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Uptake of mIBG and catecholamines in noradrenaline- and organic cation transporter-expressing cells: potential use of corticosterone for a preferred uptake in neuroblastoma- and pheochromocytoma cells☆

Melanie Bayer[a,*], Zyrafete Kuçi[a], Edgar Schömig[c], Dirk Gründemann[c], Helmut Dittmann[b], Rupert Handgretinger[a], Gernot Bruchelt[a]

[a]Department of Hematology and Oncology, Children's University Hospital, D-72072 Tuebingen, Germany
[b]Department of Nuclear Medicine, University of Tuebingen, D-72072 Tuebingen, Germany
[c]Department of Pharmacology, University of Koeln, D-50924 Koeln, Germany

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Abstract

For imaging of neuroblastoma and phaeochromocytoma, [^{123}I]meta-iodobenzylguanidine ([^{123}I]mIBG) is routinely used, whereas [^{18}F]6-fluorodopamine ([^{18}F]6-FDA) is sporadically applied for positron emission tomography in pheochromocytoma. Both substances are taken up by catecholamine transporters (CATs). In competition, some other cell types are able to take up catecholamines and related compounds probably by organic cation (OCT) [extraneuronal monoamine (EMT)] transporters (OCT1, OCT2, OCT3=EMT). In this study, we investigated the uptake of radioiodine-labeled meta-iodobenzylguanidine (mIBG) as well as [^{3}H]dopamine (mimicring 6-fluorodopamine) and [^{3}H]noradrenaline. SK-N-SH (neuroblastoma) and PC-12 (phaeochromocytoma) cells were used and compared with HEK-293 cells transfected with OCT1, OCT2 and OCT3, respectively. In order to gain a more selective uptake in CAT expressing tumor cells, different specific inhibitors were measured. Uptake of mIBG into OCT-expressing cells was similar or even better as into both CAT-expressing cell lines, whereas dopamine and noradrenaline uptake was much lower in OCT-expressing cells. In presence of corticosterone (f.c. 10^{-4} M], catecholamine and mIBG uptake into SK-N-SH and PC-12 cells was only slightly reduced. In contrast, this process was significantly inhibited in OCT2 and OCT3 transfected HEK-293 as well as in Caki-1 cells, which naturally express OCT3. We conclude that the well-known corticosteroid corticosterone might be used in combination with [^{18}F]6-FDA or [^{123}I]mIBG to improve specific imaging of neuroblastoma and pheochromocytoma and to reduce irradiation dose to nontarget organs in [^{131}I]mIBG treatment.

Keywords: mIBG; 6-FDA; Catecholamine transporter; Organic cation transporter; Corticosterone; Neuroblastoma

1. Introduction

Phaeochromocytoma and most neuroblastoma express neuronal catecholamine transporters [CATs: noradrenaline (NA) transporter (NAT); dopamine (DA) transporter (DAT) [1,2]]. Because of the capability of these two tumors to take up radioiodine-labeled meta-iodobenzylguanidine (mIBG) by NAT [3], this compound is widely used for diagnostics and therapy. Since 1981 and 1984, respectively, phaeochromocytoma and neuroblastoma can be imaged by scintigraphy with radioiodine-labeled mIBG. An alternate imaging method, which is only sporadically used up to now, is positron emission tomography (PET) with [^{18}F]6-fluorodopamine ([^{18}F]6-FDA) [4–7]. 6-Fluorodopamine (6-FDA) has a similar structure compared to DA. Therefore, 6-FDA (like DA) can be taken up by NAT and DAT [8]. In addition, several other cells types can incorporate catecholamines and related compounds. Table 1 gives an overview of the characteristics of the different catecholamine-transporting

Abbreviations: CAT, catecholamine transporter; DA, dopamine; DAT, dopamine transporter; DMSO, dimethylsulfoxide; EMT, extraneuronal monoamine transporter; f.c., final concentration; 6-FDA, 6-fluorodopamine; mIBG, meta-Iodobenzylguanidine; NA, noradrenaline; NAT, noradrenaline transporter; OCT, organic cation transporter; PBS, phosphate-buffered saline; PET, Positron emission tomography.

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* Corresponding author. Tel.: +0049 7071 2980894; fax: +0049 7071 294713.
E-mail address: melanie.bayer@med.uni-tuebingen.de (M. Bayer).

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Table 1
Characteristics of the different neuronal and extraneuronal catecholamine transporters [9–22]

Transporter	Specificity of the substrate	Physiological distribution in the organism	Cells	Inhibitors
NAT	DA>NA>A	Sympathetic tissue	Neurones	Cocaine
		Adrenal medulla	Chromaffin cells	Desipramine
		Liver	Endothelial cells	Tricyclic anti-depressants
		Placenta	Syncytiotrophoblast	Nisoxetine
DAT	DA≫NA>A	Kidney	Endothelial cells	GBR-12783
		Stomach	Endothelial cells	GBR-12909
		Pancreas	Ductus pancreaticus	Cocaine
				Mazindol
OCT1	DA≈A>NA	Liver	Hepatocytes	D 22
		Intestine	Epithelial cells	DP 24
				Corticosterone
				Famotidin
				Ranitidine
				Prazosin
				Pb
OCT2	DA≫NA>A	Kidney	Tubulus cells	D 22
		CNS	Glia, neurones	DP 24
				Corticosterone
				Famotidin
				Ranitidine
				Cimetidine
				SKF-550
OCT3=EMT	A≫NA>DA	Liver	Hepatocytes	DP 24
		CNS	Glia	D 22
		Heart	Myocytes	Corticosterone
		Vessels	Endothelial cells	O-MISP
		Kidney	Tubulus, cortex	Estrogene
		Placenta	Syncytiotrophoblast	Famotidin
		Retina	Photo receptors	
		Intestine	Epithelial cells	
		Lung		

A, adrenaline; D 22, decynium; 22; DP 24, disprocynium 24; O-MISP: *o*-methylisoprenalin; Pb, phenoxybenzamine; SKF-550, (9-fluorenyl)-*N*-methyl-β-chlorethylamin.

neuronal and extraneuronal monoamine [organic cation (OCT)] transporters. Up to now, little is known about whether mIBG is also taken up by OCT-expressing cells. Nevertheless, this assumption is obvious if the nontumoral uptake pattern [23–25] is compared to the distribution of the OCTs in the body. This is, e.g., shown in Fig. 1, presenting a 4-year-old boy with a paravertebral neuroblastoma. Fig. 1A represents anterior (left) and posterior (right) images acquired 4 h after injection of [^{123}I]mIBG, while Fig. 1B demonstrates equal projections, acquired 24 h after injection. Noticeable is the intense liver and moderate lung uptake after 4 h, which is considerably reduced after 24 h. Only with the decrease of liver uptake on the late image does intensive tumor uptake (see arrow) become evident. In contrast, uptake into myocardium is prominent throughout. Since many other cells in different tissues compete with neuroblastoma cells for mIBG and catecholamine uptake, it would be advantageous to inhibit this transport in order to shift mIBG/6-FDA uptake towards the CAT-expressing tumor cells. As we assume that most of the nontumoral uptake is caused by OCT, we were looking for a less toxic specific inhibitor, which does not inhibit NAT or DAT. Among the different inhibitors of extraneuronal catecholamine transporters described in the literature (Table 1), corticosteroids, like corticosterone, are already widely used in different clinical applications.

Therefore, the aim of this study was to investigate (1) whether mIBG can be taken up by OCT-expressing cells and (2) whether the uptake of mIBG or 6-FDA into OCT-expressing cells can be preferentially inhibited by corticosterone in order to gain concentration in CAT-expressing tumor cells. Since DA behaves like 6-FDA and mIBG is taken up like NA, uptake studies were carried out using [^{3}H]DA, [^{3}H]NA and [^{123}I/^{131}I]-labeled mIBG.

2. Materials and methods

2.1. Chemicals and reagents

7,8-[^{3}H]DA (37 MBq/ml; specific activity: 1.52 TBq/mmol), 7,8-[^{3}H] NA (37 MBq/ml; specific activity: 0,44 TBq/mmol), [^{123}I]mIBG (4.1 MBq (<2.95 μg mIBG)/ml H_2O at the beginning of the experiment) and [^{131}I]mIBG (aliquots