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Short communication

# The effect of acute administration of risperidone on local cerebral glucose utilization in the rat

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**Abstract**

Risperidone (R 64 766, 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-pyperidinyl]ethyl}-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one) has superior effects in treating negative symptoms of schizophrenia and causes less extrapyramidal side effects than traditional antipsychotics. In this study, we employed the [$^{14}$C]2-deoxy-D-glucose method to map local cerebral metabolic activity of rats acutely administrated i.p. with 0.0, 0.1, 0.5, 1.0 and 2.0 mg kg$^{-1}$ risperidone. Risperidone in the highest dose produced a reduction of glucose utilization in 11 of the 38 regions examined. The results showed that the regions with metabolic change are somewhat different from those results studied with microdialysis and the Fos immunohistochemistry. Among the nuclei with metabolic changes, the hippocampus and the mediodorsal nucleus of the thalamus may be related to the therapeutic action of risperidone and require further study. 

*Keywords:* [$^{14}$C]2-Deoxyglucose; Antipsychotic; Glucose utilization; Hippocampus; Risperidone; Mediodorsal thalamus

## 1. Introduction

Despite the availability of numerous antipsychotic drugs for the treatment of schizophrenia, there remains a need for the development of more effective and less toxic compound. Traditional antipsychotic such as haloperidol has a well-established efficacy in the acute and maintenance treatment of the illness. However, the clinical utility of these agents had some limitations including the associated extrapyramidal side effects and the inefficacy in the negative symptoms of schizophrenia such as apathy, lack of motivation and anhedonia. Risperidone (R 64 766, 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-pyperidinyl]ethyl}-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one), a benzisoxazol derivative, is of at least comparable efficacy to haloperidol in improving the positive symptoms of schizophrenia (Grant and Fitton, 1994). Advantages offered by risperidone over haloperidol include a low propensity to induce extrapyramidal side effects and possibly a greater effect on the negative symptoms of schizophrenia (Grant and Fitton, 1994). These particular properties have been attributed to the very potent 5-HT$_2$ receptor antagonism of the drug combined with less potent dopamine D$_2$ receptor antagonism (Grant and Fitton, 1994). Except 5-HT$_2$ receptor and dopamine D$_2$ receptors, risperidone exhibits rather high affinity for central adrenergic $\alpha_1$ and histamine H$_1$ receptors and a moderate affinity for $\alpha_2$-adrenoceptors (Leysen et al., 1992, 1994).

A diverse range of methods has been employed to characterize the neuroanatomical and the neurochemical basis of risperidone. By employing microdialysis in rats, previous studies had demonstrated that risperidone increase dopamine and serotonin metabolism in the medial prefrontal cortex, the nucleus accumbens and the striatum (Hertel et al., 1996, 1997). However, in contrast to the regionally rather homogenous activation of brain dopaminergic systems caused by risperidone, the drug was found to enhance brain serotonin metabolism preferentially in the medial prefrontal cortex, as indicated by the elevated extracellular concentration of 5-hydroxyindoleacetic acid (5-HIAA) in this region (Hertel et al., 1996). The Fos immunohistochemistry which can map functional pathways in brain has been used to study risperidone. The results in two studies (Robertson et al., 1994; Wan et al.,

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1995) showed that risperidone enhances Fos-like immunoreactivity in the striatum, the nucleus accumbens but not in the prefrontal cortex.

The [$^{14}$C]2-deoxy-D-glucose method which assesses rates of local cerebral glucose utilization (LCGU) can be used to determine the localization of the functional action of a specific drug in mammalian brain (Sokoloff et al., 1977). This method gives information about the sites of drug action in the brain, including not only areas directly affected, but also areas connected with the drug's extended functional effects. In view of the complex neurochemical profiles of risperidone, we employed the [$^{14}$C]2-deoxy-D-glucose method for measuring local rates of glucose utilization in rats treated acutely with different doses of

Table 1
Effects of the acute administration of risperidone on local cerebral glucose utilization (mean ± S.E.M. μmol (100 g)$^{-1}$ min$^{-1}$) in rats

| Structure | Risperidone (mg kg$^{-1}$) | | | | | ANOVA $p$ value ($df$ = 4, 27) |
|---|---|---|---|---|---|---|
| | 0.0 (6) | 0.1 (7) | 0.5 (5) | 1.0 (5) | 2.0 (5) | |
| *Extrapyramidal system* | | | | | | |
| Striatum | 107 ± 9 | 106 ± 5 | 123 ± 12 | 117 ± 8 | 103 ± 9 | 0.4451 |
| Globus pallidus | 69 ± 7 | 57 ± 5 | 62 ± 3 | 54 ± 5 | 42 ± 4[a] | 0.0170 |
| Substantia nigra pars compacta | 86 ± 5 | 71 ± 5 | 79 ± 8 | 74 ± 7 | 60 ± 3 | 0.0541 |
| Substantia nigra pars reticulata | 53 ± 3 | 43 ± 2 | 42 ± 5 | 38 ± 6 | 56 ± 3 | 0.0419 |
| Subthalamic nucleus | 84 ± 5 | 71 ± 5 | 73 ± 6 | 69 ± 8 | 56 ± 4[a] | 0.0384 |
| *Limbic and related areas* | | | | | | |
| Anterior pretectal nucleus | 98 ± 4 | 80 ± 4 | 94 ± 11 | 89 ± 8 | 66 ± 4[a] | 0.0175 |
| Arcuate nucleus | 50 ± 5 | 43 ± 4 | 49 ± 3 | 40 ± 5 | 34 ± 2 | 0.0841 |
| Basomedial amygdala | 79 ± 5 | 66 ± 4 | 88 ± 6 | 69 ± 6 | 54 ± 5[a,c] | 0.0023 |
| Central amygdala | 62 ± 4 | 52 ± 3 | 61 ± 4 | 51 ± 6 | 41 ± 5 | 0.0273 |
| Hippocampus CA1 | 74 ± 4 | 62 ± 3 | 83 ± 7 | 61 ± 5 | 52 ± 3[a,c] | 0.0011 |
| Interpeduncular nucleus | 107 ± 5 | 85 ± 5 | 124 ± 18 | 96 ± 5 | 77 ± 7[c] | 0.0092 |
| Lateral habenular nucleus | 98 ± 6 | 83 ± 4 | 112 ± 13 | 100 ± 11 | 76 ± 5 | 0.0396 |
| Lateral septal nucleus | 63 ± 7 | 62 ± 5 | 61 ± 5 | 64 ± 5 | 62 ± 7 | 0.9973 |
| Medial preoptic nucleus | 44 ± 4 | 35 ± 3 | 40 ± 2 | 36 ± 2 | 28 ± 4[a] | 0.0142 |
| Medial septal nucleus | 74 ± 7 | 60 ± 4 | 73 ± 6 | 65 ± 6 | 55 ± 5 | 0.1260 |
| *Nucleus accumbens* | | | | | | |
| core | 97 ± 7 | 104 ± 6 | 124 ± 11 | 117 ± 8 | 110 ± 12 | 0.2723 |
| shell | 85 ± 8 | 86 ± 6 | 95 ± 4 | 90 ± 7 | 89 ± 8 | 0.8621 |
| *Nucleus diagonal band of Broca* | | | | | | |
| horizontal limb | 81 ± 8 | 68 ± 4 | 83 ± 8 | 71 ± 4 | 55 ± 3 | 0.0280 |
| vertical limb | 75 ± 7 | 62 ± 5 | 72 ± 6 | 67 ± 6 | 53 ± 4 | 0.1295 |
| Paraventricular nucleus | 60 ± 6 | 43 ± 3 | 57 ± 6 | 52 ± 6 | 37 ± 3 | 0.0234 |
| Posterior cingulate cortex | 106 ± 8 | 92 ± 4 | 125 ± 14 | 100 ± 5 | 78 ± 6[c] | 0.0073 |
| Ventral tegmental areas | 67 ± 4 | 58 ± 6 | 62 ± 8 | 61 ± 6 | 46 ± 2 | 0.1572 |
| Ventromedial nucleus, hypothalamus | 67 ± 7 | 55 ± 4 | 69 ± 5 | 59 ± 7 | 44 ± 2 | 0.0196 |
| *Neocortex* | | | | | | |
| Anterior cingulate cortex | 106 ± 10 | 101 ± 5 | 114 ± 12 | 103 ± 5 | 98 ± 7 | 0.7571 |
| Anterior orbital cortex | 160 ± 10 | 150 ± 5 | 163 ± 10 | 151 ± 11 | 144 ± 10 | 0.5993 |
| Auditory cortex | 136 ± 7 | 116 ± 5 | 149 ± 20 | 124 ± 13 | 90 ± 11[c] | 0.0241 |
| Frontal cortex | 110 ± 6 | 106 ± 5 | 105 ± 7 | 97 ± 8 | 103 ± 10 | 0.7909 |
| Medial prefrontal cortex | 129 ± 9 | 122 ± 7 | 129 ± 8 | 117 ± 11 | 118 ± 11 | 0.8042 |
| Motor cortex | 89 ± 7 | 81 ± 3 | 98 ± 9 | 89 ± 4 | 77 ± 5 | 0.1486 |
| Somatosensory cortex I | 101 ± 8 | 95 ± 3 | 113 ± 9 | 103 ± 6 | 90 ± 5 | 0.1767 |
| Somatosensory cortex II | 114 ± 6 | 98 ± 6 | 125 ± 14 | 108 ± 10 | 93 ± 8 | 0.1257 |
| *Sensorimotor system* | | | | | | |
| Lateral geniculate nucleus | 84 ± 5 | 73 ± 4 | 86 ± 9 | 80 ± 8 | 64 ± 4 | 0.1271 |
| Medial geniculate nucleus | 101 ± 4 | 85 ± 4 | 104 ± 12 | 92 ± 9 | 61 ± 5[a,c] | 0.0017 |
| Mediodorsal nucleus, thalamus | 103 ± 4 | 89 ± 4 | 102 ± 9 | 86 ± 9 | 62 ± 4[a,b,c] | 0.0005 |
| Parafasicular nucleus | 94 ± 7 | 77 ± 3 | 86 ± 9 | 80 ± 7 | 63 ± 4[a] | 0.0276 |
| Paratenial nucleus | 86 ± 9 | 74 ± 5 | 94 ± 7 | 73 ± 9 | 60 ± 3 | 0.0302 |
| Superior colliculus | 84 ± 5 | 84 ± 3 | 84 ± 9 | 69 ± 6 | 55 ± 3[a,c] | 0.0051 |
| Ventrobasal nucleus, thalamus | 93 ± 8 | 75 ± 4 | 90 ± 7 | 69 ± 8 | 55 ± 4[a,c] | 0.0018 |

Statistics: one-way ANOVA.
[a] $p < 0.05$ compared to control group; [b] $p < 0.05$ compared to 0.1 mg kg$^{-1}$ group; [c] $p < 0.05$ compared to 0.5 mg kg$^{-1}$ group.

risperidone. It is hoped that it may help to locate the nuclei or neural circuit responsible for the treatment effect of risperidone.

## 2. Materials and methods

### 2.1. Animals

Male Sprague–Dawley rats weighing from 200 to 250 g (2 months old), were housed with three rats per cage. They were maintained under standard controlled temperatures, on a 12-h light/dark schedule. They had free access to food and water until the morning of the [$^{14}$C]2-deoxy-D-glucose experiment.

### 2.2. Drug administration

Risperidone (R 64 766, 3-{2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-pyperidinyl]ethyl}-6,7,8,9-tetrahydro-2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one, Janssen, Belgium) was dissolved in methanol. Animals were randomly divided into five treatment groups and administrated (i.p.) risperidone with the doses of 0.0 (control), 0.1, 0.5, 1.0 or 2.0 mg kg$^{-1}$. The [$^{14}$C]2-deoxy-D-glucose method was performed 15 min after the injection.

### 2.3. Local cerebral glucose utilization

The experimental procedures and analysis of LCGU were made according to the original description by Sokoloff et al. (1977). Briefly, polyethylene catheters were inserted into the femoral artery and vein of the rat under 1% halothane anesthesia. Rats were partially restrained on wooden blocks. At least 3 h were allowed for complete recovery from the effects of anesthesia. 15 min after the administration of risperidone or saline, a pulse of 100 μCi kg$^{-1}$ of 2-[$^{14}$C]deoxyglucose (New England Nuclear; specific activity = 58.0 Ci mmol$^{-1}$) was injected through the venous catheter. Sixteen timed arterial blood samples were then collected for glucose analysis during the subsequent 45 min. Then, the animals were killed by an intravenous administration of a lethal dose of sodium pentobarbital. Brains were then rapidly removed, and frozen in isopentane at −50°C. The brains were then coated with embedding medium and stored in a freezer at −70°C. Brains were sectioned into 20 μm brain slices in a cryostat. Every third section was picked up on glass coverslips, dried on a standard slide-warming tray at 65°C and then exposed along with a set of calibrated standards (Amersham, [$^{14}$C] Micro-Scales RPA 504L) on Kodak SB-5 X-ray films. Film was exposed for 10 days, and developed automatically. The resulting autoradiographs were analyzed using a computerized image-processing system (MCID, BRS2). Tissue tracer concentrations were measured by densitometry of the autoradiograms with reference to the actual polymer activity value of the calibrated standards. LCGU was calculated from brain sections, autoradiogram, plasma $^{14}$C radioactivities and plasma glucose concentrations by using the equations and constants given by Sokoloff et al. (1977).

### 2.4. Statistical analysis

Rates of local cerebral glucose utilization were measured in 38 brain areas. For each brain area, a one-way analysis of variance followed by Scheffe's multiple range test was evaluated for comparison of the means among groups. In all of the tests, the criterion for significance was set at $p < 0.05$.

## 3. Results

The effects of acute treatment with risperidone on the LCGU in rat brain were examined on 38 regions shown on Table 1. Among the 38 regions examined, significant reductions ($p < 0.05$, Scheffe's test) in LCGU as compared to those of the control group were observed in 11 regions of the highest dose (2.0 mg kg$^{-1}$) group. These regions included two in the extrapyramidal system (the globus pallidus, and the subthalamic nucleus), four in the limbic and related areas (the basomedial amygdala, the hippocampus CA1, the medial preoptic nucleus, and the auditory cortex), and five regions in the sensorimotor system (including the thalamic mediodorsal nucleus).

In the lowest dose (0.1 mg kg$^{-1}$), the rates of glucose utilization of the animals were lower than control in most of the structure surveyed. However, the difference is not statistically significant. In the 0.5 mg kg$^{-1}$ group, the LCGU generally returned to the value of the control group, and even got higher in several regions. While the dose of risperidone increased to 1.0 mg kg$^{-1}$, the LCGU values were globally reduced again.

## 4. Discussion

The [$^{14}$C]2-deoxy-D-glucose method provides a powerful mean for simultaneously surveying metabolic activity in multiple brain regions. In the present study, we have shown that highest dose (2.0 mg kg$^{-1}$) risperidone significantly ($p < 0.05$, Scheffe's test) reduced LCGU in selective cerebral nuclei.

In the extrapyramidal dopaminergic system, LCGU was significantly decreased ($p < 0.05$, Scheffe's test) in the globus pallidus but not in the striatum and the substantia nigra pars reticulata in the 2.0 mg kg$^{-1}$ group. The striatum has high density of dopaminergic receptors. However, glucose metabolism in a particular brain region is thought to reflect predominantly activity in nerve terminals as opposed to cell bodies (Kadekaro et al., 1985). Activa-

tion of either dopamine $D_1$ or dopamine $D_2$ receptors in the striatum can modify different striatal efferent pathways. In the [$^{14}$C]2-deoxy-D-glucose study, it was found that dopamine $D_1$ receptor agonist can increase LCGU in the substantia nigra pars reticulata, while dopamine $D_2$ agonist has a great effect on the LCGU in the globus pallidus (Engber et al., 1990). The binding affinity of risperidone for the dopamine $D_2$ family receptors (D2, D3, D4) was one order of magnitude lower than their affinity to serotonin 5-$HT_{2a}$ receptors (Leysen et al., 1994). Its affinity for dopamine $D_1$ receptors is weaker and is 100 times lower than that for dopamine $D_4$ receptors (Leysen et al., 1994). Thus, the risperidone-induced decrease in metabolism in the globus pallidus may represents dopamine $D_2$ blockade on the striatopallidal pathway. The subthalamic nucleus is influenced by striatal output via the globus pallidus. A significant decrease ($p < 0.05$, Scheffe's test) in glucose utilization in response to high dose risperidone in the subthalamic nucleus most likely reflects decrease activity in the pallidal–subthalamic pathway. These findings are similar to the [$^{14}$C]2-deoxy-D-glucose study in a highly selective dopamine $D_2$ receptor antagonist, raclopride (Tarazi et al., 1993).

The rate of glucose utilization in the hippocampus was significantly decreased ($p < 0.05$, Scheffe's test) in high dose risperidone, which was also found in studies using other antipsychotics (McCulloch et al., 1982; Pizzolato et al., 1987; Room et al., 1991; Colangelo et al., 1997). Although the hippocampus contains few dopaminergic receptors, its major afferent projections arise from a region, the lateral septal nucleus, which contain dopaminergic nerve terminal. Recently, a growing body of data points to structural alterations of the hippocampus in schizophrenia (Conrad and Scheibel, 1987; Scheibel and Conrad, 1993). The metabolic change in the hippocampus after risperidone administration suggested that this area is a potential region for drug action.

A major observation in this study is that high dose risperidone significantly ($p < 0.05$, Scheffe's test) decreased LCGU in the mediodorsal nucleus of the thalamus. Similar finding was also found in previous [$^{14}$C]2-deoxy-D-glucose study using haloperidol (McCulloch et al., 1982), sulpiride (Pizzolato et al., 1987), ORG 5222 (Room et al., 1991) and clozapine (Colangelo et al., 1997). This nucleus is specifically related to the limbic system and the prefrontal regions, which regulate emotional and cognitive function (Giguere and Goldman-Rakic, 1988; Jones, 1997). In addition, Carlsson (1988) has proposed that the thalamus could be looked upon as a filter for sensory inputs and this filter function may be defective in schizophrenic patients, leading to a hyperarousal state. The mediodorsal nucleus of the thalamus is the only structure in the thalamus for which a pathologic change has been demonstrated in schizophrenic patients (Pakkenberg, 1990). The decreased glucose utilization found in the mediodorsal nucleus of the thalamus in this study suggests that the antipsychotic effect of risperidone may be a response to a defect in this region. The finding reported here suggest that some of the actions of risperidone, both the improvements of negative symptoms and positive symptoms, may mediated through the mediodorsal nucleus of the thalamus. The precise mechanisms of these actions will require further study.

In this study, we found no significant LCGU change in the nucleus accumbens or the prefrontal cortex with any dose of risperidone. This lack of effects of risperidone in these regions contrast with the results of the neurochemical studies, which showed a dose-dependent increase in dopamine and serotonin metabolism (Leysen et al., 1992; Hertel et al., 1996). The discrepancy between LCGU and neurotransmitter change was also found in another study using haloperidol (Kurachi et al., 1993). The reason is open to a variety of interpretations. First, alteration in glucose utilization occurring within one neural system may be balanced by alterations of an opposite nature within another neurotransmitter system. For example, Hertel et al. (1997) have reported the enhanced serotonin output in the frontal cortex by risperidone may be related to its adrenergic $\alpha 2$ antagonistic action at the serotonin nerve terminal. The increased serotonin availability may secondarily inhibit the serotonin cell firing. The increased action by adrenergic $\alpha 2$ input and decreased serotonin input result in no change in LCGU.

Second, since the $ED_{50}$-value for dopamine $D_2$ receptor occupancy in the striatum for risperidone was 4.3 mg $kg^{-1}$, the highest dose (2.0 mg $kg^{-1}$) we used in this study may be not high enough to cause metabolic change in these regions (Schotte et al., 1996). Finally, the failure to observe changes in metabolic rate not necessary indicates non-involvement of this structure but may reflect the limited resolution of the technique itself or heterogeneity in the regions. Problems such as these may only be resolved when the LCGU is examined with finer resolution.

In summary, risperidone in high dose significantly decreased LCGU in selected regions of the rat brain, including the hippocampus and the mediodorsal nucleus of the thalamus. The precise effect of risperidone in these regions will require further study.

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