Regional Blockade by Neuroleptic Drugs of \textit{in vivo} \(^3\text{H}\)-Spi-perone Binding in the Rat Brain. Relation to Blockade of Apomorphine Induced Hyperactivity and Stereotypies

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With 1 Figure

Summary

The regional prevention by neuroleptic drugs of specific \textit{in vivo} \(^3\text{H}\)-spiperone binding was studied in the rat brain. L-sulpiride, thioridazine and clozapine were found to reduce the \(^3\text{H}\)-spiperone binding selectively in the olfactory tubercle, septum, substantia nigra region and frontal cortex but not the striatum at dose levels which preferentially block apomorphine (APO) induced hyperactivity. The maximal prevention of specific \(^3\text{H}\)-spiperone binding by l-sulpiride and clozapine reached 60—80 \(^\circ\) in the former structures while the displacement of striatal \(^3\text{H}\)-spiperone binding did not exceed 40 \(^\circ\). In contrast to l-sulpiride, thioridazine and clozapine both chlorpromazine and haloperidol reduced the \(^3\text{H}\)-spiperone binding to the same extent in all regions studied. Chlorpromazine and haloperidol were potent in prevention of striatal \(^3\text{H}\)-spiperone binding \textit{in vivo} which reached 60—80 \(^\circ\) in this structure.

Introduction

It has been suggested that the stereotypies and the hyperactivity induced by the dopamine (DA) agonist apomorphine (APO) are mediated via stimulation of DA receptors localized in the striatum and in extra-striatal brain areas, respectively (Cools \textit{et al.}, 1976; Costall and Naylor, 1973, 1975; Costall \textit{et al.}, 1977; Fuxe \textit{et al.}, 1976).
1977; Ljungberg and Ungerstedt, 1978). Sulpiride and clozapine, two DA-antagonists which have been reported to produce few signs of extrapyramidal side effects, block the APO induced hyperactivity at dose levels which do not affect the stereotypies in the rat (Fuxe et al., 1977; Ljungberg and Ungerstedt, 1978; Ögren et al., 1978). Furthermore, in several biochemical studies both drugs have been shown to enhance DA turnover preferentially in the nucleus accumbens and olfactory tubercle in the rat (Andén and Stock, 1973; Bartholini, 1976; Fuxe et al., 1977; Scatton et al., 1979; Waldmeier and Maitre, 1976; Westerink et al., 1977). Thus, an interesting neuroanatomical separation seems to exist between functional DA receptors localized in the striatum and in extra-striatal tissue, respectively.

In vivo binding of neuroleptic drugs (Kubar et al., 1978; Laduron and Leysen, 1977, Le Fur et al., 1980; Bischoff et al., 1980) offers a new approach to study the regional interaction of DA antagonists with neuroleptic receptors in relation to their behavioural effects. We recently reported (Köhler et al., 1979) that sulpiride displaces the in vivo $^3$H-spiperone binding in limbic, but not in striatal tissue at doses which selectively block APO induced hyperactivity. Displacement of $^3$H-spiperone in the striatum, on the other hand, occurred only at dose-levels where also blockade of the APO induced stereotypies was observed. In the present study we have further examined the effects of different classes of neuroleptic drugs on the regional in vivo $^3$H-spiperone binding in relation to the blockade of APO induced hyperactivity and stereotypies, respectively.

**Material and Methods**

The method for the in vivo binding of $^3$H-spiperone was similar to that reported earlier (Köhler et al., 1979). The rats (n = 4—8 in each group) were given tail vein injections (1.1 μg: 15 μCi in 0.3 μl saline) of $^3$H-spiperone (New England Nuclear, spec. act. 26 Ci mmol$^{-1}$). This dose has been found (Köhler et al., 1979) to saturate spiperone receptors in all regions studied in the present experiment. The doses of neuroleptics used in the displacement experiments were based on the doses which blocked APO induced hyperactivity and stereotypies, respectively (see below). The test compounds were administered (i.p.) 30 min before the injections of $^3$H-spiperone. Two hours after administration of $^3$H-spiperone the animals were decapitated and the following brain regions were rapidly dissected on ice: the olfactory tubercle (weight in mg: mean ± S.E.M. 14.9 ± 0.4), frontal cortex (18.3 ± 0.9), nucleus accumbens (22.9 ± 1.0), septum (17.7 ± 0.5), striatum (41.3 ± 1.0), substantia nigra, this area contains more tissue than just the substantia nigra and will thus be referred to as the substantia nigra region (including the ventromedial tegmentum 15.3 ± 1.0) and the cerebellar