

# Effects of Anesthesia and Recovery from Ketamine Racemate and Enantiomers on Regional Cerebral Glucose Metabolism in Rats

Ulderico Freo, M.D.,\* Carlo Ori, M.D.†

**Background:** Unlike most anesthetics, ketamine racemate ( $S,R(\pm)$ -ketamine) induces heterogeneous changes in cerebral metabolism.  $S,R(\pm)$ -ketamine is an equimolar mixture of two enantiomers,  $S(+)$ -ketamine and  $R(-)$ -ketamine, which differ in affinity for neuroreceptors and pharmacologic activities. This study investigated comparatively the effects of ketamine racemate and enantiomers on cerebral metabolism.

**Methods:** Regional cerebral metabolic rates for glucose (rCMRglc) were determined with the quantitative, autoradiographic [ $^{14}\text{C}$ ]2-deoxy-D-glucose technique in 40 brain regions of Fischer-344 rats. rCMRglc were measured in three groups of rats during equimolar anesthesia, 10 min after intraperitoneal injection of 170 mg/kg  $S,R(\pm)$ -ketamine,  $S(+)$ -ketamine, or  $R(-)$ -ketamine; in three groups of rats during recovery from equivalent anesthesia, 20 min after intravenous injection of 20, 12.5, and 30 mg/kg  $S,R(\pm)$ -ketamine,  $S(+)$ -ketamine, or  $R(-)$ -ketamine; and in two groups of saline-injected control rats.

**Results:**  $S,R(\pm)$ -ketamine and  $S(+)$ -ketamine induced a sustained anesthesia; deep rCMRglc decreases in 22 and 14 cortical, thalamic, cerebellar, and brainstem regions; and rCMRglc increases in two limbic regions (average decreases, 23 and 15%).  $R(-)$ -ketamine determined a shorter anesthesia, lesser rCMRglc decreases in 11 brain areas, and marked rCMRglc increases in 14 basal ganglia and limbic regions (average decrease, 4%).  $S,R(\pm)$ -ketamine,  $S(+)$ -ketamine, and  $R(-)$ -ketamine all produced postanesthetic behavioral activation; widespread rCMRglc increases in 28, 16, and 20 cortical, thalamic, basal ganglia, limbic, and brainstem regions; and rCMRglc decreases in few auditory and limbic regions (average increases, 35, 13, and 20%).

**Conclusions:**  $S,R(\pm)$ -ketamine and  $S(+)$ -ketamine anesthesia but not  $R(-)$ -ketamine anesthesia induced widespread rCMRglc reductions that were unreported but are typical of gaseous and intravenous general anesthetics. Postanesthetic recovery led to divergent, sharp behavioral and rCMRglc activations. The relation to dose of behavioral and rCMRglc effects differs from those of aminergic agents and resembles those of *N*-methyl-D-aspartate receptor antagonists, suggesting that ketamine racemate and enantiomers may preferentially interact with this receptor type.

AMONG anesthetics, ketamine is a dissociative agent uniquely featured by low cardiovascular and respiratory depression and a good analgesia but also by postanesthetic psychotomimetic effects.<sup>1,2</sup> Also, in contrast to the diffuse cerebral metabolic depression typically in-

duced by general anesthetics,<sup>3-6</sup> ketamine determines both cerebral metabolic decreases and increases in the anesthetic phase<sup>7-10</sup> and sharp cerebral metabolic increases in the following recovery phase.<sup>9</sup> The discrepant activating features of ketamine have in the past led some authors to hypothesize that ketamine acts as an "excitatory anesthetic"<sup>9,11</sup> but may actually be caused by an insufficient level of anesthesia or inappropriate timing when measuring cerebral metabolism. Further, ketamine has long been used in clinical settings as an equimolar, racemic mixture ( $S,R(\pm)$ -ketamine) of two enantiomers,  $S(+)$ -ketamine and  $R(-)$ -ketamine, which have different pharmacologic profiles.  $S(+)$ -ketamine is several-fold more effective as an analgesic and anesthetic than both  $S,R(\pm)$ -ketamine and  $R(-)$ -ketamine.<sup>1,12,13</sup>  $S(+)$ -ketamine is also more potent in binding to *N*-methyl-D-aspartate (NMDA)<sup>14</sup> and opioid receptors,<sup>15</sup> blocking NMDA- and acetylcholine-induced neuronal currents<sup>16</sup> and increasing dopamine release<sup>17</sup> and opioid analgesia.<sup>18</sup>  $S(+)$ -ketamine is instead equipotent with  $R(-)$ -ketamine in inhibiting muscarinic<sup>19</sup> and nicotinic receptors<sup>20</sup> and substituting phencyclidine drug stimulus<sup>21</sup> and is less potent than  $R(-)$ -ketamine in binding to sigma receptors,<sup>14</sup> inhibiting acetylcholinesterase,<sup>22</sup> and activating motor behavior.<sup>13</sup> Hence, doses, timing of administration, and pharmacology of ketamine enantiomers are all relevant for  $S,R(\pm)$ -ketamine cerebral metabolic effects.

The autoradiographic [ $^{14}\text{C}$ ]2-deoxy-D-glucose technique allows mapping of the regional cerebral metabolic rates for glucose (rCMRglc), a direct index of neuronal function.<sup>23,24</sup> rCMRglc measures have been used to characterize and compare neuroactive agents acting on neurotransmitter systems<sup>25-27</sup> and general anesthetics.<sup>6</sup> The aim of this study was to determine the patterns of rCMRglc during sustained anesthesia and during recovery from equivalent anesthesia with ketamine racemate and enantiomers and to compare them with those of known neurotransmitter agents and general anesthetics.

## Materials and Methods

### Materials

Experiments were performed in 3- to 4-month-old (average weight, 225-275 g) male Fisher-344 rats (Charles River Italia, Como, Italy). The study was conducted according to a protocol approved by the Animal Care Committee of the Anesthesiology Department of Padova

\* Assistant Professor, † Professor.

Received from the Department of Pharmacology and Anesthesiology, Padova University, Padova, Italy. Submitted for publication July 9, 2003. Accepted for publication November 21, 2003. Support was provided solely from institutional and/or departmental sources. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Dallas, Texas, October 9-13, 1999.

Address reprint requests to Dr. Freo: Divisione di Neurologia, Ospedale Civile, Via Ospedale, Castelfranco Veneto, Treviso, Italy. Address electronic mail to: ulderico.freo@libero.it. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

University (Italy) and the guidelines for animal care of the National Institutes of Health.<sup>28</sup>

[<sup>14</sup>C]2-deoxy-D-glucose (specific activity, 50–55 mCi/mmol) was purchased from Amersham International (Arlington Heights, IL). Ketamine racemate and enantiomers were kindly provided by Parke Davis (Freiburg, Germany) and were dissolved in saline (1 ml/kg body weight).

#### *Drug Dose Finding and Treatment*

Drug doses, timing, and routes of administration for the [<sup>14</sup>C]2-deoxy-D-glucose study were chosen on the base of preliminary behavioral studies. To study rCMRglc during anesthesia, doses of ketamine racemate and enantiomers were sought that ensured a deep anesthesia for the entire duration of the [<sup>14</sup>C]2-deoxy-D-glucose experiment, *i.e.*, 50 min, and prevented confounding from postanesthetic behavioral activation. To study rCMRglc during recovery from anesthesia, doses of ketamine racemate and enantiomers were sought that induced an anesthesia of similar duration and minimized potential confounding from different anesthetic potencies. The righting reflex was used as an index of duration of anesthesia.<sup>12,29</sup> A single observer evaluated reflex changes after intraperitoneal (dose range, 80–170 mg/kg) or intravenous (dose range, 10–100 mg/kg) administration of ketamine to separate groups of four rats each. After drug injection, rats were positioned in a dorsal recumbent position every minute or until the righting reflex was lost, *i.e.*, the animals remained in the recumbent position for at least 30 s; animals were then observed until the righting reflex was regained, *i.e.*, animals returned to their normal prone position. Times elapsing from drug administration to loss and to regaining of the righting reflex were recorded and considered as the onset and end of anesthesia. The lowest dose of the least active agent, *i.e.*, *R*(–)-ketamine, that was required for the anesthesia to endure for the [<sup>14</sup>C]2-deoxy-D-glucose experiment corresponded to an intraperitoneal dose of 170 mg/kg. Such an anesthesia could not be achieved by bolus intravenous injection of ketamine without significant toxicity. An anesthesia of similar duration was instead obtained most reliably (*i.e.*, least intergroup variations) with intravenous doses. Hence, to study rCMRglc during recovery, we chose doses of 20, 12.5, and 30 mg/kg *S,R*(±)-ketamine, *S*(+)-ketamine, or *R*(–)-ketamine, which had also been used in previous behavioral studies.<sup>29</sup>

In the pilot study, after an intraperitoneal equimolar dose of 170 mg/kg *S,R*(±)-ketamine, *S*(+)-ketamine, or *R*(–)-ketamine, rats became rapidly anesthetized and remained so for 106 ± 9, 111 ± 10, and 57 ± 5 min (mean ± SD); anesthesia by *R*(–)-ketamine was significantly ( $P < 0.01$ ) shorter than by congeners but exceeded the duration of the [<sup>14</sup>C]2-deoxy-D-glucose experiment. After equianesthetic doses of 20, 12.5, and

30 mg/kg *S,R*(±)-ketamine, *S*(+)-ketamine, and *R*(–)-ketamine, rats were anesthetized for 12 ± 2, 11 ± 3, and 10 ± 3 min (mean ± SD) but were fully awake by 20 min. Hence, anesthesia times from the pilot study indicated that *S,R*(±)-ketamine, *S*(+)-ketamine, and *R*(–)-ketamine differed in anesthetic potency with a ratio that was approximately 2:1.2:3 at low doses and approached to 2:2:1 at higher doses. At the end of anesthesia, *S,R*(±)-ketamine- and *R*(–)-ketamine-treated rats presented ataxia, hyperreactivity to sensory stimuli (*i.e.*, noise and touch), and intense stereotyped movements (not quantified); *S*(+)-ketamine-treated rats were awake but not agitated.

In the rCMRglc study, four groups of rats were injected intraperitoneally with saline or 170 mg/kg *S,R*(±)-ketamine, *S*(+)-ketamine, or *R*(–)-ketamine, 10 min before [<sup>14</sup>C]2-deoxy-D-glucose, and four groups of rats were injected intravenously with saline or 20, 12.5, or 30 mg/kg *S,R*(±)-ketamine, *S*(+)-ketamine, or *R*(–)-ketamine, 20 min before [<sup>14</sup>C]2-deoxy-D-glucose.

#### *[<sup>14</sup>C]2-deoxy-D-glucose Study*

Rats were allowed free access to water until the day of the experiment, and food was withheld the night before to provide steady plasma glucose concentration. Under 1.5% isoflurane anesthesia, polyethylene catheters (PE-50) were introduced into a femoral artery (for blood pressure measurements and collection of arterial blood samples) and a vein (for injection of drug and of the isotope). The incision site was infiltrated with 0.2 ml bupivacaine hydrochloride, 0.25%. Then, a loose-fitting plaster cast was applied around the lower abdomen, and the rats were allowed to recover for 3 h in a temperature-controlled, sound-insulated wooden box.

Throughout the experimental period, arterial blood pressure and heart rate were measured by connecting the arterial catheter with a pressure transducer, and body temperature was measured with a rectal thermoprobe; both were connected to a monitor (model PM-2A; Honeywell, Minneapolis, MN). Arterial oxygen tension (P<sub>aO<sub>2</sub></sub>) and arterial carbon dioxide tension (P<sub>aCO<sub>2</sub></sub>) were determined before and 40 min after [<sup>14</sup>C]2-deoxy-D-glucose administration. A thermostatic device activated an ambient heating element when body temperature decreased below 35.5°C. rCMRglc was quantitatively determined as described previously. Briefly, a bolus of 125 μCi/kg [<sup>14</sup>C]2-deoxy-D-glucose was injected. Timed arterial samples were drawn to measure plasma glucose (Glucose Analyzer II; Beckman Instruments, Fullerton, CA) and [<sup>14</sup>C]2-deoxy-D-glucose concentrations (Liquid Scintillation Spectrometer model B2450; Packard, Downers Grove, IL). At the end of the 45-min period, the rats were killed by an overdose of thiopental, and the brains were removed, frozen in isopentane at –50°C, and cut in a cryostat (Cryocut E; Reichert-Jung, Heidelberg, Germany) maintained at –22°C. Coronal sections (20 μm

thick) were exposed to Kodak SB-5 films (Eastman Kodak Company, Rochester, MN) for 7 days, together with a set of precalibrated  $^{14}\text{C}$ -methacrylate standards (Amersham International). Local tissue  $^{14}\text{C}$  concentrations were determined in 40 brain regions using a computer-based densitometer (BRS2 System; MCID, Ontario, Canada) comparing the optical densities of the autoradiographic sections with those of the calibrated [ $^{14}\text{C}$ ]2-deoxy-D-glucose standards. Twelve determinations were made for each region in the left and right sides of the brain, and the means were averaged. Mean rCMRglc values from all brain regions investigated were calculated. Each anatomic brain region evaluated was defined by comparison with an atlas of the rat brain.<sup>30</sup> rCMRglc values were calculated from brain and plasma radioactivities and plasma glucose concentrations according to equations and constants given by Sokoloff *et al.*<sup>23,24</sup>

### Statistical Analysis

Data were analyzed for statistical significance by one-way analysis of variance and the Bonferroni multiple comparison test. Mean values of physiologic parameters and rCMRglc of each ketamine-treated group were compared with controls; the mean times of ketamine enantiomer anesthesia were compared with those of  $S,R(\pm)$ -ketamine anesthesia. Statistical significance was taken in all cases as  $P < 0.01$ .

## Results

### Physiologic Parameters

In comparison with control rats,  $R(-)$ -ketamine anesthesia increased heart rate significantly ( $P < 0.01$ ) by 3 min (*i.e.*,  $440 \pm 6$  beats/min, +18%) and decreased heart rate and mean arterial blood pressure by 12 min (*i.e.*, 263 beats/min, -28%; 91 mmHg, -19%) and 30 min (*i.e.*, 272 beats/min, -27%; 82 mmHg, -18%) after [ $^{14}\text{C}$ ]2-deoxy-D-glucose administration. During recovery from  $S,R(\pm)$ -ketamine,  $S(+)$ -ketamine, and  $R(-)$ -ketamine, arterial blood pressure increased significantly ( $P < 0.01$ ) by 3 min (*i.e.*, 154, 156, and 146 mmHg; +26, 27, and 21%) and 12 min (*i.e.*, 140, 135, and 133 mmHg; +24, 19, and 18%) after [ $^{14}\text{C}$ ]2-deoxy-D-glucose administration. Reportedly, ketamine has predominant stimulatory effects on cardiovascular parameters<sup>1,6</sup> that were apparent in this study during recovery; when a deeper anesthesia is achieved, however, cardiovascular parameters are more commonly depressed.<sup>6</sup>

### Regional Cerebral Metabolic Rates for Glucose

$S,R(\pm)$ -ketamine and  $S(+)$ -ketamine anesthesia significantly ( $P < 0.01$ ) decreased rCMRglc in 22 and 14 brain areas (average reductions, 23 and 15%) and increased rCMRglc in two limbic regions (table 1).  $R(-)$ -ketamine anesthesia decreased rCMRglc in 11 and increased

rCMRglc in 14 brain regions (average decrease, 4%) (fig. 1). Ketamine racemate and enantiomer anesthetics all decreased rCMRglc in the sensorimotor and auditory cortices, the superior and inferior colliculi, the interpositus, the cochlear and vestibular nuclei, the medial and lateral habenula, the median raphe, and the mesencephalic reticular formation; in addition, anesthesia with  $S,R(\pm)$ -ketamine and  $S(+)$ -ketamine decreased rCMRglc in the frontal, visual, and posterior cingulate cortices; anesthesia with  $S,R(\pm)$ -ketamine and with  $R(-)$ -ketamine decreased rCMRglc in the cerebellar vermis; anesthesia with  $S,R(\pm)$ -ketamine decreased rCMRglc in the mediodorsal thalamic nucleus, the medial and lateral geniculate nuclei, the substantia nigra and the subthalamic nucleus, the anterior cingulate cortices, and the locus ceruleus; anesthesia with  $S(+)$ -ketamine decreased rCMRglc in the interpeduncular nucleus; and anesthesia with  $R(-)$ -ketamine decreased rCMRglc in the pontine reticular formation (fig. 2). Ketamine racemate and enantiomer anesthetics all increased rCMRglc in the dentate gyrus;  $S,R(\pm)$ -ketamine anesthesia increased rCMRglc in the fasciculus retroflexus;  $S(+)$ -ketamine anesthesia increased rCMRglc in the lateral septum; and  $R(-)$ -ketamine anesthesia increased rCMRglc in the basal ganglia (*i.e.*, caudate-putamen and globus pallidus nuclei) and the limbic regions (*i.e.*, accumbens nucleus, anterior cingulate and entorhinal cortices, presubicular and hippocampal fields, and lateral amygdala).

Postanesthetic recovery from  $S,R(\pm)$ -ketamine,  $S(+)$ -ketamine, and  $R(-)$ -ketamine anesthesia increased rCMRglc significantly ( $P < 0.01$ ) in 28, 16, and 20 cortical, basal ganglia, limbic, and brainstem regions (average increases, 35, 13, and 20%). In addition, recovery from  $S,R(\pm)$ -ketamine decreased rCMRglc in 1 brain region (*i.e.*, inferior colliculus), recovery from  $S(+)$ -ketamine decreased in 6 brain regions (*i.e.*, inferior colliculus, medial geniculate and auditory cortex, posterior cingulate cortex and habenular nuclei), and recovery from  $R(-)$ -ketamine decreased in 5 brain regions (*i.e.*, sensorimotor cortex, medial geniculate and inferior colliculus, globus pallidus and posterior cingulate cortex) (fig. 2).

## Discussion

Ketamine anesthesia decreased and postanesthetic recovery increased rCMRglc.  $S,R(\pm)$ -ketamine and  $S(+)$ -ketamine determined deep anesthesia and rCMRglc depression, and  $S,R(\pm)$ -ketamine and  $R(-)$ -ketamine determined large postanesthetic rCMRglc activations.

Until now, ketamine anesthesia had induced a pattern of cerebral metabolic decreases in few sensory areas and large metabolic increases in basal ganglia and limbic regions.<sup>3,8-10</sup> Such findings on ketamine were in contrast with reports of diffuse cerebral hypometabolism



**Table 1. Regional Cerebral Metabolic Rates for Glucose during Anesthesia with and Recovery from ( $\pm$ )-ketamine, *S*( $\pm$ )-ketamine, or *R*(-)-ketamine**

Brain Region	Anesthesia				Recovery			
	Saline	170 mg/kg <i>S,R</i> ( $\pm$ )-ketamine	170 mg/kg <i>S</i> (-)-ketamine	170 mg/kg <i>R</i> (-)-ketamine	Saline	20 mg/kg <i>S,R</i> ( $\pm$ )-ketamine	12.5 mg/kg <i>S</i> (-)-ketamine	30 mg/kg <i>R</i> (-)-ketamine
<b>Cortical regions</b>								
Frontal	87 $\pm$ 4	54 $\pm$ 4*	56 $\pm$ 4*	98 $\pm$ 4*	90 $\pm$ 6	111 $\pm$ 6*	91 $\pm$ 4	94 $\pm$ 6
Sensorimotor	89 $\pm$ 2	56 $\pm$ 4*	49 $\pm$ 4*	58 $\pm$ 4*	91 $\pm$ 8	112 $\pm$ 6*	82 $\pm$ 6	75 $\pm$ 4*
Auditory	120 $\pm$ 12	81 $\pm$ 4*	72 $\pm$ 4*	97 $\pm$ 10	130 $\pm$ 8	118 $\pm$ 8	101 $\pm$ 4*	109 $\pm$ 6
Visual	87 $\pm$ 6	61 $\pm$ 2*	75 $\pm$ 4	82 $\pm$ 6	90 $\pm$ 6	119 $\pm$ 12*	104 $\pm$ 6	105 $\pm$ 6
Entorhinal	61 $\pm$ 4	66 $\pm$ 6	69 $\pm$ 8	85 $\pm$ 4*	64 $\pm$ 6	70 $\pm$ 6	80 $\pm$ 6*	80 $\pm$ 4*
<b>Cingulate</b>								
Anterior	90 $\pm$ 8	62 $\pm$ 4*	82 $\pm$ 8	109 $\pm$ 8	92 $\pm$ 7	126 $\pm$ 8*	104 $\pm$ 4	111 $\pm$ 6*
Posterior	74 $\pm$ 6	31 $\pm$ 2*	65 $\pm$ 2	81 $\pm$ 4	77 $\pm$ 4	132 $\pm$ 3*	58 $\pm$ 4*	60 $\pm$ 6*
<b>Limbic regions</b>								
<b>Hippocampus</b>								
(pyramidal layer)								
<b>Dorsal</b>								
CA1	42 $\pm$ 2	48 $\pm$ 4	44 $\pm$ 2	45 $\pm$ 6	39 $\pm$ 4	53 $\pm$ 4	60 $\pm$ 8*	81 $\pm$ 6*
CA3	50 $\pm$ 4	58 $\pm$ 4	57 $\pm$ 4	61 $\pm$ 4*	48 $\pm$ 6	75 $\pm$ 4*	64 $\pm$ 6*	70 $\pm$ 6*
Dentate	47 $\pm$ 4	60 $\pm$ 6*	57 $\pm$ 3*	67 $\pm$ 8*	45 $\pm$ 6	78 $\pm$ 4*	66 $\pm$ 4*	87 $\pm$ 8*
Presubiculum	57 $\pm$ 4	49 $\pm$ 4	62 $\pm$ 6	71 $\pm$ 4*	55 $\pm$ 6	112 $\pm$ 10*	81 $\pm$ 4*	76 $\pm$ 4*
Lateral amygdala	68 $\pm$ 6	58 $\pm$ 4	70 $\pm$ 6	98 $\pm$ 4*	66 $\pm$ 4	96 $\pm$ 6*	90 $\pm$ 4*	95 $\pm$ 10*
Fasciculus retroflexus	47 $\pm$ 4	58 $\pm$ 4*	47 $\pm$ 6	56 $\pm$ 6	40 $\pm$ 4	88 $\pm$ 6*	47 $\pm$ 4	48 $\pm$ 6
Lateral septum	31 $\pm$ 1	38 $\pm$ 4	39 $\pm$ 4*	32 $\pm$ 4	29 $\pm$ 2	41 $\pm$ 4*	33 $\pm$ 4	31 $\pm$ 4
Interpeduncular nucleus	42 $\pm$ 4	37 $\pm$ 2	34 $\pm$ 4*	37 $\pm$ 4	40 $\pm$ 2	52 $\pm$ 4*	54 $\pm$ 4*	59 $\pm$ 6*
Mammillary bodies	96 $\pm$ 4	88 $\pm$ 4	109 $\pm$ 6	105 $\pm$ 14	92 $\pm$ 6	144 $\pm$ 14*	111 $\pm$ 8	108 $\pm$ 6
<b>Thalamus and subthalamus</b>								
<b>Thalamus</b>								
Mediodorsal nucleus	83 $\pm$ 4	68 $\pm$ 4*	94 $\pm$ 6	102 $\pm$ 6*	82 $\pm$ 4	132 $\pm$ 10*	100 $\pm$ 6*	112 $\pm$ 4*
Anteroventral nucleus	82 $\pm$ 4	86 $\pm$ 6	90 $\pm$ 6	114 $\pm$ 12*	81 $\pm$ 4	77 $\pm$ 10	88 $\pm$ 4	83 $\pm$ 8
Ventroposteromedial nucleus	83 $\pm$ 4	60 $\pm$ 4	84 $\pm$ 6	93 $\pm$ 6	81 $\pm$ 4	118 $\pm$ 4*	96 $\pm$ 4*	104 $\pm$ 8*
<b>Lateral habenula</b>								
Lateral nucleus	114 $\pm$ 10	56 $\pm$ 6*	57 $\pm$ 6*	63 $\pm$ 2*	116 $\pm$ 6	105 $\pm$ 6	92 $\pm$ 6*	110 $\pm$ 6
Medial nucleus	87 $\pm$ 8	56 $\pm$ 4*	53 $\pm$ 2*	55 $\pm$ 4*	95 $\pm$ 8	86 $\pm$ 2	73 $\pm$ 6*	95 $\pm$ 4
Lateral geniculate nucleus	73 $\pm$ 4	56 $\pm$ 4*	71 $\pm$ 4	83 $\pm$ 6	75 $\pm$ 6	113 $\pm$ 8*	89 $\pm$ 10	106 $\pm$ 8*
Medial geniculate nucleus	105 $\pm$ 3	68 $\pm$ 4*	93 $\pm$ 10	114 $\pm$ 16	110 $\pm$ 8	101 $\pm$ 6	84 $\pm$ 6*	93 $\pm$ 6*
Subthalamic nucleus	70 $\pm$ 6	51 $\pm$ 6*	59 $\pm$ 6	71 $\pm$ 8	66 $\pm$ 6	102 $\pm$ 6*	92 $\pm$ 6*	103 $\pm$ 8*
<b>Basal ganglia</b>								
Caudate-putamen nucleus	82 $\pm$ 6	76 $\pm$ 4	85 $\pm$ 10	101 $\pm$ 8*	79 $\pm$ 4	120 $\pm$ 6*	100 $\pm$ 4*	108 $\pm$ 8*
Globus pallidus nucleus	42 $\pm$ 4	48 $\pm$ 4	37 $\pm$ 4	56 $\pm$ 4*	39 $\pm$ 8	84 $\pm$ 4*	36 $\pm$ 4	24 $\pm$ 4*
Accumbens nucleus	62 $\pm$ 4	70 $\pm$ 6	75 $\pm$ 6	97 $\pm$ 12*	60 $\pm$ 1	105 $\pm$ 10*	83 $\pm$ 8*	89 $\pm$ 8*
<b>Brainstem and cerebellum</b>								
Superior colliculus	63 $\pm$ 4	48 $\pm$ 4*	50 $\pm$ 4*	51 $\pm$ 4*	60 $\pm$ 6	74 $\pm$ 4*	77 $\pm$ 6*	82 $\pm$ 4*
Inferior colliculus	177 $\pm$ 12	72 $\pm$ 4*	84 $\pm$ 8*	82 $\pm$ 8*	169 $\pm$ 8	133 $\pm$ 10*	132 $\pm$ 6*	148 $\pm$ 12
<b>Substantia nigra</b>								
Pars reticulata	38 $\pm$ 4	31 $\pm$ 2	36 $\pm$ 2	48 $\pm$ 4*	32 $\pm$ 8	66 $\pm$ 6*	55 $\pm$ 4*	50 $\pm$ 4*
Pars compacta	59 $\pm$ 2	47 $\pm$ 2*	61 $\pm$ 4	73 $\pm$ 6*	55 $\pm$ 4	93 $\pm$ 8*	75 $\pm$ 6*	71 $\pm$ 4*
Dorsal cochlear nucleus	73 $\pm$ 6	49 $\pm$ 4*	61 $\pm$ 4*	57 $\pm$ 8	70 $\pm$ 8	78 $\pm$ 6	79 $\pm$ 8	86 $\pm$ 6
Medial vestibular nucleus	91 $\pm$ 8	54 $\pm$ 2*	69 $\pm$ 8*	62 $\pm$ 6*	90 $\pm$ 4	107 $\pm$ 6*	87 $\pm$ 4	93 $\pm$ 4
Red nucleus	61 $\pm$ 4	57 $\pm$ 4	53 $\pm$ 6	54 $\pm$ 4	61 $\pm$ 8	94 $\pm$ 8*	67 $\pm$ 4	79 $\pm$ 6*
<b>Reticular formation</b>								
Mesencephalic	53 $\pm$ 2	35 $\pm$ 2*	36 $\pm$ 2*	41 $\pm$ 4*	51 $\pm$ 4	68 $\pm$ 2*	54 $\pm$ 2	61 $\pm$ 4*
Pontine	47 $\pm$ 4	42 $\pm$ 4	43 $\pm$ 6	37 $\pm$ 2*	47 $\pm$ 2	58 $\pm$ 2*	50 $\pm$ 4	52 $\pm$ 2
Median raphe nucleus	83 $\pm$ 4	45 $\pm$ 4*	48 $\pm$ 6*	55 $\pm$ 6*	81 $\pm$ 4	76 $\pm$ 4	77 $\pm$ 8	75 $\pm$ 4
Locus ceruleus nucleus	36 $\pm$ 4	23 $\pm$ 2*	31 $\pm$ 4	29 $\pm$ 4	32 $\pm$ 6	44 $\pm$ 2*	46 $\pm$ 4*	54 $\pm$ 2*
Interpositus nucleus	90 $\pm$ 8	71 $\pm$ 2*	69 $\pm$ 6*	73 $\pm$ 6*	91 $\pm$ 8	87 $\pm$ 8	84 $\pm$ 8	84 $\pm$ 8
Vermis	56 $\pm$ 6	44 $\pm$ 4*	45 $\pm$ 4	41 $\pm$ 4*	53 $\pm$ 6	62 $\pm$ 4	56 $\pm$ 4	64 $\pm$ 6
Mean of above	73 $\pm$ 4	56 $\pm$ 6*	62 $\pm$ 4*	70 $\pm$ 6	69 $\pm$ 6	93 $\pm$ 4*	78 $\pm$ 4*	83 $\pm$ 6*

Data are presented as mean value of regional cerebral metabolic rates for glucose  $\pm$  SD ( $\mu\text{mol} \cdot 100 \text{g}^{-1} \cdot \text{min}^{-1}$ ) for groups of six animals. Drug or saline was injected intraperitoneally 10 and 20 min before [ $^{14}\text{C}$ ]2-deoxy-D-glucose in the anesthesia study and in the recovery study. Columns 2–4 compared with column 1, columns 6–8 compared with column 5.

\* Significantly different from controls (Bonferroni test),  $P < 0.01$ .

during general anesthesia by intravenous or gaseous anesthetics.<sup>2,4–6</sup> Cerebral hypometabolism, however, attenuates during postanesthetic recovery in the case of most anesthetics but reverses into a marked cerebral

hypermetabolism in the case of ketamine.<sup>9</sup> Therefore, a possible cerebral hypometabolism during ketamine anesthesia could have been overshadowed by metabolic activation of an initial recovery whose onset is a critical

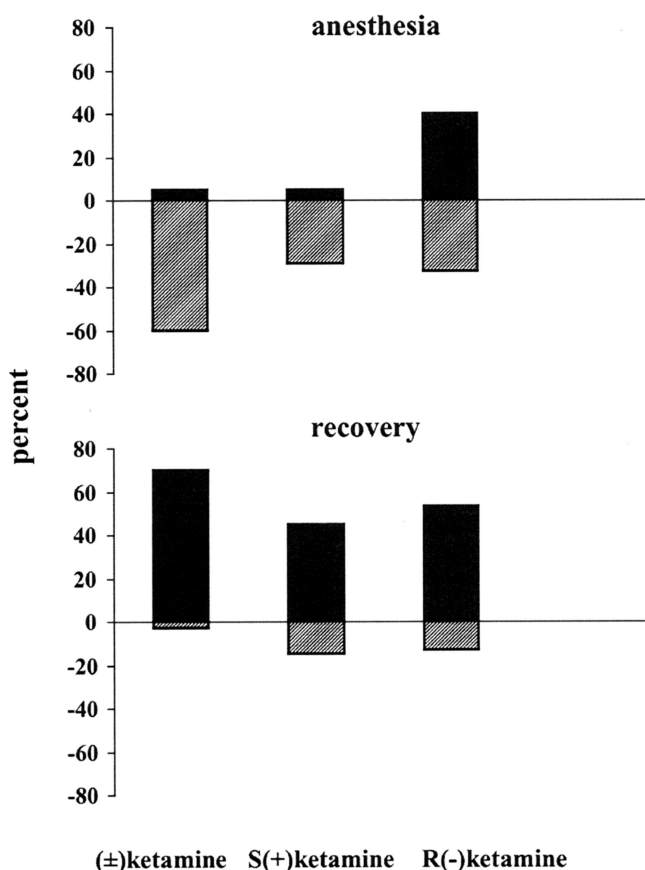


Fig. 1. Effects of anesthesia with (*top*) and recovery from (*bottom*)  $S,R(\pm)$ -ketamine,  $S(+)$ -ketamine, and  $R(-)$ -ketamine on regional cerebral metabolic rate for glucose. Regional cerebral metabolic rate for glucose was measured while rats were anesthetized with equimolar doses or were recovering from equianesthetic doses. Bars indicate the percentage of regions in which regional cerebral metabolic rate for glucose was significantly ( $P < 0.01$ ) increased (*solid*) and decreased (*hatched*).

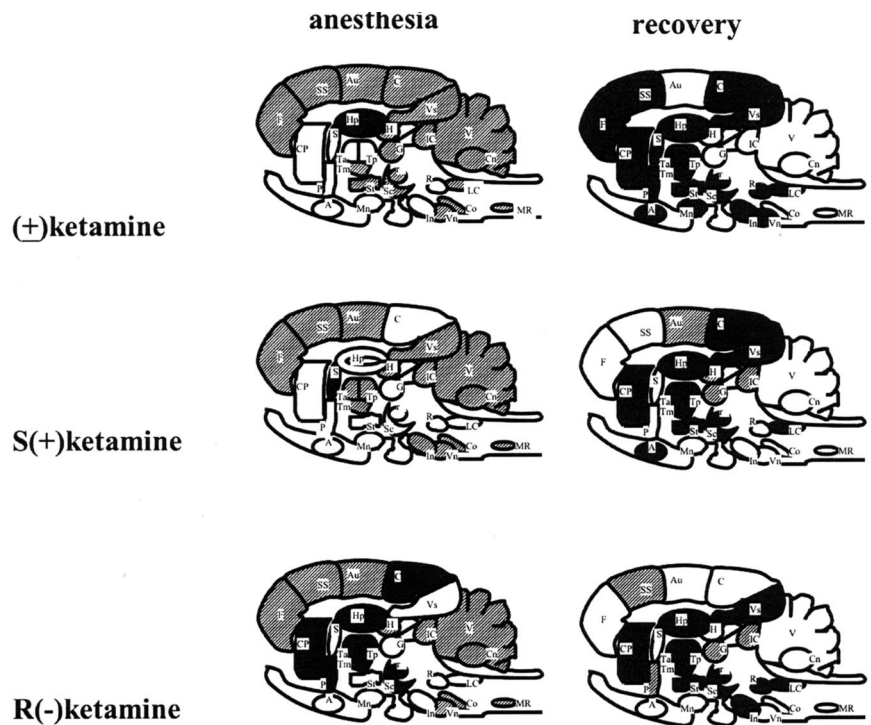
methodologic issue when ketamine anesthesia is being studied. Duration and depth of ketamine anesthesia are dose dependent,<sup>7-9</sup> and in previous studies, ketamine doses may have been barely sufficient or insufficient to ensure an anesthetic state for the entire [<sup>14</sup>C]2-deoxy-D-glucose experiment.<sup>7-9</sup> In this study, large doses of  $S,R(\pm)$ -ketamine induced a long-lasting anesthesia and widespread rCMRglc decreases in the neocortical, sensory thalamic, and brainstem regions and rCMRglc increases in the dorsal hippocampus. This rCMRglc pattern is consistent with animal and human reports of diffuse rCMRglc decreases and few rCMRglc increases during intravenous or gaseous anesthesia.<sup>3-5</sup> Specifically, benzodiazepine and propofol anesthesia determined rCMRglc decreases only.<sup>5,6,10</sup> Barbiturate and halogenated gas anesthesia determined widespread rCMRglc decreases but also rCMRglc sparing or increase in few brain regions (*i.e.*, hippocampal regions, habenulo-interpeduncular and brainstem nuclei).<sup>3,4,6</sup> Hence, rCMRglc increases in limbic regions have not been observed universally during general anesthesia and likely reflect the

property of some anesthetics,<sup>6</sup> including ketamine,<sup>2</sup> of increasing electrical activity of hippocampal neurons.

$S(+)$ -ketamine anesthesia decreased cerebral metabolism to a larger extent than  $R(-)$ -ketamine but less than  $S,R(\pm)$ -ketamine anesthesia. Because  $S(+)$ -ketamine is known to be approximately twofold to fivefold more potent as an anesthetic than both  $R(-)$ -ketamine and  $S,R(\pm)$ -ketamine,<sup>12</sup> the first finding was expected, but the latter was less so.  $S(+)$ -ketamine is cleared from the bloodstream at the same<sup>29</sup> or higher<sup>31</sup> rates than  $R(-)$ -ketamine; therefore, larger rCMRglc decreases by  $S(+)$ -ketamine anesthesia do not depend on kinetic factors. In addition, we chose a high dose that ensured  $R(-)$ -ketamine anesthesia to last for the entire [<sup>14</sup>C]2-deoxy-D-glucose experimental without the confounding of recovery. To do so, however, we used a behavioral indicator (*i.e.*, loss of righting reflex) that may not adequately inform of anesthetic depth. In spite of an apparently identical anesthetic state, in fact,  $R(-)$ -ketamine anesthesia slowed electroencephalographic activity to a substantially lesser degree than  $S,R(\pm)$ -ketamine and  $S(+)$ -ketamine anesthesia in animals<sup>13</sup> and humans.<sup>2</sup> Consistently, our study indicates that  $R(-)$ -ketamine anesthesia does not reach the marked and widespread rCMRglc depression that is typical of more potent general anesthetics<sup>3-6</sup> and congeners. In contrast and unexpectedly,  $S(+)$ -ketamine anesthesia determined smaller rCMRglc decreases than  $S,R(\pm)$ -ketamine, which is supposedly less potent and is being used clinically in larger doses.<sup>1</sup> Data in the literature, however, are not completely consistent with this notion. In rat behavioral studies,  $S(+)$ -ketamine was more potent as an anesthetic at low-intermediate doses (*i.e.*, below 60 mg/kg)<sup>12,29</sup> but equivalent with  $S,R(\pm)$ -ketamine at doses higher than 80 mg/kg.<sup>12</sup> Similarly, in our dose-finding study,  $S(+)$ -ketamine anesthesia had a longer duration than  $S,R(\pm)$ -ketamine anesthesia at low doses but a similar duration at higher doses. Further, in neurophysiologic studies,  $S(+)$ -ketamine was equipotent with  $S,R(\pm)$ -ketamine in slowing electroencephalographic activity in cats<sup>12</sup> and was stronger<sup>32</sup> or equivalent<sup>33</sup> with  $S,R(\pm)$ -ketamine in humans. Hence, the current data suggest that the anesthetic potency ratio between  $S(+)$ -ketamine and  $S,R(\pm)$ -ketamine is probably not linear and that, at high doses,  $S(+)$ -ketamine may be equivalent with or even weaker than  $S,R(\pm)$ -ketamine.

Postanesthetic recovery from ketamine racemate and enantiomers determined dramatic rCMRglc increases in most neocortical, thalamic, limbic, and basal ganglia regions and rCMRglc sparing or decrease in few areas. Patterns of rCMRglc during postanesthetic recovery from ketamine are virtually indistinguishable from those of low-dose ketamine<sup>6,8,9</sup> or subanesthetic phencyclidine and MK801,<sup>34</sup> two other noncompetitive NMDA antagonists, and suggest that they all may depend on low NMDA antagonistic activity. Intriguingly, postanesthetic

Fig. 2. Schematic representation of brain regions in which anesthesia with (*left*) and recovery from (*right*) *S,R*(±)-ketamine, *S*(+)-ketamine and *R*(-)-ketamine significantly altered ( $P < 0.01$ ) regional cerebral metabolic rate for glucose. Regions showing significant decrease in regional cerebral metabolic rate for glucose are *hatched*, regions showing significant increase are *solid*. A = amygdala; Au = auditory cortex C, anterior cingulate cortex; Co = cochlear nuclei; CP = caudate-putamen nucleus; DR = dorsal raphe; F = frontal cortex; G = medial geniculate; H = habenular complex; Hp = hippocampus; IC = inferior colliculus; In = interpeduncular nucleus; LC = locus ceruleus; Mn = medial mammillary nucleus; MR = median raphe; P = globus pallidus; r = substantia nigra, pars reticulata; R = red nucleus; S = lateral septum; Sc = substantia nigra, pars compacta; SS = somatosensory cortex; St = subthalamic nucleus; Ta = thalamus, anteroventral nucleus; Tm = thalamus, mediodorsal nucleus; Tp = thalamus, posteroventral nucleus; V = cerebellum, vermis; Vn = vestibular nuclei; Vs = visual cortex.



patterns also resemble those of glutamate agonists<sup>6</sup> and may reflect a paradoxical increase of glutamatergic neurotransmission. At subanesthetic doses (*i.e.*, 10–30 mg/kg intraperitoneally), in fact, ketamine increases extracellular brain glutamate,<sup>35</sup> which in turn may activate non-NMDA glutamate receptors and unblocked NMDA receptors and may result in a net increase of glutamatergic neurotransmission.<sup>35</sup> Hence, behavioral and rCMRglc activation during recovery likely reflect ketamine concentrations abating to subanesthetic levels<sup>36</sup> and a subsequent brain glutamate increase. Postanesthetic rCMRglc activation was smaller after *S*(+)-ketamine than after *S,R*(±)-ketamine or *R*(-)-ketamine, and these findings contrast with neuroimaging and behavioral reports of more pronounced rCMRglc increases and side effects by *S*(+)-ketamine than by *R*(-)-ketamine in humans<sup>32</sup>; they are consistent instead with reports of larger behavioral activation by *R*(-)-ketamine in animals<sup>12,13</sup> and suggest possible interspecies differences.

Reportedly, ketamine binds to NMDA,<sup>14</sup>  $\mu$ - and  $\kappa$ -opioid, nicotinic, muscarinic, dopamine D<sub>2</sub>, and serotonin S<sub>2</sub> receptors; ketamine anesthesia increases brain extracellular concentrations of norepinephrine,<sup>37</sup> dopamine,<sup>38</sup> and acetylcholine<sup>39</sup> and decreases those of serotonin,<sup>40</sup> glutamate,<sup>35</sup> and the endogenous opioid met-enkephalin<sup>41</sup> but has no effect on brain  $\gamma$ -aminobutyric acid concentrations and receptors. Hence, ketamine anesthesia markedly perturbs several neurochemical parameters, which, in turn, may be involved in ketamine anesthesia. However, the relation between the dose of ketamine and behavioral and rCMRglc effects (*i.e.*, activation at low doses, inhibition at high doses) differs from those of aminergic agonists and

antagonists<sup>25–27</sup>; hence, neurochemical changes may be not relevant for or may be obscured by ketamine anesthesia. Ketamine-induced rCMRglc changes are instead similar during anesthesia to those of general anesthetics and during recovery to those of noncompetitive NMDA antagonists such as MK801 and phencyclidine, which also possess anesthetic properties.<sup>42</sup> Some reports contrast with an NMDA hypothesis of ketamine anesthesia: NMDA receptors are already blocked at nonanesthetic doses<sup>43</sup>; NMDA-induced swallowing responses are not blocked at anesthetic doses<sup>44</sup>; and some competitive NMDA antagonists, such as 3-((R)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid, may be not anesthetic.<sup>45</sup> On the other hand, ketamine interacts with NMDA receptors in fashions that are not shared by other NMDA antagonists; ketamine anesthesia is stereospecifically counteracted by NMDA<sup>6</sup>; and several noncompetitive or functional NMDA receptor antagonists, including MK801, dextrorphan, (+)-N-allylnormetazocine, and riluzole, increase the potency of general anesthetics and have analgesic and anesthetic properties themselves.<sup>45</sup> Evidence also links general anesthetics to an inhibition of glutamatergic neurotransmission: enflurane blocks glutamate-induced MK801 binding to NMDA receptors<sup>46</sup>; halothane and isoflurane block glutamate- and NMDA-induced intraneuronal entry of calcium<sup>47</sup>; and ketamine blocks non-NMDA, glutamatergic receptor second messenger.<sup>48</sup> Finally, it has been recently reported that glutamatergic synaptic transmission and rCMRglc have a tight stoichiometric relation, and rCMRglc would be a direct index not only of neuronal metabolism but also of glutamate neurotransmission. If this holds true, a



diffuse cerebral hypometabolism may be a common feature of gaseous and intravenous anesthesia that reflects a diffuse depression of glutamatergic neurotransmission.

## References

1. Reich DL, Silvay G: Ketamine: An update on the first twenty-five years of clinical experience. *Can J Anaesth* 1989; 36:186-97
2. Corssen G, Domino EF: Dissociative anesthesia: Further pharmacological studies and first clinical experience with phencyclidine derivative C1-581. *Anesth Analg* 1966; 45:29-40
3. Crosby G, Crane AM, Sokoloff L: A comparison of local rates of glucose utilization in spinal cord and brain in conscious and nitrous oxide- or pentobarbital-treated rats. *ANESTHESIOLOGY* 1984; 61:434-8
4. Ori C, Dam M, Pizzolato G, Battistin L, Giron G: Effects of isoflurane anesthesia on local cerebral glucose utilization in the rat. *ANESTHESIOLOGY* 1986; 65:152-6
5. Dam M, Ori C, Pizzolato G, Ricchieri GL, Pellegrini A, Giron GP, Battistin L: The effects of propofol anesthesia on local cerebral glucose utilization in the rat. *ANESTHESIOLOGY* 1990; 73:499-505
6. Freo U, Ori C: Mapping cerebral metabolic and blood effects of general anesthetics, Anaesthesia, Pain, Intensive Care and Emergency Medicine. Vol 17. Edited by Gullo A. Milan, Spinger-Verlag, 2003, pp 877-90
7. Cavazzuti M, Porro CA, Biral GP, Benassi C, Barbieri GC: Ketamine effects on local cerebral blood flow and metabolism in the rat. *J Cereb Blood Flow Metab* 1987; 7:806-11
8. Crosby G, Crane AM, Sokoloff L: Local changes in cerebral glucose utilization during ketamine anesthesia. *ANESTHESIOLOGY* 1982; 56:437-43
9. Davis DW, Mans AM, Biebuyck JF, Hawkins RA: The influence of ketamine on regional brain glucose use. *ANESTHESIOLOGY* 1988; 69:199-205
10. Oguchi K, Arakawa K, Nelson SR, Samson F: The influence of droperidol, diazepam, and physostigmine on ketamine-induced behavior and brain regional glucose utilization in rat. *ANESTHESIOLOGY* 1982; 57:353-8
11. Winters WD, Ferrar-Allado T, Guzman-Flores C, Alcaraz M: The cataleptic state induced by ketamine: A review of the neuropharmacology of anesthesia. *Neuropharmacology* 1972; 11:303-15
12. Benthuisen JL, Hance AJ, Quam DD, Winters WD: Comparison of isomers of ketamine on catalepsy in the rat and electrical activity of the brain and behaviour in the cat. *Neuropharmacology* 1989; 28:1003-9
13. Ryder S, Way WL, Trevor AJ: Comparative pharmacology of the optical isomers of ketamine in mice. *Eur J Pharmacol* 1978; 49:15-23
14. Oye I, Huseveit O, Maurset A, Ratti Moberg E, Paulsen O, Skoglund LA: The chiral forms of ketamine as probes for NMDA-receptor function in humans, NMDA Receptors Related Agents: Biochemistry, Pharmacology and Behaviour. Edited by Kameyama T, Nabeshima T, Domino EF. Ann Arbor, NPP Books, 1992, pp 381-9
15. Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG: Stereoselective interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in Chinese hamster ovary cells. *ANESTHESIOLOGY* 1999; 90:174-82
16. Anis NA, Berry SC, Burton NR, Lodge D: The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. *Br J Pharmacol* 1983; 79:565-75
17. Hancock PJ, Stamford JA: Stereospecific effects of ketamine on dopamine efflux and uptake in the rat nucleus accumbens. *Br J Anaesth* 1999; 82:603-8
18. Joo G, Horvath G, Klimscha W, Kekesi G, Dobos I, Szikszay M, Benedek G: The effects of ketamine and its enantiomers on the morphine- or dexmedetomidine-induced antinociception after intrathecal administration in rats. *ANESTHESIOLOGY* 2000; 93:231-41
19. Durieux ME, Nietgen GW: Synergistic inhibition of muscarinic signaling by ketamine stereoisomers and the preservative benzethonium chloride. *ANESTHESIOLOGY* 1997; 86:1326-33
20. Sasaki T, Andoh T, Watanabe I, Kamiya Y, Itoh H, Higashi T, Matsuura T: Nonstereoselective inhibition of neuronal nicotinic acetylcholine receptors by ketamine isomers. *Anesth Analg* 2000; 91:741-8
21. Brady KT, Balster RL: Discriminative stimulus properties of ketamine stereoisomers in phencyclidine-trained rats. *Pharmacol Biochem Behav* 1982; 17:291-305
22. Puu G, Koch M, Artursson E: Ketamine enantiomers and acetylcholinesterase. *Biochem Pharmacol* 1991; 41:2043-5
23. Sokoloff L: The radioactive deoxyglucose method: Theory, procedure and applications for the measurements of local glucose utilization in the central nervous system. *Adv Neurochem* 1982; 4:1-82
24. Sokoloff L, Reivich AA, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD, Sakurada O, Shinohara M: The [<sup>14</sup>C]deoxyglucose method for measurement of local cerebral glucose utilization: Theory, procedure and normal value in the conscious and anesthetized albino rat. *J Neurochem* 1985; 28:897-916
25. Freo U: Cerebral metabolic effects of serotonin drugs and neurotoxins. *Life Sci* 1996; 59:877-91
26. Freo U, Pizzolato G, Dam M, Ori C, Battistin L: A short review of cognitive and functional neuroimaging studies of cholinergic drugs: Implications for therapeutic potentials. *J Neural Transm* 2002; 109:857-70
27. Orzi F, Morelli M, Fieschi C, Pontieri FE: Metabolic mapping of the pharmacological and toxicological effects of dopaminergic drugs in experimental animals. *Cerebrovasc Brain Metab Rev* 1993; 5:95-121
28. National Institutes of Health: Guide for the Care and Use of Laboratory Animals. Bethesda, National Institutes of Health, revised 1978. Publication No. 80-23
29. Marietta MP, Way WL, Castagnoli N Jr, Trevor AJ: On the pharmacology of the ketamine enantiomorphs in the rat. *J Pharmacol Exp Ther* 1977; 202:157-65
30. Paxinos G, Watson C: *The Rat Brain in Stereotaxic Coordinates*. New York, Academic, 1982
31. Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, Brune K: Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. *Br J Anaesth* 1993; 70:666-71
32. Schuttler J, Stanski DR, White PF, Trevor AJ, Horai Y, Verotta D, Sheiner LB: Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers in man. *J Pharmacokinetic Biopharm* 1987; 15:241-53
33. Engelhardt W, Stahl K, Marouche A, Hartung E, Dierks T: Ketamine racemate versus S-(+)-ketamine with or without antagonism with physostigmine: A quantitative EEG study on volunteers. *Anaesthesist* 1994; 43(suppl 2):S76-82
34. Sharkey J, Ritchie IM, Butcher SP, Kelly JS: Differential effects of competitive (CGS19755) and non-competitive (MK 801) NMDA receptor antagonists upon local cerebral blood flow and local cerebral glucose utilisation in the rat. *Brain Res* 1994; 651:27-36
35. Moghaddam B, Adams B, Verma A, Daly D: Activation of glutamatergic neurotransmission by ketamine: A novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci* 1997; 17:2921-7
36. Persson J, Hasselstrom J, Maurset A, Oye I, Svensson JO, Almqvist O, Scheinin H, Gustafsson LL, Almqvist O: Pharmacokinetics and non-analgesic effects of S- and R-ketamines in healthy volunteers with normal and reduced metabolic capacity. *Eur J Clin Pharmacol* 2002; 57:869-75
37. Kubota T, Anzawa N, Hirota K, Yoshida H, Kushikata T, Matsuki A: Effects of ketamine and pentobarbital on noradrenaline release from the medial prefrontal cortex in rats. *Can J Anaesth* 1999; 46:388-92
38. Lindfors N, Barati S, O'Connor WT: Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. *Brain Res* 1997; 759:205-12
39. Taguchi K, Andresen MJ, Hentall ID: Acetylcholine release from the mid-brain interpeduncular nucleus during anesthesia. *Neuroreport* 1991; 2:789-92
40. Irifune M, Fukuda T, Nomoto M, Sato T, Kamata Y, Nishikawa T, Miettani W, Yokoyama K, Sugiyama K, Kawahara M: Effects of ketamine on dopamine metabolism during anesthesia in discrete brain regions in mice: Comparison with the effects during the recovery and subanesthetic phases. *Brain Res* 1997; 763:281-4
41. Kolada I, Kmiecik-Kolada K, Huzarska M, Dyaczynska-Herman A, Herman ZS: Influence of ketamine and its interactions with morphine and nalbuphine on the level of enkephalins in some parts of the brain and spinal cord. *Pol J Pharmacol* 1994; 46:139-46
42. Kelland MD, Soltis RP, Boldry RC, Walters JR: Behavioral and electrophysiological comparison of ketamine with dizocilpine in the rat. *Physiol Behav* 1993; 54:547-54
43. Church J, Lodge D, Berry SC: Differential effects of dextrorphan and levorphanol on the excitation of rat spinal neurons by amino acids. *Eur J Pharmacol* 1985; 111:185-90
44. Kessler JP, Cherkaoui N, Catalin D, Jean A: Swallowing responses induced by microinjection of glutamate and glutamate agonists into the nucleus tractus solitarius of ketamine-anesthetized rats. *Exp Brain Res* 1990; 83:151-8
45. Daniell LC: The noncompetitive N-methyl-D-aspartate antagonists, MK-801, phencyclidine and ketamine, increase the potency of general anesthetics. *Pharmacol Biochem Behav* 1990; 36:111-5
46. Martin DC, Abraham JE, Plagenhoef M, Aronstam RS: Volatile anesthetics and NMDA receptors: Enflurane inhibition of glutamate-stimulated [<sup>3</sup>H]MK-801 binding and reversal by glycine. *Neurosci Lett* 1991; 132:73-6
47. Puil E, el-Beheiry H, Baimbridge KG: Anesthetic effects on glutamate-stimulated increase in intraneuronal calcium. *J Pharmacol Exp Ther* 1990; 255:955-61
48. Gonzales JM, Loeb AL, Reichard PS, Irvine S: Ketamine inhibits glutamate-, N-methyl-D-aspartate-, and quisqualate-stimulated cGMP production in cultured cerebral neurons. *ANESTHESIOLOGY* 1995; 82:205-13