Neuroleptics: relation between cataleptic and anti-turning actions, and role of the cholinergic system

Ever since Ungerstedt & Arbuthnott (1970) designed a rotometer for quantifying the turning behaviour of rodents with the unilateral lesion of the nigrostriatal pathway, the turning model has become popular in studies of proposed direct (Ungerstedt, 1971; Corrodi, Fuxe & Ungerstedt, 1971) and indirect (Ungerstedt, 1971; Crow & Gilbe, 1973) dopamine receptor stimulants as well as proposed dopamine receptor inhibitors, the neuroleptics.

The turning is thought to occur as the animal's compensation for a differential sensory input from the lesioned and intact side of the extrapyramidal system (Ungerstedt, 1973). The stimulants presumably augment this difference between lesioned and intact side by stimulating differentially the dopamine receptors of the caudate nucleus. The neuroleptics are thought to diminish this difference by supposedly blocking the dopamine receptors.

Crow & Gilbe (1973) used this model to test whether the mechanism of action of neuroleptics as antipsychotics is related to their blockade of the dopaminergic receptor (Matthysse, 1973). They compared the anti-turning potency, which was presumably a measure of the dopamine receptor-blocking potency, of chlorpromazine and thioridazine with their antipsychotic potency. They found that 8 mg kg^{-1} of thioridazine did not block the methylamphetamine-induced turning, even though chlorpromazine, an equipotent antipsychotic, blocked the turning almost completely. Crow & Gilbe (1973) considered their finding as evidence against the dopamine receptor hypothesis. Their argument would be justified only if the turning behaviour and its blockade was related to the dopamine receptor. There is, however, some evidence that the cholinergic system might be modifying the dopamine-mediated turning (Costall, Naylor & Olley, 1972a; Andén & Bédard, 1971). Costall & others (1972a) have demonstrated that the injection of either haloperidol or arecoline (unilaterally into the striatum) induced ipsilateral turning. Further, arecoline and haloperidol had synergistic effects when injected into the same nucleus. Atropine antagonized the effect of either haloperidol or arecoline, when injected into the same nucleus. Andén & Bédard (1971) reported blockade of haloperidol-induced turning with scopolamine in the rats with a unilateral striatal lesion. Miller & Hiley (1974) recently reported that thioridazine has a low dissociation constant for the central muscarinic receptors, indicating that it is likely to have high antiacetylcholine activity.

In this study, we tested whether the difference in the antiacetylcholine potency of thioridazine and chlorpromazine could account for their different anti-turning potencies. We also studied the possibility that the anti-turning property of the neuroleptic might be related to its ability to induce catalepsy which would leave the rats irresponsive to the locomotor stimulants; such irresponsiveness might be similar to that wherein the neuroleptic causes the animal to be irresponsive to external stimuli. For example, it is known that spiroperidol (0·1 mg kg^{-1}) and haloperidol (1 mg kg^{-1}), used by Ungerstedt (1971), or chlorpromazine (8 mg kg^{-1}), used by Crow & Gilbe (1973) to block amphetamine turning, are cataleptogenic doses (Janssen, Niemegeers & Schelekens, 1965).

The experimental procedure was essentially that employed by Crow & Gilbe (1973). The following are the only modifications: (1) Wistar instead of Lister rats were used, (2) 6-OH dopamine (6 μg per 3 μl) lesions of the pars compacta substantiae nigrae replaced electrolytic lesions, and (3) 5 mg kg^{-1} of (+)-amphetamine was used instead of methylamphetamine.

Catalepsy was measured by the bar test. The bar time represents an average of

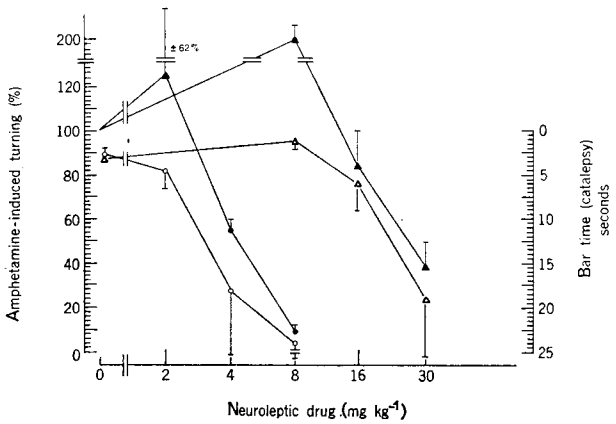

FIG. 1. Dose-response data for the cataleptic and turning-blocking actions of two neuroleptics in rats with unilateral nigral lesions. The rats (5 to 9 animals per point) were pretreated with chlorpromazine or thioridazine 180 min before the experiment. (+)-Amphetamine (5 mg kg^{-1}) was used to induce turning. The anti-turning effects of both neuroleptics were associated with concomitant catalepsy (○, catalepsy with chlorpromazine; △ catalepsy with thioridazine; ●, turning-blockade with chlorpromazine; ▲, turning-blockade with thioridazine). Standard error of the mean for chlorpromazine catalepsy was 44 s at 8 mg kg^{-1}.

three readings of the time a rat maintained its front paws on the horizontal bar, elevated to the height of approximately 15 cm.

As with the procedure used by Crow & Gilbe (1973), the rats were pretreated with chlorpromazine or thioridazine 3 h before the experiment. When scopolamine was used, it was administered 20 min before the turning measurements were initiated. Eserine (when used) was administered at the same time as amphetamine 3 min before the measurements were initiated.

In agreement with the results of Crow & Gilbe (1973), 4 and 8 mg kg^{-1} of chlorpromazine depressed the turning by 45 and 91% respectively. 8 mg kg^{-1} thioridazine did not affect turning. Crow & Gilbe (1973) did not report the effect of higher thioridazine doses, but in our experiments 16 and 32 mg kg^{-1} depressed the turning by 25 and 61% respectively. The doses that decreased turning also induced statistically significant longer bar times, suggesting the presence of catalepsy (Fig. 1).

The results in Fig. 2 show that scopolamine (0·4 mg kg^{-1}) completely blocked the catalepsy induced by 8 mg kg^{-1} chlorpromazine, and, at the same time, scopolamine antagonized (by 38%) the blockade of turning by chlorpromazine. Fig. 2 also shows that although eserine caused catalepsy, there was no significant change in turning.

The finding that scopolamine antagonized the turning-blockade induced by chlorpromazine agrees with the findings of Andén & Bédard (1971) and Costall & others (1972a), whose findings suggest that the turning is controlled by a dopamine-acetylcholine balance. The same was demonstrated for most other tests used to study the dopaminergic system, including catalepsy (Zetler, 1971; Costall & Olley, 1971), to a lesser extent stereotyped behaviour (Scheel-Krüger, 1970; Arnfred & Randrup, 1968; Costall, Naylor & Wright, 1972b), caudate cell firing rate (Steg, 1969) and caudate dopamine turnover (O'Keefe, Sharman & Vogt, 1970; Corrodi, Fuxe & others, 1967). The extrapyramidal side-effects of the neuroleptics are also thought to be mediated by a shift in the dopamine-acetylcholine balance (Bartholini, Stadler & Lloyd, 1973; Kelly & Miller, 1974).

Our studies demonstrate that the anticholinergic drugs antagonize the neuroleptic-blockade of amphetamine-induced turning. Since Miller & Hiley (1974) demonstrated that thioridazine is a more potent anti-acetylcholine drug than chlorpromazine,

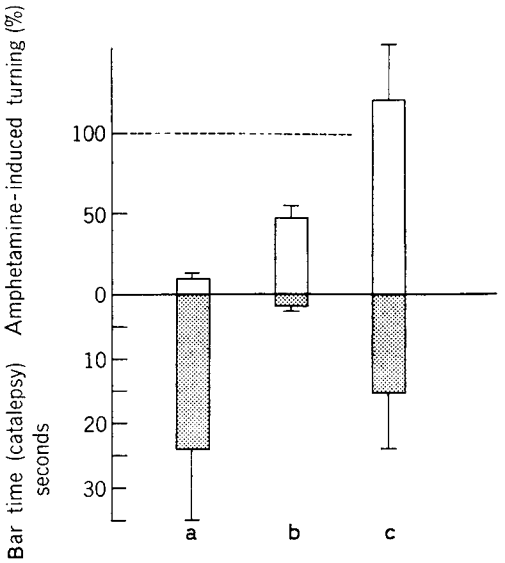

FIG. 2. The cataleptic and turning-blocking actions of chlorpromazine were both antagonized by scopolamine. Eserine caused catalepsy but did not affect the turning. a, Chlorpromazine (8 mg kg^{-1}) and amphetamine (5 mg kg^{-1}); b, chlorpromazine (8 mg kg^{-1}), amphetamine (5 mg kg^{-1}) and scopolamine (0·4 mg kg^{-1}), c, eserine (0·4 mg kg^{-1}) and amphetamine (5 mg kg^{-1}).

we agree with their conclusion that the difference of the two neuroleptics as turning-blockers is best explained by their different antiacetylcholine properties. The experiments of Crow and Gilbe (1973) are thus compatible with the antidopaminergic mechanism of action of the antipsychotics.

Our experiments further suggest that neuroleptic turning-blockade might be related to neuroleptic catalepsy. The doses of the neuroleptic which decreased turning also prolonged the bar time index of catalepsy. The same is true for the amphetamine turning-blocking doses of the neuroleptic used by other experimenters (Ungerstedt, 1971; Crow & Gilbe, 1973). Costall, & others (1972) reported that microinjection of the neuroleptic in the caudate nucleus, globus pallidus or substantia nigra (unilaterally) induces turning behaviour, while bilateral injections in the same regions resulted in catalepsy. We did not observe any simple correlation of catalepsy and turning with the acetylcholine-like drugs—scopolamine completely abolished chlorpromazine catalepsy, but only partly reversed the turning-blocking action of the neuroleptic; eserine caused catalepsy, but had no effect on turning. Costall & others (1972) also found that pallidal, caudate or nigral microinjection of arecoline or atropine had no effect on catalepsy, even though unilateral injections into these areas affected turning behaviour. It appears, therefore, that neuroleptic-, but not cholinergic-, catalepsy could be related to the anti-turning effects of the neuroleptics.

In conclusion, our experiments suggest that the lack of correlation between the antipsychotic and anti-turning potencies (as reported by Crow & Gilbe, 1973) could be explained by a relatively strong thioridazine antiacetylcholine action.

Secondly, the results reveal a relation between the cataleptic and anti-turning action of neuroleptic drugs.

Finally, our experiments indicate that the turning model is not specific for drugs that interact directly with the dopaminergic system and thus the results obtained on this model should be evaluated with caution. After completing this work, we found that Kelly & Miller (1974) had recently come to somewhat similar conclusions.

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