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## Effect of Intracarotid Injection of Iopamidol on Local Cerebral Glucose Utilization in Rat Brain

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We assessed, by means of the [14C]-2-deoxy-D-glucose autoradiography method, the effect of intracarotid injection of a nonionic, low-osmolar contrast medium (iopamidol) on local cerebral glucose utilization in the rat brain. Contrast medium was injected at 20°C and at 37°C, and the relative changes in local cerebral glucose utilization were measured. At 20°C the viscosity of the contrast agent was about twice that of the same solution at 37°C, and resulted in a statistically significant increase in local cerebral glucose utilization in the hemisphere ipsilateral to the side of intracarotid infusion. Saline control studies showed that the metabolic change was not related to either the solution temperature or the osmolality.

These findings suggest that increased viscosity of a contrast medium may contribute to its neurotoxic effects during cerebral angiography, hence emphasizing the importance of preheating contrast material to avoid adverse reactions.

In the last decade several nonionic, water-soluble, low-osmolar contrast media have been synthesized and marketed that are said to provoke negligible neurotoxicity when used for cerebral angiography [1]. Nevertheless, the neuroangiographic complication rate has been reported to be around 8.5% with a frequency of permanent neurologic deficit of 0.33% [2]. Among these new nonionic contrast media, iopamidol has been proposed as a particularly safe product in a variety of experimental and clinical conditions [3-5]. From a survey of the literature relevant to adverse reactions from the use of iopamidol, it appears that its neurotoxicity is similar to that of the newest low-osmolar contrast medium [6].

Though widely investigated, the cause of adverse reactions by contrast media is not yet completely understood [7]. Adverse effects resulting from intraarterial injection of contrast material can be attributed to either the contrast agents themselves and/or to technical factors such as arterial damage and emboli. It has been experimentally demonstrated that intracarotid injection of conventional ionic contrast material results in a pronounced but reversible disorder of vascular permeability related to changes in the blood-brain barrier [8, 9]. Although the osmotic action of contrast agents on the endothelial cells of brain vasculature is well known, other physicochemical parameters are also involved [10]. The role of viscosity has recently been pointed out by Wilcox and Sage [11], who proved that the blood-brain barrier could be dissimilarly affected by the same agent depending on modified viscosity.

Autoradiography with [14C]-2-deoxy-D-glucose ([14C]-2-DG) permits measurement of local cerebral glucose utilization and results in both a pictorial (qualitative) and a densitometric (quantitative) representation of brain glucose utilization; hence, those regions or pathways of the brain affected by exposure to neurotoxic agents can be identified [12]. This technique has also been used to assess the effect of nonionic contrast material on brain metabolism after intrathecal administration [13, 14]. The present study has further adopted the [14C]-2-DG method to test the effect of intracarotid injection of iopamidol on local cerebral glucose utilization in the rat brain under a variety of experimental conditions.

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This article describes the relevant results and is anticipated to be the first in a series designed to contribute to the understanding of the mechanisms of contrast-media neurotoxicity.

## Materials and Methods

Studies were performed on 24 conscious male Sprague-Dawley albino rats weighing 200–250 g. Twelve rats were injected with iopamidol; eight control rats were injected with double concentrated saline (1.8% NaCl); four sham-operated animals were used as controls for the surgical procedure. Intracarotid injections of the test solutions were administered either at body (37°C) or room (20°C) temperature. Before the experiments, rats were conditioned to restraint in loose-fitting plaster casts. Environmental conditions were standardized. Under anesthesia, polyethylene catheters were inserted into the left common carotid artery (to inject either iopamidol or saline) and into both the femoral artery and vein (to collect arterial blood samples and to inject [14C]-2-DG, respectively). Incision sites were sutured and infiltrated with local anesthetic.

Rats were allowed to recover from anesthesia before the experiments were initiated. Conscious, loosely restrained rats were injected with iopamidol (Iopamiro [R])<sup>\*</sup> from commercially available ampoules. The contrast material (300 mg I/ml) was administered by an automatic injector: the dose was 2.5 g I/kg/min. Iopamidol, at a concentration of 300 mg I/ml, displays an osmolarity of 616 mOs/l (i.e., nearly twice that of blood). When administered either after preheating to 37°C or at room temperature (20°C) the osmolarity and other physicochemical characteristics of the contrast material are unaltered; whereas viscosity shifts from 4.7 mPa/sec at 37°C to 8.8 mPa/sec at 20°C. For comparison, double concentrated saline (1.8 g NaCl/100 ml, about 620 mOs/l) was injected at the same infusion rate at 20°C and 37°C to reproduce the hyperosmolar characteristics of the solution; however, saline viscosity does not change significantly with the change of temperature [11]. In rats used as sham controls the left common carotid artery was exposed and ligated for a time period identical to that necessary to prepare and inject the rats of the other experimental groups. Blood pressure, heart rate, body temperature, blood glucose, and blood gas concentrations were intermittently monitored throughout the experiments. Local cerebral glucose utilization was determined according to the method originally described by Sokoloff et al. [12] and to standard techniques originated in our laboratory [15, 16]. Either iopamidol or saline was injected intraarterially 1 min before an IV pulse of 100  $\mu$ Ci/kg of [14C]-2-DG (specific activity 55–57  $\mu$ Ci/mM).<sup>†</sup> In the following 45 min, plasma samples were withdrawn to assess glucose concentrations by enzymatic assay. Forty-five minutes after the [14C]-2-DG pulse, rats were sacrificed with an overdose of pentobarbital. Brains were quickly removed and immediately frozen in isopentane (–50°C).

Brain frontal plane serial sections, 20  $\mu$ m thick, were obtained by using a cryostat microtome at –20°C. The sections were mounted on glass coverslips and dried on a hotplate at 50°C. The serial sections were exposed to medical X-ray film (Kodak MR-1) in X-ray cassettes for 16 days to produce autoradiographs. The films were then developed by standard techniques with automatic equipment. Brains from sham-operated (carotid ligated) rats were processed according to the same procedure. Local tissue concentrations of [14C]-2-DG were determined by quantitative densitometric analysis by using, as reference controls, calibrated [14C]-methylmethacrylate standards<sup>†</sup> exposed together with the film and brain sections. Optical

densities of single brain areas were read by a microdensitometer coupled to a computerized image-processing system: the [14C]-2-DG content was measured in nCi/g tissue.

To facilitate visual inspection of the different patterns and the relative amounts of glucose utilization, color-coded pictures of the autoradiographs were prepared according to the method described by Goochee et al. [17]. Differences in nCi/g tissue between right (noninfused) and left (iopamidol- or saline-injected) hemispheres in each animal were measured to evaluate the following areas: caudate-putamen, frontal cortex, temporal cortex, parietal cortex, occipital cortex, corpus callosum, and hemispheric white matter, cerebellar gray matter, and cerebellar white matter. In at least two rats from each experimental group a further set of experiments was carried out by using the intraperitoneal (IP) route, injecting the same amount of [14C]-2-DG. This route, proposed by Meibach et al. [18], allows use of naive, unrestrained animals and avoids multiple vascular cannulations. Preliminary free-run experiments had confirmed the high correlation between autoradiographs from IP- and IV-injected animals and glucose utilization values. Therefore, the data presented here express results from both IP- and IV-injected animals. Since in this study blood concentrations of [14C]-2-DG were not assayed, it is not possible to provide absolute values for local cerebral glucose utilization. However, if one assumes nearly identical arterial blood-time curves and similar lumped constants among the animals within all test groups and between groups, then the [14C]-2-DG tissue concentrations should reflect the relative local cerebral glucose utilization for the regions. Injection into a single carotid artery also allowed us to use each animal as an internal control. The focus of this study was to examine incidental differences between the [14C]-2-DG concentrations in anatomically matched areas of the two hemispheres. To compare variability we computed percent differences for the above measures. Values of regional percent differences for the four groups (high- and low-viscosity iopamidol and saline 1.8% at 20°C and 37°C) were compared by using Student's paired t-test. The desired level of significance was set at  $p < .05$ .

To evaluate the in vivo cerebrovascular distribution of the contrast medium, an additional trial of angiographic examinations was carried out in a separate group of rats. Animals were anesthetized with IP sodium pentobarbitone. The left common carotid artery was exposed along a midline incision, ligated caudally, and a propylene tube (PE 50) was inserted into the vessel. The tip was pushed up to about 5 mm below the bifurcation of the internal and external carotid arteries. Angiograms were obtained according to the method proposed by Boullin et al. [19] 3 sec after starting the injection of contrast material at the same dose and flow rate used in the experimental rats.

## Results

### *Sham-Injected (Ligated Carotid) Rats (n = 4)*

After ligation of one common carotid artery (without injecting either iopamidol or saline) for time periods of up to 3 hr no significant change in the regional uptake of [14C]-2-DG was observed: both hemispheres were autoradiographically identical in all the examined animals. The distribution pattern of glucose metabolism was highly correlated with Sokoloff's reference values for local cerebral glucose utilization in anatomically matched areas [12]. Statistical comparison showed no difference between the two patterns transformed in regression slopes plotted against each other according to the method proposed by Meibach et al. [18] (Fig. 1) ( $r = .8949$ ,  $p < .0001$ ).

<sup>\*</sup> Bracco Industria Chimica S.p.A., Milan, Italy.

<sup>†</sup> Amersham Corp., Arlington Heights, IL.

#### Rats Injected with Iopamidol (300 mg I/ml) at 37°C (n = 6)

At body temperature the injection of the iopamidol solution did not cause any change in the [14C]-2-DG concentrations in the cerebral hemisphere or in the cerebellar areas ipsilateral to the infusion when compared with the contralateral structures. Color-coded metabolic maps (Fig. 2A), in which definite colors were assigned to fixed ranges of local cerebral glucose utilization determined according to an arbitrary scale, confirmed that no significant differences existed between the two hemispheres and allowed comparison of the concentrations of [14C]-2-DG (in nCi/g) in the selected brain areas (Table 1).

#### Rats Injected with 1.8% Saline at 37°C (n = 4)

No difference in local cerebral glucose utilization rates was detected between the two hemispheres in the rats injected

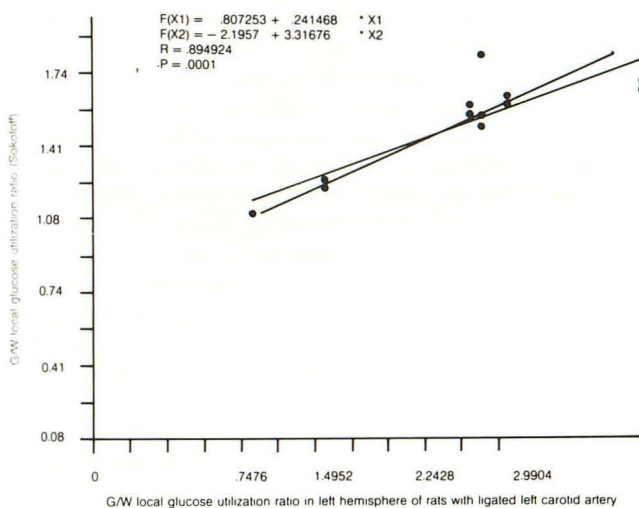
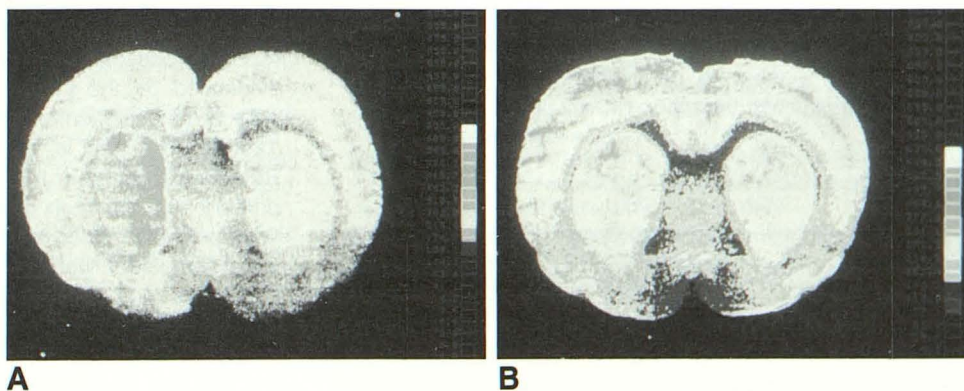


Fig. 1.—Gray/white-matter ratios obtained by dividing the glucose utilization for each structure by the glucose utilization of the corpus callosum according to the method proposed by Meibach et al. [18]. Gray/white-matter ratios from rats with ligated left common carotid artery and gray/white-matter ratios calculated from the data of Sokoloff et al. [12] were highly correlated ( $r = .8949$ ,  $p < .0001$ ).

Fig. 2.—Representative digitized, (originally) color-coded autoradiographs of rat brain. Coronal sections at levels of frontal cortex and caudate-putamen show the different metabolic pattern obtained in the two experimental groups. Scales on the right indicate [14C]-2-deoxy-D-glucose ([14C]-2-DG) concentrations in nanoCi/g tissue.

A, Iopamidol injected at 37°C. No distinct asymmetry is distinguishable between left and right homologous structures.

B, Iopamidol injected at 20°C. Consistent enhancement in [14C]-2-DG activity in caudate-putamen ipsilateral to the side of contrast medium injection. In comparison, the frontal cortices do not display any distinguishable asymmetry.



with double concentrated saline (1.8% NaCl) at 37°C (Table 1).

#### Rats Injected with Iopamidol (300 mg I/ml) at 20°C (n = 6)

When iopamidol at 20°C was injected into the left common carotid artery the autoradiographs displayed consistent enhancement in the [14C]-2-DG activity in the cerebral structures ipsilateral to the site of injection of contrast agent. The effect was particularly marked in brain areas vascularized by branches of the internal and middle cerebral arteries (Fig. 2B); that is, by the vessels directly receiving the bulk of the blood flow from the common carotid artery (Table 1). Contrarily, the frontal cortex and both the cerebellar gray and white matter revealed no significant difference as compared with the contralateral structures.

#### Rats Injected with 1.8% Saline at 20°C (n = 4)

Since iopamidol solutions at 20° and 37°C differ only in viscosity, four rats were injected with double-concentrated saline at 20°C (viscosity 0.95 mPa/sec) to assess whether the effect observed after administration of iopamidol at said temperature might depend on the different viscosities of the two solutions. No distinct asymmetry developed in any of the areas selected for investigation (Table 1).

#### Angiographic Studies

The resolution achieved was sufficient to visualize both external and internal carotid circulation. The major intracranial vessels visualized were the internal carotid and stapedal artery ipsilateral to the infusion site and the basilar trunk (Fig. 3). These studies confirm that after cannulation of the common carotid most of the test solution is delivered to the ipsilateral hemispheric vessels.

Throughout the experiments and in all experimental groups, no significant change in any of the monitored physiologic parameters was observed. It is emphasized that no seizures or gross behavioral abnormalities were noticed in the treated

TABLE 1: Regional Percent Differences in [14C]-2-DG Concentrations\*

Area	Iopamidol 20°C (n = 6)	Iopamidol 37°C (n = 6)	Saline 1.8% 20°C (n = 4)	Saline 1.8% 37°C (n = 4)
CPu	+18.1 ± 4.5**	-1.2 ± 1.1	+0.7 ± 0.8	+0.4 ± 0.2
FC	+2.7 ± 0.9	+3.0 ± 0.9	-2.2 ± 1.3	-1.3 ± 0.7
PaC	+12.4 ± 3.4**	+1.5 ± 0.7	-2.9 ± 1.5	+1.1 ± 1.0
TeC	+27.1 ± 7.2*	-3.8 ± 1.6	+2.2 ± 1.1	+3.2 ± 1.8
OC	+19.0 ± 4.6*	-1.4 ± 1.1	-3.2 ± 1.7	-0.9 ± 0.6
CG	+0.9 ± 0.6	+1.0 ± 0.5	-1.2 ± 0.8	+1.6 ± 0.3
CW	+0.7 ± 0.6	+0.5 ± 0.4	+1.6 ± 0.1	-0.3 ± 0.6

\* Regional hemispheric asymmetries in [14C]-2-DG concentrations. The values on the (left) injected side are expressed as percentages of the values on the (right) control side. Data were analyzed by comparing left vs right values (mean ± SE) for each region using the Student's paired t-test (\* =  $p < .05$ , \*\* =  $p < .001$ ). Changes were calculated individually for each experiment and then averaged.

Note.—CPu = caudate-putamen, FC = frontal cortex, PaC = parietal cortex, TeC = temporal cortex, OC = occipital cortex, CG = cerebellar gray matter, CW = cerebellar white matter.

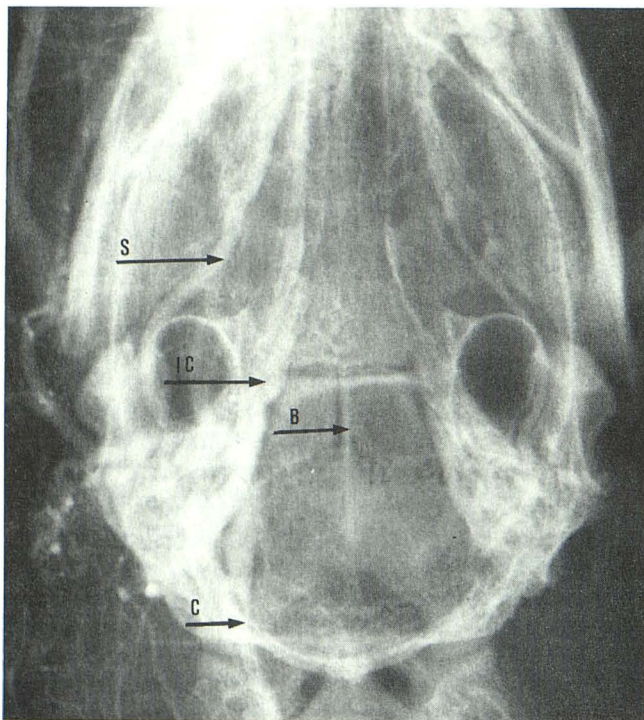


Fig. 3.—Magnification angiogram of intracranial circulation of rat obtained 3 sec after starting the injection of 2.5 g I/kg/min of iopamidol 300 mg I/ml into left common carotid artery. Internal carotid (IC) and stapedial (S) arteries are visualized on side ipsilateral to injection. Basilar artery (B) and tip of injection catheter (C) are also shown.

animals, even those with hemispheres showing enhanced local cerebral glucose utilization rates.

## Discussion

Many toxicologic methods have been developed to assess neurotoxicity of contrast agents and to predict major adverse reactions to these compounds [20]. The [14C]-2-DG method developed by Sokoloff et al. [12] is a widely accepted technique to estimate cerebral metabolic activity, since [14C]-2-DG uptake and localization appear closely linked to CNS neuronal activity. Furthermore, the choice of the [14C]-2-DG

method to assess the neurometabolic effects of contrast material is supported by data from Bech et al. [13], who observed changes in local cerebral glucose utilization after intrathecal administration of metrizamide in the rat.

In the present study the [14C]-2-DG technique was used to determine whether, under a variety of experimental conditions, the intracarotid injection of iopamidol induces cerebral metabolic alterations. The suitability of the experimental design was confirmed in preliminary studies using sham-operated animals, which showed that ligation of the common carotid artery does not influence [14C]-2-DG regional uptake in the ipsilateral hemisphere. As recently shown by Saris et al. [21], intracarotid artery infusion alone does not alter in the rat brain the normal pattern of blood flow in the ipsilateral hemisphere, indicating that cannulation and infusion can be performed without the creation of flow artifacts due to vessel spasm or emboli. Furthermore, it has been demonstrated that prolonged exposure to circulating contrast material is not sufficient per se to cause penetration of the blood-brain barrier [22]. The resultant distribution of glucose metabolism was found to be highly correlated with reference data. Using the uninjected hemisphere as an internal control, we calculated the relative changes in local cerebral glucose utilization after intraarterial administration of iopamidol. At 37°C the injection of contrast medium caused no regional change in cerebral metabolism when compared with the contralateral hemisphere. Since the injection of 1.8% saline did not alter the cerebral glucose utilization rate, it can be concluded that contrast medium osmolality itself was unable to influence cerebral metabolism. This finding is in agreement with the reported observation that cerebral metabolic changes, as evidenced by the [14C]-2-DG technique, occur only after intracarotid injection of solutions with osmolality higher than 1200 mOs/l; that is, about twice that of iopamidol [23]. Results presented in this article suggest that viscosity is of primary importance in determining cerebral metabolic alterations possibly related to blood-brain barrier changes. In fact, when iopamidol was injected under identical experimental conditions at 20°C, resulting in an increase in viscosity from 4.7 to 8.8 mPa/sec, a definite asymmetry in regional glucose utilization was observed. This pattern was not replicated by the injection of 1.8% saline at the same temperature, suggesting that the cerebral metabolic effect was not simply

related to temperature change but more probably to viscosity increase. In addition, Wilcox and Sage [11] previously reported data supporting the relationship between viscosity and blood-brain barrier damage in an experimental study carried out in a canine model with ionic contrast medium. Of course, the [14C]-2-DG method does not directly reflect incidental changes in blood-brain barrier integrity. Nevertheless, it is tempting to argue that the greater the viscosity of the contrast material the longer it will remain in contact with cerebral vascular endothelium, thus causing a regional restriction in blood flow and increasing the duration of the insult to the blood-brain barrier. Under these circumstances, it is likely that the increase in [14C]-2-DG uptake is a manifestation of a shift to anaerobic glycolysis [24]. The role played by other mechanisms such as an augmented rate of unidirectional entry of glucose into the brain at cerebral capillaries [25] needs to be more clearly defined.

It should be noted that the metabolic changes observed in the present study after iopamidol administration were of relative magnitude, and were never accompanied by either motor or behavioral alterations. These findings are in agreement with the very low neurotoxicity of this contrast material reported in clinical practice [26, 27]. However, the observed metabolic changes could explain some of the adverse reactions that occasionally occur after cerebrovascular administration of contrast medium, such as seizures and/or modifications in higher cerebral functions (short-term memory loss, mental confusion, etc). Finally, the present results further support the importance of preheating contrast material not only for technical considerations [28] but also to avoid adverse reactions possibly related to hyperviscosity of the injected solutions.

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