Vasoactive Intestinal Peptide/Pituitary Adenylate Cyclase-activating Peptide Receptor Subtypes in Human Tumors and Their Tissues of Origin

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ABSTRACT

The evaluation of peptide receptors in man is needed not only to discover the physiological target tissues of a given peptide but also to identify diseases with a sufficient receptor overexpression for diagnostic or therapeutic interventions. Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating peptide (PACAP) receptors have been evaluated in human tumors and in their tissues of origin using in vitro receptor autoradiography with $^{125}$I-VIP or $^{125}$I-acetyl-PACAP-27 in tissue sections. The VIP/PACAP receptor subtypes VPAC$_1$, VPAC$_2$, and PAC$_1$ were evaluated in these tissues by determining the rank order of potencies of VIP and PACAP as well as VPAC$_2$- and VPAC$_2$-selective analogues. The VIP/PACAP receptors expressed in the great majority of the most frequently occurring human tumors, including breast (100% receptor incidence), prostate (100%), pancreas (65%), lung (58%), colon (96%), stomach (54%), liver (49%), and urinary bladder (100%) carcinomas as well as lymphomas (58%) and meningiomas (100%), are predominantly of the VPAC$_1$ type. Their cells or tissues of origin, i.e., hepatocytes, breast lobules and ducts, urothelium, prostate glands, lymph nodes, lung acini, gastrointestinal mucosa, and lymphocytes, also predominantly express VPAC$_1$. Leiomomas predominantly express VPAC$_2$ receptors, whereas paragangliomas, pheochromocytomas, and endometrial carcinomas preferentially express PAC$_1$ receptors. Conversely, VPAC$_2$ receptors are found mainly in smooth muscle (i.e., stomach), in vessels, and in stroma (e.g., of the prostate), whereas PAC$_1$ receptors are present in the adrenal medulla and in some uterine glands. Whereas the very wide distribution of VIP/PACAP receptors in the normal human body is indicative of a key role of these peptides in human physiology, the high VIP/PACAP receptor expression in tumors may represent the molecular basis for clinical applications of VIP/PACAP such as in vivo scintigraphy and radiotherapy of tumors as well as VIP/PACAP analogue treatment for tumor growth inhibition.

INTRODUCTION

A majority of human tumors, in particular the frequently occurring carcinomas, express VIP$^3$ receptors (1–4). Based on this high occurrence of tumoral VIP receptors, a number of potential clinical applications have been evaluated. First, it could be demonstrated that selected tumors, in particular, the VIP receptor-positive colorectal cancers, can be visualized in the patient by means of in vivo VIP receptor scintigraphy (5). Moreover, several studies have reported an effect of VIP and PACAP analogues on tumor growth in animal tumor models, mediated by specific receptors (6, 7). Therefore, VIP and the related peptide PACAP may be of great potential importance for oncology.

In the last few years, molecular biology has provided evidence for the existence of several receptor subtypes within the VIP/PACAP family (8). There are two VIP receptors, VPAC$_1$ and VPAC$_2$, both with high affinity for VIP and PACAP that can be distinguished pharmacologically by the VPAC$_2$-selective analogue [K$^{13}$,R$^{16}$,L$^{22}$]VIP(1–7)/GRF(8–27) (KRL-VIP/GRF) and the VPAC$_2$-selective RO 25-1553 (9, 10). There is at least one PACAP receptor, PAC$_1$, that is characterized by high affinity for PACAP but low affinity for VIP (8, 11).

Recently, a high incidence of PAC$_1$ was found in human gliomas, neuroblastomas, and pituitary adenomas (11–14), whereas VPAC$_1$ was identified in pancreatic cancers (15). However, it is presently unknown which subtype of receptor is expressed by the great majority of the other human tumors having VIP/PACAP receptors. Generally, this information is also lacking for the normal tissues of origin of the tumors. Such data would not only be important as additional biological information on these tumors and their tissues of origin but may be decisive for the formulation of a number of clinical applications for VIP/PACAP, such as in vivo VIP/PACAP receptor scintigraphy or long-term treatment with VIP/PACAP analogues, two approaches based on receptor-selective targeting of tumors by labeled or unlabeled VIP/PACAP molecules.

To be able clinically to take advantage of a high peptide receptor expression in human tumors, a particularly high “tumor to background” ratio (where background represents nontumor tissue) is preferable for diagnostic as well as radiotherapeutic applications. It is therefore a prerequisite to also have data on the VIP/PACAP receptor expression in the normal human tissues to identify which types of receptor-positive human tumors are most adequate for clinical investigations. Although peptide receptors, including VIP/PACAP receptors, have usually been investigated extensively in normal tissues of laboratory animals, systematic investigations in human tissues are much less frequent, being limited by the difficulty in obtaining and analyzing such tissues as well as by the often great individual variability in receptor expression observed in human tissue samples.

The aim of the present investigation was to evaluate VIP/PACAP receptors and identify their subtypes in a large number of different types of human tumors, including the most frequently occurring tumors, in comparison with the VIP/PACAP receptor subtypes expressed in the normal tissues of origin of these tumors. More than 400 human primary tumors and metastases as well as numerous samples of normal tissue were therefore evaluated in vitro by means of VIP/PACAP receptor autoradiography with the use of subtype-selective analogues to differentiate VPAC$_1$, VPAC$_2$, and PAC$_1$.

MATERIALS AND METHODS

Aliquots of surgically resected tumors or of biopsy specimens submitted for diagnostic histopathological analysis were frozen immediately after surgical resection and stored at −70°C. The following tumors were investigated: (a) colonic adenocarcinomas ($n = 26$); (b) gastric carcinomas ($n = 26$); (c) duodenal pancreatic adenocarcinomas ($n = 40$); (d) non-small cell carcinomas of the lung ($n = 40$); (e) breast carcinomas ($n = 68$); (f) endometrial carcinomas ($n = 12$); (g) prostate carcinomas ($n = 37$); (h) liver carcinomas (HCCs;
Table 1  Incidence of VIP/PACAP receptor-positive tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Lung carcinoma (NSCLC)</td>
<td>23/40 (58%)</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>25/26 (96%)</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>68/68 (100%)</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td>14/26 (54%)</td>
</tr>
<tr>
<td>Prostatic carcinoma</td>
<td>37/37 (100%)</td>
</tr>
<tr>
<td>Liver carcinoma (HCC)</td>
<td>29/59 (49%)</td>
</tr>
<tr>
<td>Ductal pancreatic carcinoma</td>
<td>26/40 (65%)</td>
</tr>
<tr>
<td>Urinary bladder carcinoma</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>11/19 (58%)</td>
</tr>
<tr>
<td>Meningioma</td>
<td>27/27 (100%)</td>
</tr>
<tr>
<td>Leiomysroma</td>
<td>10/15 (66%)</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>12/12 (100%)</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td>18/25 (72%)</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>18/18 (100%)</td>
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</tbody>
</table>

<sup>a</sup> Positive tumors include those labeled with 125I-VIP and 125I-PACAP and those labeled with 125I-PACAP only.

<sup>b</sup> NSCLC, non-small cell lung carcinoma.

n = 59; (i) non-Hodgkin’s lymphomas (n = 19); (j) bladder carcinomas (n = 4); (k) meningiomas (n = 27); (l) pheochromocytomas (n = 25); (m) paragangliomas (n = 18); and (n) leiomyomas (n = 15). We also tested 11 lymph node metastases of breast cancer. Although many of the tumor samples contained adjacent normal tissue, we have also evaluated normal tissue from noncancerous patients, including tissue from the lymph nodes, gastric and colonic wall, breast, lung, prostate, liver, pancreas, bladder, uterus, and adrenal gland.

RESULTS

Table 1 summarizes the incidence of a series of VIP/PACAP receptor-expressing tumors, including all of the most frequently occurring carcinomas. It is striking to see that the overall incidence for tumors displaying 125I-VIP and/or 125I-PACAP binding was very high for colorectal cancers; breast, prostate, and bladder carcinomas; meningiomas (both meningothelial and fibroblastic meningiomas); paragangliomas; and endometrial carcinomas. More than half of the lung, gastric, and pancreatic carcinomas; lymphomas; leiomyomas; and pheochromocytomas and almost half of the HCCs expressed VIP/PACAP receptors. As seen in the subtype characterization shown in Table 2, almost all listed tumors had predominantly PAC1 (defined by a high affinity for KRL-VIP/GRF), except for the leiomyomas with PAC1 (defined by a high affinity for RO 25-1553). In the tumors listed in Table 2, the detection of a predominant PAC1 expression was extremely rare (PAC1 was detected in two HCCs listed in Table 2). Table 3 lists an additional group of tumors expressing predominantly PAC1, including most of the paragangliomas, pheochromocytomas, and endometrial cancers. In all cases, as seen in displacement curves using 125I-PACAP, VIP bound with low affinity, compared to...
the high affinity seen with PACAP. Interestingly, in the majority of the cases, there was nevertheless a specific 125I-VIP binding displaced by nanomolar concentrations of VIP, as described previously for PAC1 transfected cells by Hashimoto et al. (19). However, this 125I-VIP binding was poorly displaced by KRL-VIP/GRF or RO 25-1553. It may correspond to the PAC 1 splice variant reported recently (20).

The VIP/PACAP receptor status of the tissues of origin for the above-mentioned tumors is also summarized in Tables 2 and 3. It is striking to observe that VIP/PACAP receptors are found in most human epithelial tissues. In the majority of these tissues, the VIP/PACAP receptor subtype preferentially expressed is the VPAC1 receptor, as detected by the differential affinity of the VPAC 1- and VPAC2-selective analogues. This is the case for hepatocytes, GI mucosa, lobules and ducts of the breast, prostatic glands, urothelium of bladder and ureter, acini of the lung, and pancreatic ducts. None of the investigated epithelial tissues have been found to have a predominant VPAC2 receptor expression (Tables 2 and 3). However, several human tissues have a predominant PAC1 receptor expression. This is the case for the adrenal medulla, the tissue of origin of the catecholamine-secreting tumors. Another case is the uterus, which focally expresses PAC 1 and VPAC 1 in glands, whereas the stroma expresses mainly VPAC2 receptors (Table 3).

Conversely, smooth muscle in various locations preferentially expresses VPAC2 receptors as documented by 125I-VIP binding displaced by nanomolar concentrations of the VPAC2-selective RO 25-1553 but not of the VPAC1-selective analogue KRL-VIP/GRF. 125I-PACAP binding is displaced by nanomolar concentrations of PACAP and of VIP in these tissues. Such VPAC2 receptors are observed in smooth muscle in locations as different as the GI tract (the stomach in particular, but not the colon) and the seminal vesicle. Moreover, several blood vessels (arteries more than veins) express VIP receptors, located primarily in the smooth muscle. However, not all identified blood vessels show VIP receptor expression, and a considerable subtype variability is noticed: whereas the majority of the vessels express VPAC2 receptors, few preferentially express

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**Table 3 Incidence of PAC1-expressing tumors and comparison with the main subtype expressed in their tissue of origin**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Incidence of PAC1-positive tumors</th>
<th>Main VIP/PACAP-R subtype present in tissue of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechol-secreting tumors</td>
<td>18/25 (72%)</td>
<td>PAC1 (Adrenal medulla)</td>
</tr>
<tr>
<td>Paraganglioma</td>
<td>18/18 (100%)</td>
<td>PAC1 (Adrenal medulla)</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>12/12 (100%)</td>
<td>VPAC1 PAC1 (Glands)</td>
</tr>
</tbody>
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* PAC1-positive tumors were defined by high affinity for PACAP 27 and low affinity for VIP using 125I-PACAP tracer.

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*Fig. 1. Detection of the VPAC1 receptor subtype in invasive ductal breast carcinoma and the surrounding breast tissue. A, H&E-stained section. Tu, carcinoma; Br, normal breast tissue. Bar, 1 mm. B–D, autoradiograms showing 125I-PACAP binding. E, 125I-PACAP total binding. C, binding in the presence of 20 nM PACAP. D, binding in the presence of 20 nM VIP. E–H, autoradiograms showing 125I-VIP binding. E, 125I-VIP total binding. F, binding in the presence of 20 nM VIP. G, binding in the presence of 20 nM of the VPAC1-selective analogue (sV1) KRL-VIP/GRF. H, binding in the presence of 20 nM of the VPAC2-selective analogue (sV2) RO 25-1553. The tumor and normal breast tissues are labeled with 125I-PACAP and 125I-VIP. Complete displacement by 20 nM PACAP and VIP excludes the presence of PAC1. Complete displacement by 20 nM KRL-VIP/GRF but not RO 25-1553 strongly suggests expression of VPAC1 in both tissues. On the right, the two competition curves reveal the VPAC1 expression of breast carcinoma: the top graph shows high affinity displacement of 125I-VIP by KRL-VIP/GRF but not by RO 25-1553; the bottom graph shows high affinity displacement of 125I-PACAP by PACAP and VIP.*
VPAC₁ receptors, and some others express a mixture of VPAC₁ and VPAC₂ receptors. Furthermore, stromal tissue can also express VPAC₂ receptors: they are found, in particular, in the stroma of the uterus and prostate, whereas the glands of the prostate preferentially express VPAC₁ (see above). These VPAC₂-expressing tissues, namely, gastric smooth muscles, vessels, and the uterine and prostatic stroma, are all specifically labeled by the VPAC₂-selective ¹²⁵I-RO 25-1553 radioligand (data not shown).

Most human solid lymphoid tissues express VIP/PACAP receptors at high density, as shown previously (21, 22). In the present study, all of the investigated lymph nodes, which were removed from the axillary region in most cases, have a strong predominance of VPAC₁ receptors (Table 2).

Fig. 1 illustrates a typical VPAC₁-expressing breast carcinoma with VPAC₁-expressing adjacent breast tissue. PACAP and VIP completely displace ¹²⁵I-PACAP binding in the high affinity range, indicating the absence of PAC₁. VIP and KRL-VIP/GRF displace ¹²⁵I-VIP in the nanomolar range, whereas RO 25-1553 displaces it with low affinity, indicating a predominance of VPAC₁. Fig. 2 shows a VPAC₁-expressing ductal pancreatic carcinoma next to a VPAC₁-positive normal pancreatic duct. Fig. 3 is an autoradiography of a VPAC₁-expressing gastric carcinoma with, for comparison, a normal stomach expressing VPAC₂ in the mucosa and VPAC₂ in the smooth muscle. Complete displacement curves are shown in Fig. 4 for gastric cancer and normal stomach, including mucosa and smooth muscles. The leiomyoma in Fig. 5 expresses the same VPAC₂ subtype as found in the smooth muscle shown in Fig. 4, characterized by the low affinity of KRL-VIP/GRF and high affinity of RO 25-1553. This type of tumor can also be specifically labeled with ¹²⁵I-RO 25-1553. In contrast to the examples cited above, Fig. 6 shows a PAC₁-expressing pheochromocytoma next to normal human adrenal medulla, both characterized by a low affinity of VIP. Fig. 7 shows a PAC₁-expressing paraganglioma in a displacement experiment.

Lymph nodes are important metastasis sites of tumors. As shown in Table 4, we have measured the VIP receptor density of metastatic breast cancer tissue in axillary lymph nodes, and compared with the nonmetastatic lymphoid tissue of lymph nodes: the density of VPAC₁ receptors in lymphoid tissue was twice as high as that in the cancer tissue.

**DISCUSSION**

The present study shows that the great majority of frequently occurring carcinomas predominantly express VPAC₁ receptors, as do their normal tissues of origin. This is the case for breast, prostate, colon, lung, and bladder carcinomas as well as gastric, ductal pancreatic, and HCCs. It is rare to find tumors predominantly expressing VPAC₂. In our series, we could identify only leiomyomas as a benign mesenchymal neoplasm expressing VPAC₂, probably in relation to the VPAC₂-expressing smooth muscles.

Conversely, other benign and malignant neoplasms located in the brain or endocrine and neuroendocrine system appear to predominantly express PAC₁. It had previously been reported that gliomas, neuroblastomas, and pituitary adenomas express PAC₁ (11–13). We can now add to this list catecholamine-secreting tumors, pheochromocytomas, paragangliomas, and endometrial cancers. There is evidence that their respective tissues of origin can express PAC₁, often at high density, as seen in the human adrenal medulla.

The presence of the various VIP/PACAP receptor subtypes not only in tumors but also in the great majority of the nonneoplastic, normal tissues of origin may have a number of important implications, both advantageous and disadvantageous, with regard to the potential clinical applications for VIP/PACAP.

The diagnostic localization of tumors and their metastases using receptor scintigraphy requires a sufficiently high density of tumoral receptors, as well as a high tumor to background ratio. Whereas most tumors yield the high VIP/PACAP receptor density necessary for their visualization, the optimal tumor to background ratio is more of a concern because VIP/PACAP receptors are expressed by so many normal tissues. It may therefore be necessary to limit VIP/PACAP receptor scintigraphy to those tumors located in sites where an optimal tumor:tissue ratio of receptor density can be expected. VPAC₁-expressing colorectal cancers are probably good candidates because the normal GI tract has a relatively moderate density of VPAC₁ receptors located in very distinct areas of the mucosa. This statement is supported by the study of Virgolini et al. (5) showing that human colorectal cancers can be localized by in vivo VIP receptor scintigraphy. Conversely, lung cancers are poor candidates because of the high density of VIP/PACAP receptors in lung acini. VPAC₁-expressing prostate cancers are also inadequate candidates due to the high VPAC₁ receptor expression in normal prostatic glands. Furthermore, VPAC₁-expressing neoplasms located in the liver may not be ade-
quate for VIP receptor scintigraphy because of the high density of VPAC₁ receptors in the normal liver. We have shown that HCCs have approximately one-fourth the density of VIP receptors in the liver (3). The same low ratio is found between pancreatic or colorectal carcinomas and the normal liver, suggesting that in many cases, liver metastases of these two types of cancers as well as HCCs will not be identified as positive hot spots with VIP receptor scintigraphy but rather as cold spots. We can conclude from the present study that lymph node metastases, for example, lymph node metastases of breast cancers, will also be difficult to assess with VIP receptor scintigraphy because of the high VIP receptor content of normal lymphoid tissue (21, 22).

These density ratios identified in the present study are, of course, based on in vitro data measuring a nondynamic receptor condition in sections of normal and tumoral tissues. One cannot exclude that, in vivo, VIP receptors expressed in tumoral tissues will have characteristics distinct from those expressed in normal tissues, e.g., because of different internalization rates, different ligand dissociation rates, or different receptor turnover; this would lead to an accumulation of radioligand in both tissues at a rate different from that predicted by the in vitro measurement of receptor density. It would, of course, be particularly useful for imaging purposes if a differential receptor characteristic between tumor and normal tissue led to a higher in vivo accumulation in the tumor than in normal tissue. Experimental evidence for such mechanisms are presently lacking; it is much needed, but difficult to obtain.

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4 J. C. Reubi, unpublished data.
In the case of PAC₁ receptor-expressing tumors, one may overcome the problem of high background in liver or nodal metastases if the receptor scintigraphy is performed with a PAC₁ receptor-selective ligand such as maxadilan (23). One may assume that, under these circumstances, the background given by the liver and/or lymph node, which consists mainly of VPAC₁ receptors, may remain low: the selective PAC₁ radioligand would label the PAC₁ tumor, but not the adjacent VPAC₁ tissues.

Because it is possible to target VIP/PACAP receptor-positive tumors with radiolabeled VIP/PACAP analogues (5, 24), it should also be possible to treat these receptor-positive tumors selectively with high doses of adequately radiolabeled VIP analogues. Preliminary studies using radiolabeled somatostatin analogues suggest that both β emitters as well as Auger emitters (25, 26) can give promising results in terms of stabilization or reduction of the growth of somatostatin receptor-positive tumors. A prerequisite is that the tumor expresses a particularly high density of receptors. The limitations of such a radiotherapy include the destruction by irradiation of surrounding and distant receptor-positive normal target tissues, in particular, radiosensitive tissues such as the VIP/PACAP receptor-positive immune system. Other critical organs that may be destroyed by such a radiotherapy include the kidney and liver, not only because they express VPAC₁, but also because they excrete and eliminate large amounts of peptide.

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radiotracers from the body. It is to be hoped, however, that a careful limitation of the radiation dose given to these vital organs may partly overcome the potential side effects.

VIP and PACAP can affect the growth of normal and neoplastic tissues. Whereas several groups have reported tumor growth-promoting activities of VIP and growth inhibition properties of VIP antagonists in various tumor models (6, 15, 27–29), recent evidence by Maruno et al. (7) has suggested that VIP itself may be an inhibitor of tumor growth under certain conditions. Based on the presence of VIP/PACAP receptors in the majority of the most common human tumors, the postulate to use high doses of a growth-inhibiting VIP/PACAP analogue (agonist or antagonist) is therefore highly attractive. One crucial question is whether there will be an equally good growth-inhibiting effect in human tumors as that seen in animal tumor models or cell cultures. The present study will help to choose the type of human cancer that will be most promising for clinical trials with VIP/PACAP.

Clinical indications in which high doses of nonradioactive VIP/PACAP analogues are necessary for long-term peptide treatment should be considered carefully, due to the possible side effects related to the high number of VIP target tissues in the human body. To be able to predict such side effects, we need a better understanding of VIP/PACAP actions in various locations. Conversely, in diagnostic or radiotherapeutic indications where radiolabeled VIP/PACAP analogues can be used in very low peptide doses, a considerably lower potential risk of side effects due to undesired peptide actions may be expected. These latter indications may be an advantage when dealing with the VIP/PACAP system.

Table 4 VIP receptor density in breast cancer lymph node metastases compared with nonneoplastic lymph nodes

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Density (dpm/mg tissue; mean ± SE)</th>
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<tbody>
<tr>
<td>Breast cancer metastases</td>
<td>2672 ± 311 (n = 11)</td>
</tr>
<tr>
<td>Nonneoplastic lymph nodes</td>
<td>5563 ± 562 (n = 13)</td>
</tr>
</tbody>
</table>

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REFERENCES


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