESULTS

AMP produced pronounced changes in the HOR, VER, and PIE motility components as shown in Figure 1, in which the 100% level corresponds to that of saline-treated control rats. The lowest dose of AMP with a significant effect on HOR activity was 0.63 mg/kg; it almost doubled the control level (ED_{200} = 0.67 mg/kg). HOR activity further markedly increased up to a maximum of 350% at the dose of 2.50 mg/kg. In the dose range of 10.0 to 80.0 mg/kg HOR activity dropped, but remained higher than in control rats (150% to 210% of the control level). Also, VER activity was markedly increased by AMP at 0.63 mg/kg (ED_{200} = 0.58 mg/kg); VER activity further steadily rose (to a maximum of 327%) when the AMP dose increased up to 5.00 mg/kg. At still higher doses, VER activity decreased dose-dependently and was even completely blocked at AMP doses of 40.0 and 80.0 mg/kg. PIE activity counts almost steadily increased after AMP over the whole dose range from 0.63 to 80.0 mg/kg (ED_{200} = 2.65 mg/kg).

Figure 2 shows the HOR, Figure 3 the VER, and Figure 4 the PIE activity in rats receiving one of four AMP doses (0.63–2.50–10.0 and 40.0 mg/kg) in combination with HAL or RIS, one out of eight doses in the range of 0.01 to 1.25 mg/kg. At the AMP doses of 0.63 and 2.50 mg/kg both HAL and RIS dose-dependently reduced the stimulated HOR activity (Fig. 2). The dose-response curves were steeper with HAL than with RIS, and this was also

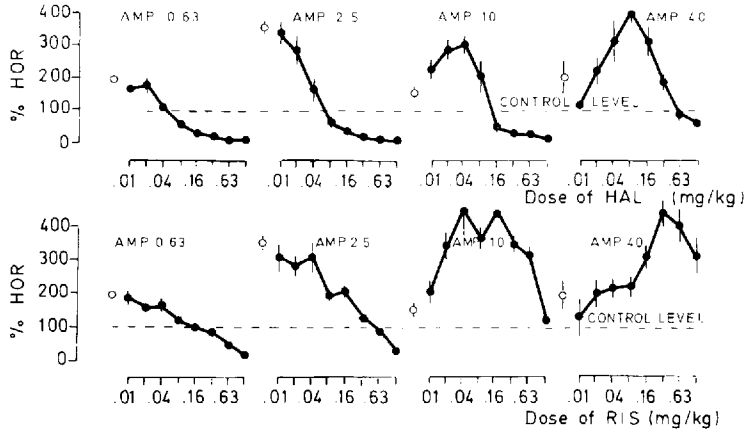

Fig. 2. Effects of 8 different doses of haloperidol (HAL) and risperidone (RIS) on horizontal (HOR) changes in activity induced by 4 doses of amphetamine (AMP). The activity measures have been expressed as percentages (mean ± S.E.M.) of the activity obtained in saline treated control rats. The S.E.M. values are represented by vertical bars. Open symbols indicate the activity measured following amphetamine alone.

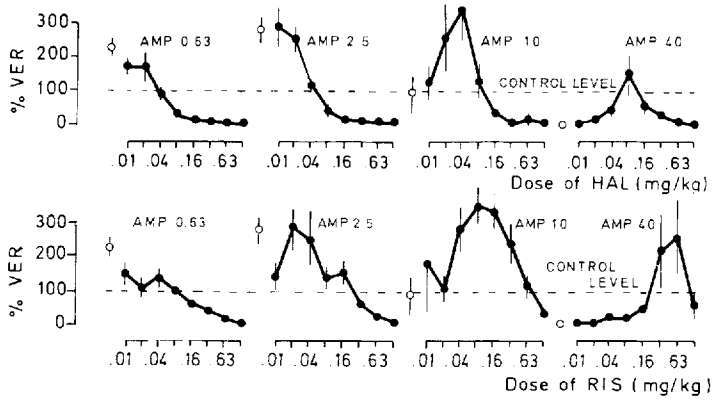

Fig. 3. Effects of 8 different doses of haloperidol (HAL) and risperidone (RIS) on vertical (VER) changes in activity induced by 4 doses of amphetamine (AMP). The activity measures have been expressed as percentages (mean ± S.E.M.) of the activity obtained in saline treated control rats. The S.E.M. values are represented by vertical bars. Open symbols indicate the activity measured following amphetamine alone.

reflected in the calculated doses that were required to restore the normal activity level (100%). For HAL, the doses were 0.046 and 0.060 mg/kg (ratio 1.3) at the AMP doses of 0.63 and 2.5 mg/kg, respectively (Table 1). For RIS the corresponding doses were 0.16 and 0.46 mg/kg, respectively (ratio 2.9). At the AMP doses of 10.0 and 40.0 mg/kg, which produced a submaximal stimulation per se (151% and 197%, respectively), the first effect of both HAL and RIS was to restore the maximal AMP response of more than 300% (Fig. 2). The required doses, calculated as ED_{300} values, were, for HAL, 0.027 and 0.036 mg/kg; and for RIS, 0.016 and 0.13 mg/kg, at the AMP doses of 10.0 and 40.0 mg/kg, respectively. Higher doses of HAL and RIS decreased HOR activity again, and normal activity (100% level) was obtained

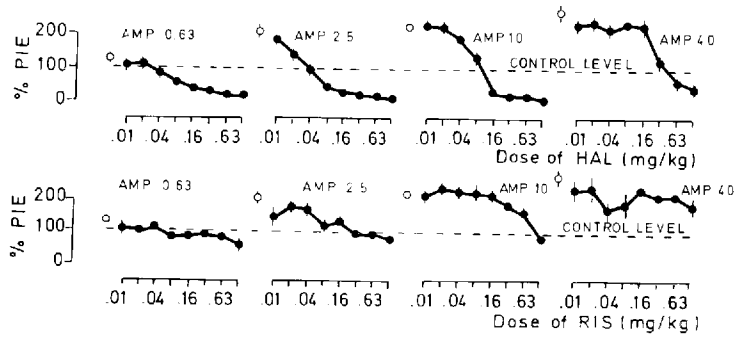

Fig. 4. Effects of 8 different doses of haloperidol (HAL) and risperidone (RIS) on piezo (PIE) activity changes induced by 4 doses of amphetamine (AMP). The activity measures have been expressed as percentages (mean ± S.E.M.) of the activity obtained in saline treated control rats. The S.E.M. values are represented by vertical bars. Open symbols indicate the activity measured following amphetamine alone.

at the calculated ED_{100} values listed in Table 1 (0.14 and 0.62 mg/kg for HAL, 1.40 and 3.84 mg/kg for RIS at AMP doses of 10.0 and 40.0 mg/kg, respectively).

Increased VER activity at the AMP doses of 0.63 and 2.50 mg/kg was also dose-dependently reduced by both HAL and RIS (Fig. 3). Again the dose-response curves were steeper with HAL than with RIS. The calculated doses required to restore the normal activity level (100%) at the AMP doses of 0.63 and 2.50 mg/kg were 0.034 and 0.047 mg/kg (ratio 1.4) for HAL and 0.049 and 0.20 mg/kg (ratio 4.1) for RIS, respectively (Table 1). VER activity reached the control level (100%) at the AMP dose of 10.0 mg/kg and was completely abolished at the AMP dose of 40.0 mg/kg. At the AMP dose of 10.0 mg/kg maximal VER activity (ED_{300}) was again restored with HAL and RIS at 0.025 and 0.042 mg/kg, respectively. At the AMP dose of 40.0 mg/kg, HAL restored normal VER activity at 0.058 mg/kg and reached a peak level of 150% at 0.080 mg/kg. RIS restored normal VER activity at 0.18 mg/kg and reached a peak level of 250% at 0.63 mg/kg. Higher doses of both compounds again restored normal activity (100%), HAL at 0.093 and 0.11 mg/kg (ratio 1.2), RIS at 0.70 and 1.08 mg/kg (ratio 1.5) for AMP doses of 10.0 and 40.0 mg/kg, respectively (Table 1).

The stimulated PIE activity (Fig. 4) at all dose levels of AMP was dose-dependently reduced by HAL and RIS. HAL restored normal PIE activity (100% level) at 0.022, 0.037, 0.095, and 0.45 mg/kg; RIS at 0.034, 0.27, 1.22, and 2.91 mg/kg for AMP doses of 0.63, 2.50, 10.0, and 40.0 mg/kg, respectively.

Table 1 also lists the doses of HAL and RIS required for restoring to normal control level (100%) the stimulated HOR, VER, and PIE activity, induced by the intermediate AMP doses of 1.25, 5, 20, and 80 mg/kg. The dose-normalization curves (ED_{100} of HAL and RIS as a function of the AMP dose) are graphically represented in Figure 5, together with the corresponding linear regression lines. Table 2 lists the slopes and 95% confidence limits of these lines. For each of the three activity measures, the normalization curves of the two antagonists diverged in the lower dose range of AMP (0.63–5 mg/kg) as indicated by the difference in slope values obtained for both compounds (Table 2; no overlap of the confidence limits). At higher doses of AMP (10–80 mg/kg), this difference between RIS and HAL disappeared and the slopes of the dose-normalization curves became comparable (Table 2; overlapping confidence limits).

TABLE 1. Doses With 95% Confidence Limits in mg/kg of Haloperidol (HAL) and Risperidone (RIS) Restoring to Normal Control Level (100%), the Stimulated Horizontal (HOR), Vertical (VER), and Piezo (PIE) Activity Induced by Different Doses of Amphetamine (AMP)

AMP	HAL (mg/kg)			RIS (mg/kg)		
(mg/kg)	HOR	VER	PIE	HOR	VER	PIE
0.63	0.046 (0.038–0.054)	0.034 (0.027–0.042)	0.022 (0.014–0.029)	0.16 (0.13–0.19)	0.049 (0.027–0.077)	0.034 (. . .)[a]
1.25	0.049 (0.040–0.063)	0.034 (0.027–0.044)	0.034 (0.016–0.046)	0.30 (0.24–0.37)	0.12 (0.096–0.16)	0.091 (0.039–0.22)
2.50	0.060 (0.049–0.085)	0.047 (0.037–0.075)	0.037 (0.031–0.044)	0.46 (0.31–0.84)	0.20 (0.14–0.33)	0.27 (0.16–0.50)
5.00	0.071 (0.057–0.099)	0.045 (0.032–0.15)	0.052 (0.044–0.064)	0.96 (0.74–1.44)	0.50 (0.27–1.30)	0.78 (0.57–1.12)
10.0	0.14 (0.11–0.18)	0.093 (0.071–0.20)	0.095 (0.076–0.12)	1.40 (1.17–2.02)	0.70 (0.51–1.35)	1.22 (0.96–1.62)
20.0	0.26 (0.20–0.45)	0.13 (0.097–0.29)	0.20 (0.14–0.32)	2.64 (1.93–5.04)	0.65 (0.50–1.21)	1.96 (1.51–2.82)
40.0	0.62 (0.49–0.91)	0.11 (0.072–0.27)	0.45 (0.36–0.63)	3.84 (2.79–7.50)	1.08 (0.80–2.01)	2.91 (2.07–4.80)
80.0	0.99 (0.69–2.10)	0.17 (...)[a]	0.83 (0.64–1.21)	7.09 (5.56–11.2)	1.00 (...)[a]	5.45 (4.17–7.86)

[a]Confidence limits were not calculable; estimated values are given in Figure 5 in order to denote that they are not zero.

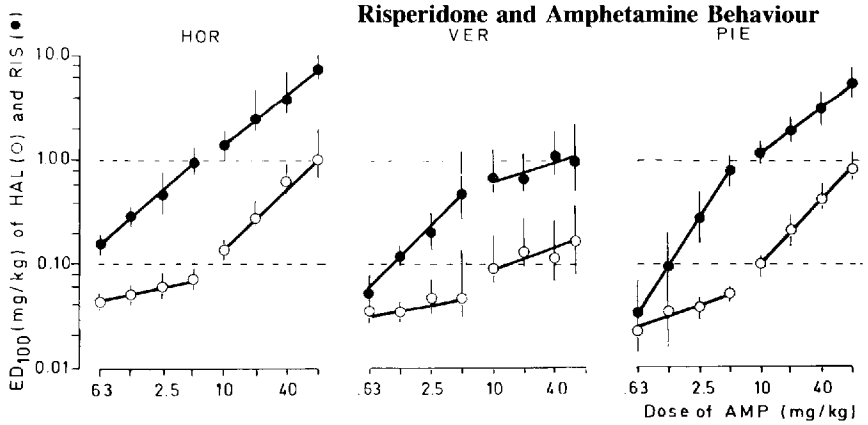

Fig. 5. Graphic representation of the effects obtained with haloperidol (HAL) and risperidone (RIS) on amphetamine (AMP)-induced changes in horizontal (HOR), vertical (VER), and piezo (PIE) motility components in rats. ED_{100} values and 95% confidence limits of HAL (open symbols) and RIS (closed symbols) for each dose of AMP are given (data from Table 1). The regression lines through the ED_{100} values were determined according to Davies [1947].

TABLE 2. Slope Values (and 95% Confidence Limits) of the Linear Regression Lines in Figure 5, Illustrating the Dose-Normalization Curves of Risperidone (RIS) and Haloperidol (HAL) for the Effects Induced by Amphetamine (AMP) on Horizontal (HOR), Vertical (VER), and Piezo (PIE) Activity*

	RIS	HAL
AMP doses 0.63–5 mg/kg		
HOR	0.22 (0.10–0.34)	0.84 (0.59–1.09)
VER	0.17 (−0.13–0.47)	1.08 (0.73–1.43)
PIE	0.39 (0.11–0.40)	1.52 (1.44–1.60)
AMP doses 10–80 mg/kg		
HOR	0.97 (0.65–1.29)	0.76 (0.54–0.98)
VER	0.24 (−0.25–0.73)	0.23 (−0.28–0.74)
PIE	1.05 (0.87–1.23)	0.70 (0.50–0.90)

*Note the overlapping confidence limits at high but not at low doses of amphetamine.

DISCUSSION

The analysis of the interaction of HAL and RIS with AMP in rats in the present study is based on the automatic recording of three types of signals. Light beam interruptions as signals for horizontal and vertical movements are relatively well known; the use of piezo-electric signals produced by even small floor deflexions has been introduced mainly to record small, stationary movements. The interpretation of the piezo signal in terms of animal movements has been discussed at length elsewhere [Megens et al., 1987, 1988].

For the present study separate piezo recordings are most essential for the measurement of the effects induced by high doses of AMP. The highest PIE counts were obtained in the dose range of 10.0 to 80.0 mg/kg, in which stationary movements as a consequence of stereotyped behaviour predominate. The simultaneous recording of HOR, VER, and PIE activity sharply demarcates the transition from the hyperactivity-inducing doses of AMP to the stereotypy-inducing doses. This transition takes place between AMP doses of 5.0 and 10.0 mg/kg and is characterized by the maintenance of a high level of piezo activity, a marked decrease of HOR activity, and an even more pronounced decrease of VER activity.

The discontinuous evolution of the larger body movements (HOR and VER) with increasing AMP dose complicates the motility patterns obtained when animals are injected with AMP in combination with an AMP antagonist. HAL [Janssen et al., 1965] and RIS [Janssen et al., 1988] have been described to decrease the behavioural and oxygen hyperconsumption effects of a standard dose of AMP. Moreover, the administration of HAL or RIS to normal, nonamphetaminized rats results in a dose-dependent decrease of the three motility components that are also studied in the present experiments, although RIS is markedly less active than HAL on PIE and the slopes of its dose-response curves are shallower [Megens et al., 1988]. When motility reduction is the consistent response to doses of HAL and RIS exceeding 0.01 mg/kg, it may be surprising at first sight that in combination with particular doses of AMP, motility counts are recorded that are much larger than those found with AMP alone. This phenomenon is first striking for the rats injected with the AMP dose of 10 mg/kg in combination with small to moderate doses of HAL and RIS, but the phenomenon further occurs at still higher doses of AMP. A similar enhancement of some activity measures, such as locomotion and rearing, following treatment of amphetaminized rats with neuroleptics has been reported by Randrup and Munkvad [1975] and was explained as disinhibition of behavioural items selectively inhibited by stereotypy-inducing doses of AMP. In fact, results of this type remain in the general line of agonist-antagonist inhibition, i.e., the antagonist at increasing doses progressively shifts the agonist effects to a pattern corresponding to that of lower agonist doses. There is, therefore, no fundamental difference between the results obtained at the AMP dose of 0.63 mg/kg and those obtained at the AMP dose of 10.0 mg/kg. The rather considerable hyperactivity induced by the low dose is significantly shifted to normal activity by low doses (of the order of 0.02–0.04 mg/kg) of HAL and RIS. Likewise, the motility pattern corresponding to the AMP dose of 10.0 mg/kg is significantly shifted towards that of 5.0 mg/kg by similar low doses of both antagonists. In this respect it is concluded that comparable doses of HAL and RIS antagonize both the hyperactivity and stereotypy induced by AMP.

Complete antagonism, i.e., reversal of the AMP effects to the motility level observed in normal animals, can also be obtained with both compounds whatever the degree of agonist stimulation. The required doses (ED_{100} values) regularly increase with increasing AMP dose and are generally lower for normalization of vertical motility than of stationary and horizontal movements (Table 1). The dose-normalization curves [ED_{100} as a function of the AMP dose] (Fig. 5), however, show consistent differences between HAL and RIS in the AMP dose range of 0.63 to 5.0 mg/kg. The three curves, corresponding to normalizing doses for horizontal, vertical, and stationary movements, are much steeper for RIS than for HAL. At still higher AMP doses the curves for RIS and HAL became comparable in slope, but separated by a factor of about 10.

The effective dose of HAL and RIS as AMP antagonists requires, therefore, much qualification. A significant antagonism, as indicated above, is obtained by both compounds at a virtually identical low dose of 0.02 mg/kg (calculated lowest dose of 0.022 mg/kg for HAL and 0.016 mg/kg for RIS). Motility normalization of the effects induced by AMP doses up to 5.0 mg/kg, requires a relatively small dose increment of HAL when compared with that of RIS. At still higher AMP doses the effectiveness of HAL and RIS follows an evolution which is comparable for both antagonists.

The observed differences between HAL and RIS in AMP interaction require a pharmacological explanation. Both HAL and RIS are potent and centrally active dopamine antagonists [Janssen et al., 1988]. Both compounds are tested at their time of peak effect [Janssen et al., 1988], which makes a pharmacokinetic explanation at least unlikely. The observed courses of the effective doses may rather have a relatively simple molecular basis. In vivo occupation of central dopamine-D_2 receptors is proposed to reach a low but effective level after injection of a low and virtually identical dose of HAL or RIS. Higher levels of functional dopamine antagonism up to saturation of the D_2 receptors are more readily obtained by

increasing the HAL than the RIS dose. This may also appear from the steeper dose-response curves obtained with HAL at the lower dose range of AMP (0.63–5 mg/kg; Figs. 2–4). Beyond the receptor saturating dose the competition between the agonist and antagonist molecules seems to follow kinetics independent of the particular antagonist that is involved.

Apart from being a central dopamine D_2-antagonist, RIS is also an antagonist of central serotonin S_2-receptors and α_1-adrenoceptors [Janssen et al., 1988]. One might argue that the difference between HAL and RIS in AMP interaction is related to the additional receptor interactions obtained with risperidone, the more so as the interactions of AMP on the central nervous system are complex: release of catecholamines; inhibition of amine uptake into neurones; agonistic stimulation of serotonin and dopamine receptors; and in high doses, an antagonistic action at α-adrenoceptors and inhibition of monoamine oxidase [Bowman and Rand, 1980; Garattini and Samanin, 1981]. Still, we believe that the present effects are primarily mediated via the central dopaminergic system. First, most investigators agree with a crucial role of the central dopaminergic system in the mediation of the amphetamine-induced motor effects, especially at the low AMP doses at which the marked difference between RIS and HAL was observed [Garattini and Samanin, 1981; Sharp et al., 1987]. Second, both the hyperactivity and stereotypy components of the AMP-induced behaviour are antagonized by doses of HAL that specifically block dopamine receptors [Niemegeers and Janssen, 1979]. The antagonistic effects of RIS are qualitatively similar to those effects of haloperidol. Third, amphetamine-induced behaviour is affected by the selective serotonin S_2-antagonist ritanserin at very high doses only [Awouters et al., 1988]. Therefore, it seems most likely that the effects of both HAL and RIS are primarily mediated via dopamine D_2-receptors. On the other hand, the additional receptor interactions obtained with RIS may partially reverse the consequences of central dopamine receptor blockade and, thereby, result in the only gradual increase of functional antidopamine activity observed with increasing doses of RIS.

Different dopaminergic systems exist within the central nervous system, e.g., the nigrostriatal and mesolimbic dopaminergic systems. Amphetamine-induced locomotor activity and antipsychotic effects of neuroleptics are sometimes thought to be mediated via the mesolimbic dopaminergic system, whereas amphetamine-induced stereotypy and extrapyramidal side effects of neuroleptics are thought to depend primarily on the nigrostriatal dopaminergic system [Berger et al., 1978; Sharp et al., 1987; Towell et al., 1987]. If this is true, HAL and RIS seem to have comparable potencies at striatal and limbic dopamine receptors since AMP-induced stereotypy and hyperactivity were antagonized by comparable low doses of both antagonists. Therefore, the present difference between HAL and RIS in AMP interaction seems not to be due to the possibility that the two compounds act differentially on the two different dopaminergic systems.

Whatever the precise molecular mechanisms, the present AMP interaction study clarifies a fundamental and clinically important difference between HAL and RIS as dopamine antagonists. This does not relate to the lowest clinically effective dose, which is in the order of 2 mg daily for both compounds. The difference applies to the objective of a clinical dose which matches dopaminergic overactivity without induction of a dopaminergic deficiency. In the comparative pharmacology of HAL and RIS [Janssen et al., 1988], it was already striking that in tests measuring dopamine antagonism the various ED_{50} values of RIS covered a much broader dose range than the corresponding values of HAL. Especially high ED_{50} values of RIS were found in the catalepsy and the conditioned food consumption tests, and both these effects may be ascribed to full blockade of the dopamine receptors. The latter may also apply to the inhibition of very small body movements, which is measured following much higher doses of RIS than of HAL [Megens et al., 1988]. The dose-normalization curves in the present amphetamine interaction study (Fig. 5) offer a more direct basis to evaluate levels of dopaminergic inhibition. With the same progression of doses HAL will reach much more rapidly than RIS an inhibition which exceeds that required by the AMP dose, and accordingly the risk for a clinical overdosage is much greater.

In conclusion, the present study shows that, even with respect to dopamine antagonism alone, RIS and HAL are not equivalent. Although both compounds are equally effective in antagonizing a low level of dopaminergic stimulation, excessive blockade of the dopamine receptors is much more likely obtained with HAL than with RIS. This is in agreement with the outcome of preliminary clinical experiments, which indicated RIS to be a highly effective antipsychotic with a low incidence of extrapyramidal side effects [Janssen, 1987].

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