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5-HT_2 and D_2 dopamine receptor occupancy in the living human brain*

A PET study with risperidone

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Abstract. It has been suggested that a combined blockade of 5-HT_2 and D_2 dopamine receptors may be superior to D_2 dopamine antagonists alone in the treatment of schizophrenia. Risperidone, which has a high affinity for 5-HT_2 and D_2 dopamine receptors in vitro, is a new antipsychotic drug that has been developed according to this hypothesis. The aim of this study was to examine if risperidone indeed induces 5-HT_2 and D_2 dopamine receptor occupancy in vivo in humans. Central receptor occupancy was examined by positron emission tomography (PET) in three healthy men after oral administration of 1 mg risperidone. [^{11}C]N-methylspiperone ([^{11}C]NMSP) was used as a radioligand for determination of 5-HT_2 receptor occupancy in the neocortex. Both an equilibrium ratio analysis and a kinetic three-compartmental analysis indicated a 5-HT_2 receptor occupancy about 60%. [^{11}C]raclopride was used as a radioligand for determination of D_2 dopamine receptor occupancy in the striatum and the calculated occupancy was about 50%. This is the first quantitative determination of 5-HT_2 receptor occupancy induced by an antipsychotic drug in the living human brain. The results indicate that 5-HT_2 receptor occupancy should be very high at the dose level of 4–10 mg risperidone daily, as suggested for clinical use. Risperidone is thus an appropriate compound for clinical evaluation of the benefit of combined 5-HT_2 and D_2 dopamine receptor blockade in the treatment of schizophrenia.

Key words: PET – Positron emission tomography – Human brain – Dopamine receptors – Serotonin receptors – Risperidone

According to the most widely accepted hypothesis concerning neuroleptic drug action the antipsychotic effect is mediated by blockade of dopamine receptors (Carlsson and Lindqvist 1963; van Rossum 1966; Creese et al. 1976; Seeman et al. 1976; Peroutka and Snyder 1980). This hypothesis has been supported by consistent PET findings of high D_2 dopamine receptor occupancy in patients treated with antipsychotic drugs (Farde et al. 1986; Smith et al. 1988; Baron et al. 1989). However, this support for the role of the central D_2 dopamine receptor does not preclude that antipsychotic effect may be induced or modulated by drugs acting on other neurotransmitter systems.

Involvement of the serotonergic (5-hydroxytryptamine, 5-HT) system in the pathophysiology of schizophrenia was suggested already in the 1950s. This suggestion was based on observations that lysergic acid diethylamide (LSD) could induce schizophrenia-like symptoms in man, and pharmacological evidence that LSD affected serotonergic transmission (Woolley and Shaw 1954). More recent support for the hypotheses of 5-HT dysfunction in schizophrenia has been provided by reports of abnormal concentrations of 5-HT in blood, and of 5-HIAA, the major 5-HT metabolite, in the cerebrospinal fluid in some groups of schizophrenic patients (van Kammen and Gelernter 1987; Bleich et al. 1988; Csernansky et al. 1990, reviews).

Preliminary clinical studies in a limited number of patients have indicated possible benefits of 5-HT antagonists in combination with classical neuroleptics in the treatment of negative schizophrenic symptoms. Drugs studied have been cyproheptadine, (Silver et al. 1989), setoperone (Ceulemans et al. 1985), ritanserin (Reyntjens et al. 1986) and mianserin (Mizuki et al. 1990).

An effect of the 5-HT system on neuroleptic-induced extrapyramidal side-effects (EPS) has been suggested by experimental studies. In animals, neuroleptic catalepsy was diminished by destruction of the 5-HT raphe nuclei (Kostowski et al. 1972; Costall et al. 1975) or by the administration of 5-HT antagonists (Balsara et al. 1979; Korsgaard et al. 1985; Hicks 1990). 5-HT antagonists have been claimed to reduce the risk for neuroleptic-induced EPS in schizophrenic patients.

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Risperidone, a benzisoxazole derivative, is a new antipsychotic drug with high affinity for central 5-HT_2 and D_2 dopamine receptors, and also some affinity for histamine, α_1 and α_2 receptors (Leysen et al. 1988). In a recent double-blind study, risperidone at a mean dose of 12 mg daily was found to have antipsychotic efficacy similar to that of haloperidol at a mean dose 10 mg daily, but a lower propensity to induce EPS (Claus et al. 1992).

The object of this PET study was to examine whether a clinical dose of risperidone induces occupancy of D_2 dopamine and 5-HT_2 receptors in the living human brain.

Subjects and methods

The study was approved by the Ethics and the Radiation Safety Committees of the Karolinska Hospital, and the Medical Products Agency of Sweden. The subjects were examined at the Departments of Psychiatry and Neuroradiology at the Karolinska Hospital.

Design. This open exploratory study was performed on 2 experimental days in each one of three subjects. On day 1 experiments were performed to establish baseline. On day 2, risperidone was administered orally as a 1 mg tablet to fasting subjects at 9 A.M. The 1 mg dose was chosen for reasons of tolerability in healthy subjects. Two consecutive PET experiments with different radioligands were conducted on each day. [^{11}C]raclopride, a radioligand highly selective for D_2 dopamine receptors (Farde et al. 1985, 1986) was used in the first experiment at 1 P.M. [^{11}C]N-methylspiperone ([^{11}C]NMSP), which has a high affinity for both D_2 dopamine and 5-HT_2 receptors (Wagner Jr et al. 1983; Lyon et al. 1986) was used in the second experiment at 3.30 P.M.

Subjects. Three male volunteers aged 40, 35 and 40 years were recruited after giving their informed consent. Their body weight and length was 92 kg/192 cm, 80 kg/189 cm, and 83 kg/179 cm, respectively. They were healthy according to history, physical examination, psychiatric interview, blood and urine analysis, and computerised tomography (CT) of the brain.

The metabolism of risperidone is sensitive to the debrisoquine hydroxylation type genetic polymorphism (Mannens et al. 1990). To exclude subjects with slow metabolism of risperidone, a debrisoquine hydroxylation test (Mahgoub et al. 1977) was performed in each subject. The metabolic ratio was defined as the ratio of recovery in the urine of debrisoquine to that of the 4-hydroxy metabolite determined over a period of 8 hours after an oral dose of 10 mg debrisoquine. All three subjects were characterised as "rapid hydroxylators" (Steiner et al. 1988), with metabolic ratios of 2.0, 3.0 and 3.4, respectively.

Risperidone concentration in plasma. A cannula was inserted into the right antecubital vein for the determination of plasma risperidone concentrations. Blood samples (10 ml) were collected 1, 2, 3, 4, 5, 6, 7, 8, and 24 h after administration. The samples were drawn into lithium-heparin tubes, centrifuged and plasma was frozen at −20° C until analysed. Plasma concentrations of risperidone and the main active metabolite 9-OH risperidone were determined by radio-immunoassay (Woestenborghs et al. 1990).

Pharmacodynamics. The subjects were observed during 14 h after risperidone intake. Observed effects were recorded when they appeared. Subjective experiences were noted on the basis of open questioning 10 h after administration of risperidone. The subjects were asked to describe each event with regard to nature, severity, onset and cessation. EPS were rated at baseline and after 2, 4, 6, 8, and 24 h according to "A rating scale for drug-induced akathisia" (Barnes 1989) and "A rating scale for extrapyramidal side effects" (Simpson and Angus 1970).

Radiochemistry and PET camera system. [^{11}C]raclopride was prepared as previously described (Halldin et al. 1991). [^{11}C]NMSP was prepared with a slight modification of the method described by Dannals et al. (1986). The specific activity at the time of injection was >500 Ci/mmol for both ligands. Radioactivity in brain tissue was measured with the PET camera system Scanditronix PC2048-15B. This PET camera consists of 8 rings with 256 detectors in each ring and measures radioactivity in 15 brain sections with a thickness of 6 mm each. The resolution of the reconstructed images is 4.5 mm (Litton et al. 1990).

PET experimental procedure. A plaster helmet was made for each subject. The helmet was used with a head fixation system to allow transfer of positioning from CT to PET, and to allow repeated PET experiments with the same positioning of the head (Bergström et al. 1981) The foramen of Monro was identified by CT so that the position of the head could be standardised (Farde et al. 1988).

In each PET experiment the subject was placed recumbent with his head in the PET camera system. A cannula was inserted into the left brachial artery. A saline solution of 270–300 MBq [^{11}C]raclopride or [^{11}C]NMSP was injected intravenously as a bolus during 2 s. The cannula was then immediately flushed with 10 ml saline. Radioactivity in the brain was measured for 51 min according to a preprogrammed sequence of 19 scans. Each scan lasted from 20 s initially to 6 min by the end of the experiment. An automatic blood sampling system was used to measure radioactivity in arterial blood during the first 5 min of the experiment (Eriksson et al. 1988). Thereafter, arterial blood samples were taken manually at the midpoint of each scan until the end of the experiment. Radioactivity in the blood samples was measured using a well-counter (see Farde et al. 1989 for a detailed experimental description). The fraction of radioactivity representing unchanged [^{11}C]NMSP was determined by high pressure liquid chromatography for control of input function (Swahn et al. 1992).

Regions of interest. All regions were drawn on the reconstructed PET images from the baseline experiments. Regions were drawn bilaterally for the putamen in two adjacent sections, covering the level of foramen of Monro. For the frontal cortex, regions were drawn in six adjacent sections. Data from adjacent regions were pooled before calculation of regional radioactivity. The cerebellar region was drawn in one section.

To obtain uptake curves, regional radioactivity was calculated for each scan, corrected for decay and plotted versus time.

Calculation of D_2 dopamine receptor occupancy by the ratio method. The theory for the calculation of D_2 dopamine receptor occupancy using [^{11}C]raclopride has been presented earlier (Farde et al. 1989). The cerebellum is a reference region with a negligible density of D_2 dopamine receptors (Hall et al. 1988). The total radioactivity in the cerebellum, $C_f(t)$, was used as an estimate of the free radioligand concentration in the brain. Radioactivity representing ligand bound specifically to D_2 dopamine receptors, $C_b(t)$, was defined as

$$C_b(t) = C_{put}(t) - C_f(t) \quad (1)$$

where $C_{put}(t)$ is the regional radioactivity in the putamen.

The curves for $C_b(t)$ and $C_f(t)$ were integrated from 9 to 45 min after radioligand injection and a ratio R was obtained according to the equation

$$R = \int_9^{45} C_b(t)\,dt \Big/ \int_9^{45} C_f(t)\,dt \quad (2)$$

D_2 dopamine receptor occupancy was defined as the percent reduction in R after administration of risperidone as compared to the baseline experiment, i.e. in the absence of active drug.

Calculation of 5-HT_2 receptor occupancy. The ratio of frontal cortical to cerebellar uptake of [^{11}C]NMSP (C_{fr}/C_{cer}) has been sug-

gested as an index of $5HT_2$ receptor density (Wong et al. 1984). The relative reduction in C_{fr}/C_{cer} may be used for the calculation of 5-HT_2 receptor occupancy according to the method described above for calculation of D_2 dopamine receptor occupancy.

Radioactivity representing ligand bound specifically to 5-HT_2 receptors, $C_{b*}(t)$, was defined as

$$C_{b*}(t) = C_{fr}(t) - C_{cer}(t) \quad (3)$$

where $C_{fr}(t)$ is the regional radioactivity in the frontal cortex.

The curves for $C_{b*}(t)$ and $C_{cer}(t)$ were then integrated from 9 to 45 min after radioligand injection and a ratio R was obtained according to the equation

$$R^* = \int_9^{45} C_{b*}(t)dt \Big/ \int_9^{45} C_{cer}(t)dt \quad (4)$$

5-HT_2 receptor occupancy was defined as the percent reduction in R after administration of risperidone as compared to the baseline experiment, i.e. in the absence of active drug.

Kinetic analysis of 5-HT_2 receptor occupancy. A kinetic three-compartmental analysis of radioligand binding was also applied (Fig. 1) (Sokoloff et al. 1977; Mintun et al. 1984; Wong et al. 1986). Such an analysis is based on the curve for unchanged radioligand in arterial blood and on the uptake curve for the regional brain radioactivity as input functions (see Farde et al. 1989, for equations). A major advantage of the kinetic approach is that comparison with a reference region is not required for the estimation of free radioligand in the brain. The kinetic analysis was applied to validate the use of the cerebellum as a reference region in the ratio analysis.

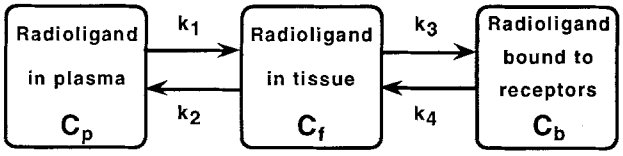

Fig. 1. The three-compartmental model used to interpret regional brain radioactivity after iv injection of radioligand

The rate constant k_3 is the product of the bimolecular association rate constant, k_{on} (ml/pmol/min), and the concentration of available receptors, $B_{max} - B$. B_{max} is the density of receptors (pmol/ml) and B is the specific binding of radioligand or unlabelled substance. With a compartmental analysis of [^{11}C]NMSP binding performed on the data collected before and after administration of risperidone, specific binding of risperidone is expected to be reflected in a reduction of k_3.

By means of an iterative procedure the three-compartmental model was fitted to the experimental data (Farde et al. 1989). It was assumed that only k_3 was affected by the presence of risperidone, and that k_1, k_2, and k_4 were unchanged.

In the kinetic analysis, 5-HT_2 receptor occupancy (in percent) was defined by the equation

$$\left(1 - \frac{k_{3\,\text{risperidone}}}{k_{3\,\text{baseline}}}\right) \cdot 100 \quad (5)$$

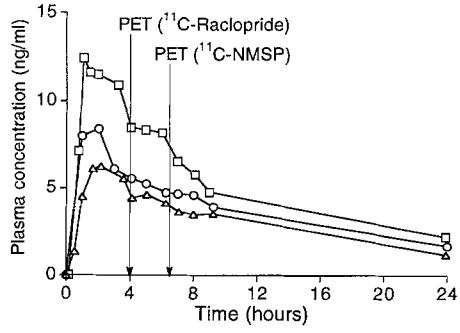

Fig. 2. Time curves showing plasma concentrations after administration of 1 mg risperidone orally to three healthy subjects (*A–C*). The curves represent the sum of risperidone and the main, equally active metabolite 9-OH-risperidone. Time at start of the two PET experiments is indicated. (–○–) A; (–□–) B; (–△–) C

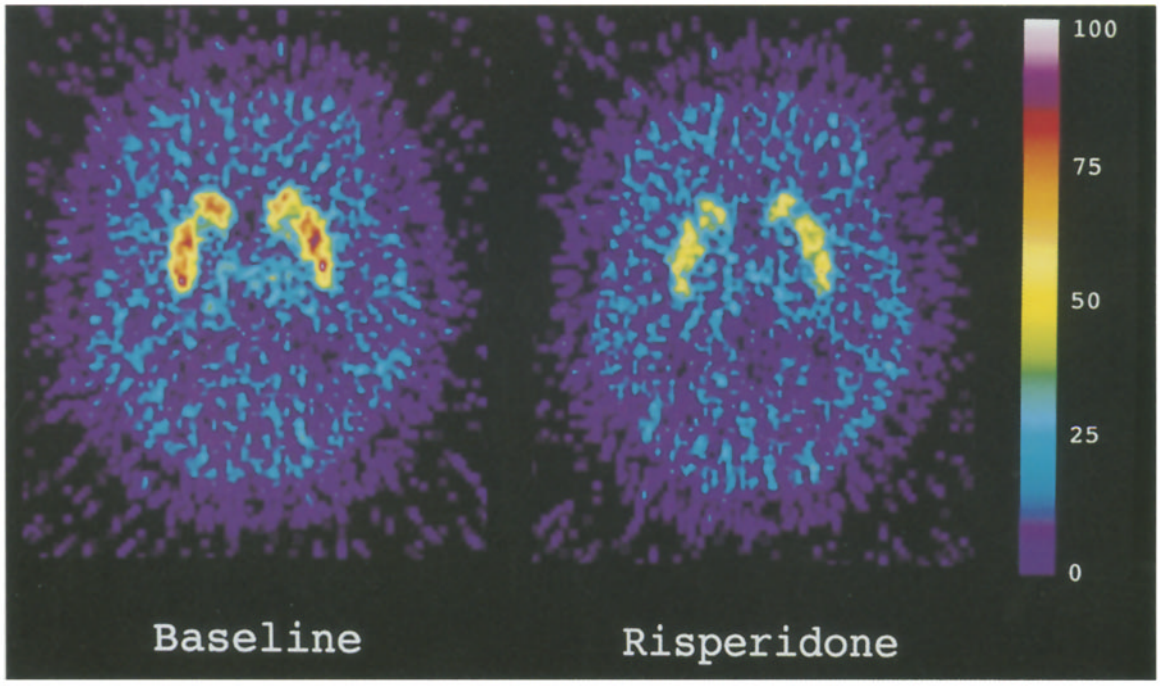

Fig. 3. PET images showing the distribution of radioligand in a horizontal section of the brain through the striatum in a healthy man (subject *C*) after iv injection of [^{11}C]raclopride, before (*left*) and after oral administration of 1 mg risperidone (*right*)

where $k_{3\,\text{risperidone}}$ is the rate constant k_3 after risperidone administration.

The kinetic analysis was also applied for calculation of D_2 dopamine receptor occupancy in the experiments with [^{11}C]raclopride.

Results

All three volunteers completed the PET experiments according to the schedule. After the administration of risperidone, all three subjects reported mild sedation, appearing within the first hour and with a maximal intensity during the first 6 h. Extrapyramidal side effects or akathisia were not recorded. There were no changes in blood pressure, pulse rate, or temperature.

Concentrations of risperidone and its main, equally active metabolite 9-OH-risperidone in plasma were summed and plotted versus time (Fig. 2). Maximal concentrations were attained within 2 h after drug administration.

PET experiments with [^{11}C]raclopride

In the baseline experiment there was a marked accumulation of radioactivity in the striatum (Fig. 3, left). After risperidone, the striatal uptake of radioactivity was reduced (Fig. 3, right, and Fig. 4).

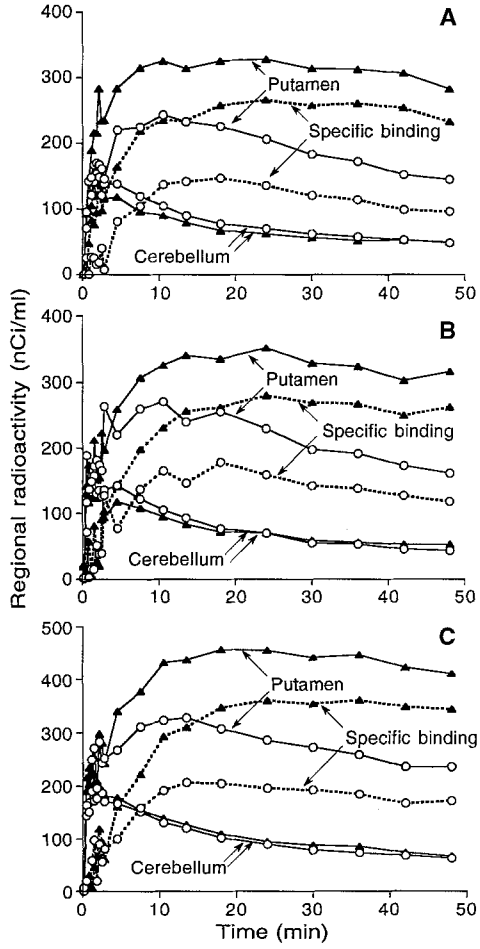

Fig. 4A–C. Regional radioactivity, corrected for decay, in the putamen and the cerebellum, and the calculated specific binding in the putamen (putamen reduced by cerebellum) in three healthy men (subjects **A–C**) after iv injection of [^{11}C]raclopride, before (–▲–) and after (–○–) risperidone administration. Data were normated for injected radioactivity dose

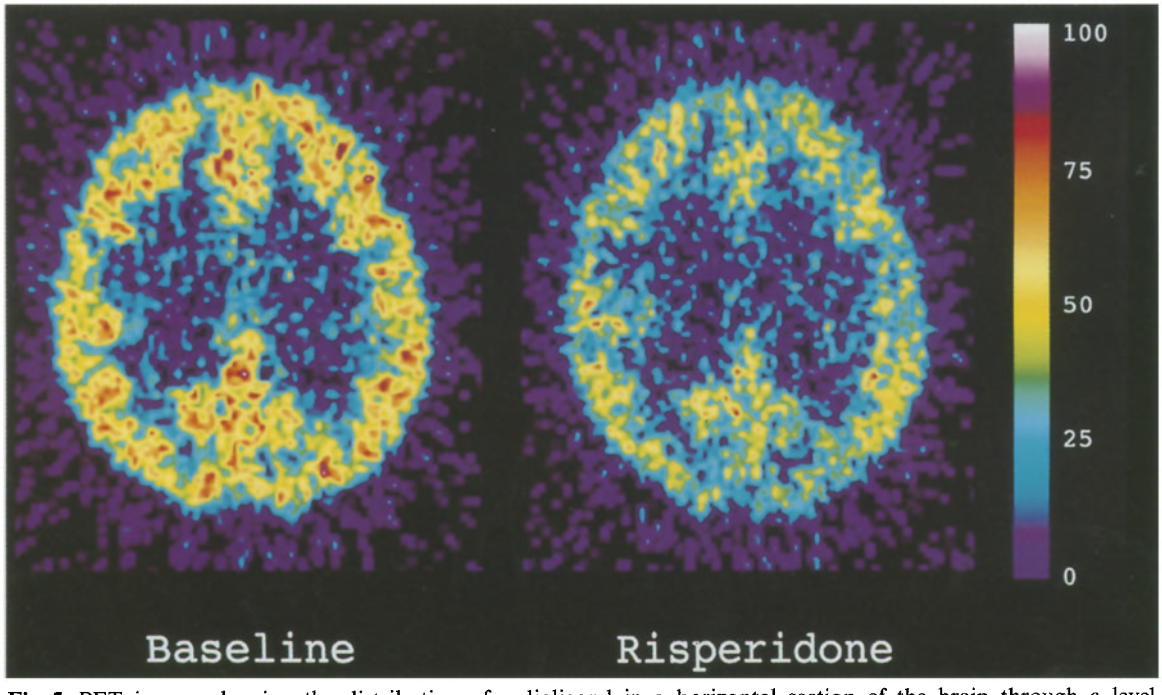

Fig. 5. PET images showing the distribution of radioligand in a horizontal section of the brain through a level above the striatum in a healthy man (subject *B*) after iv injection of [^{11}C]NMSP, before (*left*) and after oral administration of 1 mg risperidone (*right*)

The occupancy of D_2 dopamine receptors in the putamen calculated with the ratio method was 55%, 43% and 40% (Fig. 7).

In the kinetic analysis, all k_3 values for the putamen were lower after risperidone as compared to baseline. The calculated occupancy of D_2 dopamine receptors in the putamen was 61%, 64% and 53%.

PET experiments with [^{11}C]NMSP

There was a uniformly high uptake of radioactivity in all neocortical regions (Fig. 5, left). After risperidone, there was a marked reduction in the neocortical uptake of [^{11}C]NMSP as compared to baseline (Fig. 5, right, and Fig. 6).

Using the ratio analysis, the calculated occupancy of 5-HT_2 receptors in the frontal cortex for each subject was 68%, 56% and 45% (Fig. 7).

In the kinetic analysis, all k_3 values for the frontal cortex were lower after risperidone as compared to baseline. The calculated occupancy of 5-HT_2 receptors in the frontal cortex was 45%, 65% and 63%.

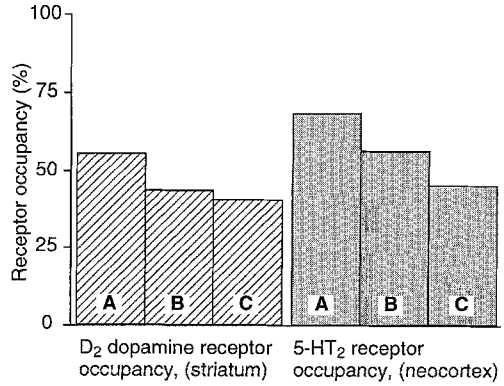

Fig. 7. D_2 dopamine receptor occupancy in the striatum (radioligand: [^{11}C]raclopride) and 5-HT_2 receptor occupancy in the frontal cortex (radiologand [^{11}C]NMSP) in three healthy subjects (*A–C*) after a single oral dose of 1 mg risperidone. Receptor occupancy was calculated according to the ratio approach (cf Methods)

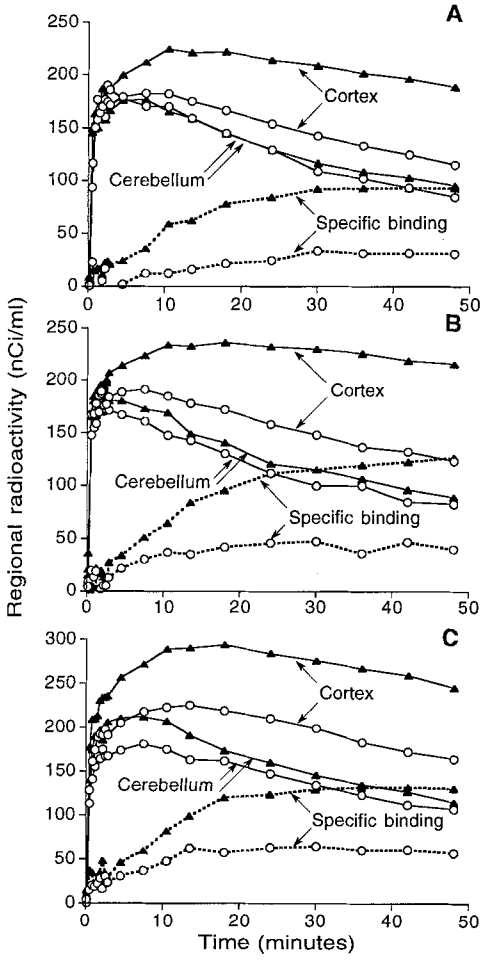

Fig. 6A–C. Regional radioactivity, corrected for decay, in the frontal cortex and the cerebellum, and the calculated specific binding in the frontal cortex (frontal cortex reduced by cerebellum) in three healthy men (subjects **A–C**) after iv injection of [^{11}C]NMSP, before (–▲–) and after (–○–) risperidone administration. Data were normated for injected radioactivity dose

Discussion

The present PET study indicates that risperidone induces marked occupancy of central 5-HT_2 and D_2 dopamine receptors in vivo in humans. About 60% (range 45–68%) of the 5-HT_2 receptors in the frontal cortex and about 50% (range 40–64%) of the D_2 dopamine receptors in the striatum were occupied 4 and 7 h after a single oral dose of 1 mg risperidone. To our knowledge, this is the first quantitative determination of 5-HT_2 receptor occupancy induced by an antipsychotic drug in the living human brain.

Radioligands

The methods for determination of receptor occupancy are dependent on the pharmacokinetics of the radioligands used. Several ligands have been proposed for the investigation of central 5-HT_2 receptors. None of these ligands have proved to be ideal. All the ligands developed so far have the disadvantage of a low total-to-nonspecific binding ratio, which limits the accuracy of any quantitative analysis.

[^{18}F]altanserin and [^{18}F]setoperone have recently been suggested as suitable ligands for the study of 5-HT_2 receptor populations (Blin et al. 1988, 1990; Crouzel et al. 1992). A major reason for this recommendation is the rather high cortex to cerebellum ratio, about 2.5 for both ligands. In this study the PET experiments with the two different radioligands were performed 2.5 h apart so that comparable pharmacological conditions could be achieved. The long half-life of [^{18}F] (110 min) precludes the use of this isotope in experiments repeated after short time intervals. An [^{11}C]-labelled ligand with a shorter half-life (20 min) is required for such purposes. The highest total-to-nonspecific (cortex to cerebellum) binding ratio during the PET experiments with

[^{11}C]NMSP was 2.0, 2.4 and 2.1 in the three subjects of the present study. Since these ratios are close to the maximal ratios for the [^{18}F]-labelled ligands, the present use of [^{11}C]NMSP instead of the newer ligands should not be disadvantageous.

[^{11}C]raclopride was used for the determination of D_2 dopamine receptor occupancy. Raclopride is selective for D_2 dopamine receptors. No significant binding has been demonstrated in the human cerebellum in PET studies with [^{11}C]raclopride (Farde et al. 1985) or in studies in vitro with [^{3}H]raclopride (Hall et al. 1988). The radioactivity in the cerebellum should thus be a valid estimate of free and unspecifically bound radioligand in the brain.

Specificity and regional differences in central [^{11}C]NMSP binding

[^{11}C]NMSP was used as a radioligand for the determination of 5-HT_2 receptor binding in the frontal cortex. [^{3}H]-labelled NMSP has a subnanomolar affinity for both 5-HT_2 and D_2 dopamine receptors (Lyon et al. 1986; Frost et al. 1987). In vitro and in vivo studies indicate that the neocortical accumulation of NMSP mainly reflects binding to 5-HT_2 receptors (Lyon et al. 1986; Frost et al. 1987; Swart et al. 1990). The 5-HT_2 receptors are widely distributed in the brain, with the highest densities above 250 fmol/mg protein in the frontal neocortex (Schotte et al. 1983; Pazos et al. 1987). On the contrary, the density of D_2 dopamine receptors in the neocortex is very low, no more than 1% of the 5-HT_2 receptor density (Martres et al. 1985; Hall et al. 1988; Lidow et al. 1989). The affinity of [^{3}H]NMSP to human D_2 dopamine receptors is four times greater than to 5-HT_2 receptors in vitro (Lyon et al. 1986). In PET studies in humans with [^{11}C]raclopride no specific binding could be demonstrated in the neocortex (Farde et al. 1988). Consequently, no significant binding to D_2 dopamine receptors of either of the two ligands used is expected in the neocortex. This is supported by our finding in this study that there was no change in the cortex-to cerebellum ratio in the [^{11}C]raclopride experiments before and after the administration of risperidone.

The 5-HT_2 receptor resembles the 5-HT_{1C} receptor (Peroutka 1990). Despite this similarity, spiperone is selective for the 5-HT_2 receptor, and has a low affinity for the 5-HT_{1C} receptor (Hoyer et al. 1986). The spiperone derivative NMSP should thus also be selective for the 5-HT_2 receptor subtype. In addition, the density of 5-HT_{1C} receptors in the human frontal cortex is at least 5-fold lower than that of 5-HT_2 receptors (Hoyer et al. 1986). The contribution of 5-HT_{1C} receptors to the cortical accumulation of [^{11}C]NMSP should thus be negligible.

Models for quantitative analysis of 5-HT_2 receptor occupancy

To calculate 5-HT_2 receptor occupancy according to the ratio approach, the total radioactivity in the cerebellum was used as an estimate of free and unspecifically bound [^{11}C]NMSP. In the human cerebellum a low but significant density of 5-HT_2 receptors has been demonstrated in vitro, 30–50 fmol/mg protein, which is 5–10 times lower than in the frontal cortex (Pazos et al. 1987). Hence some specific binding of [^{11}C]NMSP to 5-HT_2 receptors in the cerebellum was expected. Such specific binding would be reflected in a reduced ratio of radioactivity in the cerebellum over that in blood after the administration of risperidone.

The radioactivity in blood was corrected for the metabolism of the ligand and the ratio of radioactivity in cerebellum to that in blood was calculated before and after administration of risperidone (data not shown). After administration of risperidone, the cerebellum to blood radioactivity ratio was about 10% lower than at baseline. If specific binding in the cerebellum is taken into account in equations 3 and 4 the ratio-equilibrium calculation of 5-HT_2 receptor occupancy in the frontal cortex will be about 5% higher than the results presented in this paper.

The ratio method has the advantage of a rather simple experimental procedure, with no need for arterial blood sampling, and with a less complicated numerical analysis of data. The results obtained from the kinetic analysis of [^{11}C]NMSP binding to 5-HT_2 receptors in the frontal cortex were similar to those obtained with the ratio approach. Both analyses yielded an average occupancy of about 60%. However, the individual differences between the ratio and kinetic method were −23%, +9% and +18%. The number of subjects in this study does not permit a statistical comparison between the two analytical approaches. Clearly both methods yield results of the same order. The results from the kinetic analysis do not contradict that the use of the cerebellum as a reference region in the ratio analysis is a valid approach to the calculation of 5-HT_2 receptor occupancy.

Risperidone administered in an oral dose of 1 mg induced an about 50% D_2 dopamine and an about 60% 5-HT_2 receptor occupancy in healthy men. This finding is consistent with in vitro and in vivo animal studies, in which risperidone displayed a high affinity for both 5-HT_2 and D_2 dopamine receptors (Janssen et al. 1988; Leysen et al. 1988). Our results indicate that 5-HT_2 receptor occupancy should be very high at the dose level of 4–10 mg risperidone daily suggested for clinical use. This study shows that risperidone is an appropriate compound for clinical evaluation of the benefit of combined 5-HT_2 and D_2 dopamine receptor blockade in the treatment of schizophrenia.

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