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Mini-review

Photodynamic modulation of cellular function[1]

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ABSTRACT Photodynamic action with a large number of photosensitisers has important practical implications such as photodynamic cancer therapy. But the cellular and molecular mechanisms involved have been rather poorly understood. In this paper, photodynamic modulation of cell signal transduction and the resultant changes in cellular function are reviewed, with a particular emphasis on smooth muscle and the pancreas.

Certain light-absorbing molecules excited by photons are raised from the ground state to the singlet excited state which, with a given probability, may undergo intersystem crossing to reach the triplet state. The excitation energy of the triplet state can be transferred to ground state oxygen to generate excited singlet molecular oxygen. The extremely reactive singlet oxygen ($94.1\ kJ \cdot mol^{-1}$) reacts with various cellular components to trigger different cellular responses, a process termed type Ⅱ photosensitization or photodynamic action[1]. The light-absorbing molecules are therefore photosensitizers. During a type Ⅱ photodynamic action, photon energy is transformed into chemical energy (covalent bond) via the singlet oxygen molecule. Singlet oxygen in a cellular *milieu* has a lifetime of about 1 μs which limits its effective reactive distance to within 20 nm of its site of generation. Because of this unique property of chemical bond formation and restricted volume of reaction, photosensitizers have multiple applications: photodynamic therapy of solid tumors, photodynamic ablation of atherosclerotic plaques, extracorporeal photochemotherapy such as photodynamic therapy of leukemia and photodynamic stem cell purging for bone marrow transplantation, photodynamic therapy of skin lesions, photodynamic sterilization of whole blood and blood products, and photon-activated pest eradication (photon-activated pesticides). However, the cellular and molecular mechanisms involved are poorly undersdtood. Therefore, the last few years have witnessed the emergence of a new field: photodynamic modulation of cellular function.

Optical properties of biological tissues and different classes of photosensitizers

Light penetration into biological tissues is determined by both scattering and absorption. Longer wavelengths encounter less scattering and penetrate biological tissues deeper than shorter wavelengths. Light absorption at lower wavelengths is decreased by endogenous chromophores: eg, nucleic acids (λ_{max} 260 nm), aromatic amino acids tryptophan and tyrosine (λ_{max} 275 nm), urocanic acid (λ_{max} 277 nm), hemoglobin and deoxy-hemoglobin (λ_{max} 420 nm), bilirubin (λ_{max} 460 nm), flavins (flavoproteins), porphyrins (cytochromes, myoglobin), and melanins. As a consequence, there is an optical window from 600 - 1200 nm where light can penetrate biological tissues maximally.

Subcellular localization of a photosensitizer determines its site of action, and the photosensitizer absorption spectrum determines the wavelengths for optimal light activation and therefore its suitability for *in vivo* application. Negatively charged photosensitizers (fluoresceins and sulfonated phthalocyanines) tend not to enter intact cells and therefore the plasma membrane is the primary site of action. Lipophilic cationic sensitizers (such as rhodamine 123) accumulate

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inside mitochondria because of a net negative potential inside mitochondrial membrane. DNA intercalators (psoralens) specifically target the genomic DNA (Tab 1).

Tab 1. Representative photosensitizers, their major absorption maximum (λ_{max}), primary subcellular target, and recognized or potential (in parentheses) clinical use.

Photosensitizer	λ_{max}/nm	Subcellular target	Clinical treatment
Chlorins	660		(cancer therapy)
Fluoresceins	550	plasma membrane	pesticide
Fullerines (C_{60}, C_{70})	UV		(cancer therapy)
Hypericin	600		depression
Hypocrellins	460		skin lesions
Merocyanine 540	533	plasma membrane	leukemia
Methelene blue	664		blood sterilization
Naphthalocyanines	776		(cancer therapy)
Photofrin Ⅱ	640		cancer therapy
Phthalocyanines	670	phospholipase C	(cancer therapy)
Porphycenes	633		(cancer therapy)
Psoralens	UVA	DNA	psoriasis, vitiligo
Purpurins	700		(cancer therapy)
Platyrins	650		(cancer therapy)
Rhodamine 123	500	mitochondria	
Texaphyrins	730	phospholipase C	(cancer therapy)

Photodynamic cellular responses

After brief incubation, certain photosensitizers mainly localize to the plasma membrane[1,2]. Upon subsequent light activation, these membrane-bound agents activate or modulate a number of physiologic processes: contraction or relaxation of smooth muscle cells[3,4], slow phasic increases of intracellular calcium concentration ($[Ca^{2+}]_i$) in fibroblasts, thymocytes, cardiomyocytes, colon adenocarcinoma cells[2,5-10], amylase secretion in pancreatic acinar cells[11,12], inhibition of amylase secretion in AR4-2J cells[13,14].

A number of photosensitizers trigger the physiologic process of apoptosis: psoralen in lymphocytes[15]; phthalocyanine in lymphoma cells, fibrosarcoma cells, leukemia cells, HIV-infected lymphocytes, and promonocytic cells[16-18]; photofrin Ⅱ in fibrosarcoma cells[19]; purpurin and porphycene in leukemia cells[20,21].

Photodynamic modulation of smooth muscle

Targeting the tumor vasculature is a form of tumor eradication that after repeated treatment does not generate drug resistance. Therefore, work on photodynamic modulation of smooth muscle cells is critical for a rational design of tumor therapy. To elucidate direct photodynamic effects on smooth muscle cells without the complicating factor of endothelial cells, guinea pig taenia coli has been used.

In the isolated guinea pig taenia coli, the photodynamic action of halogenated fluoresceins (erythrosine, rose bengal), and sulfonated aluminium phthalocyanine (SALPC)[3,4] triggered complex patterns of contraction/relaxation. SALPC photodynamic action induced a triphasic contraction: an initial rapid contraction, a relaxation followed by a sustained contraction. This contraction pattern was dependent on the presence of extracellular calcium ($[Ca^{2+}]_o$). Thiol reductants *L*-cysteine, *N*-acetyl-*L*-cysteine, and *DL*-dithiothreitol reduced the sustained phase of contraction. In taenia coli precontracted with carbachol, SALPC photodynamic action induced a triphasic relaxation: a rapid relaxation, a transient contraction, and a sustained relaxation. The sustained phase of relaxation was potentiated by the thiol reductants *L*-cysteine, *N*-acetyl-*L*-cysteine, *DL*-dithiothreitol, and reduced glutathione. A cGMP analogue 8-PCPT-cGMP in the carbachol-precontracted taenia produced a triphasic relaxation very similar to the photodynamic relaxation. These data indicate that photodynamic action of SALPC produced a rapid contraction which may be due to activation of receptor-mediated contractile signalling pathway; direct activation of guanylate cyclase leads to the transient relaxation which is also seen in precontracted muscle cells and potentiated by the thiol reductants; while permeabilization of the smooth muscle cell plasma membrane leads to calcium influx, and subsequent sustained muscle contraction[4].

Photodynamic modulation of pancreatic acinar cells

Pancreatic cancer has the poorest prognosis: a 5-year survival rate of 3 %. Therefore, the photodynamic modulation of both normal and tumoral pancreatic acinar cell functions has been investigated.

Stimulation of amylase secretion Halogenated fluorescein rose bengal and SALPC were

used. Rose bengal photodynamic action in perfused pancreatic acinar cells induced amylase secretion, which was monophasic when the perfusing major anion was chloride; it became biphasic when chloride was replaced with glutamate[11]. The initial response was possibly due to a direct stimulation of the receptor-mediated secretory machinery, whereas plasma membrane permeabilization led to a delayed entry of glutamate anion through plasma membrane and zymogen granule membrane to support the exocytotic process further. Amylase secretion was also seen in SALPC photodynamic action[12,14], which also became biphasic when chloride was replaced with glutamate (Matthews & Cui, unpublished). The stimulation of secretion did not depend on an intact acinus configuration, since a similar stimulation was also seen in single isolated pancreatic acinar cells[13]. The time course of amylase secretion and membrane permeabilization (^{86}Rb efflux and LDH leakage) was compared. It was found that amylase secretion generally preceded membrane permeabilization (^{86}Rb efflux and LDH leakage). In addition, after buffering $[Ca^{2+}]_i$ with BAPTA, photodynamic amylase secretion was inhibited[14]. These data suggest that membrane permeabilization is not a major cause for initial amylase secretion which must be due to a direct stimulation of the secretory machinery at the plasma membrane with a resultant net increase in $[Ca^{2+}]_i$. The target site for photodynamic action could be receptors, G proteins, or coupled effectors[12].

Inhibition of amylase secretion In contrast to stimulation of secretion in normal pancreatic acinar cells, SALPC photodynamic action in the pancreatic tumor cell line AR4-2J led to an inhibition of secretion[13,14]. Basal secretion could be completely obliterated. Inhibition persisted even when the plasma membrane was permeabilized (indicated by LDH leakage). In control experiments, membrane permeabilization with digitonin stimulated amylase secretion. Removal of $[Ca^{2+}]_o$ reversed photodynamic inhibition, resulting in an increase instead. BAPTA buffering of $[Ca^{2+}]_i$ did not affect the photodynamic inhibition of secretion in AR4-2J cells[14]. From these experiments it is obvious that certain plasma membrane components essential for amylase secretion are damaged in photodynamic action in AR4-2J cells, and this process is calcium-dependent. Interestingly, similar to SALPC photodynamic inhibition in AR4-2J cells, photodynamic action by protoporphyrin also leads to inhibition of secretion in rat peritoneal mast cells[22].

Work on presynaptic membrane and in yeast indicates that exocytotic process is controlled by an elaborate system of SNAP (membrane fusion proteins) receptor proteins (SNARE) which include v-SNARE (v for vesicular) and t-SNARE (t for target). Plasma membrane t-SNARE include syntaxins (isoform 1A, 1B, 2, 3, 4, and 5) and SNAP-25[23]. It is possible that syntaxin isoforms involved in secretion in normal acinar cells and those involved in secretion in tumor AR4-2J cells and mast cells are different, hence they are subject to differential photodynamic modulation. As a result, in normal acinar cells photodynamic action results in stimulation, whereas in tumoral acinar cells and mast cells the result is inhibition.

Arachidonic acid release Other than stimulation of amylase secretion, SALPC photodynamic action has been found to stimulate liberation of arachidonic acid and prostaglandin production in pancreatic acinar cells[24]. Photodynamic liberation of arachidonic acid were biphasic: an initial inhibition followed by stimulation. Both arachidonic acid release and prostaglandin production was delayed in comparison with amylase secretion; furthermore, blockade of prostaglandin production with indometacin did not affect amylase secretion. It is concluded that photodynamic action may directly activate phospholipase A_2 (PLA_2) to liberate arachidonic acid, which is subsequently acted upon by cyclooxygenase to produce prostaglandins; but neither arachidonic acid liberation nor prostaglandin production is responsible for photodynamic stimulation of amylase secretion. Therefore, photodynamic action must stimulate amylase secretion through mechanisms other than arachidonic acid release.

Triggering of $[Ca^{2+}]_i$ oscillation A number of studies have found that photodynamic action led to an increase in $[Ca^{2+}]_i$ (Tab 2). Earlier works were performed in populations of

Tab 2. Photodynamic action induced increases in $[Ca^{2+}]_i$.

Type of cell	Photosensitizer	Reference
Adrenal chromaffin cells	SALPC	Hayashi & Kanno, personal communication
Bladder carcinoma cells	photofrin	51
Cardiomyocytes	erythrosine B	8
CHO cells	SALPC	5
Colon adenocarcinoma cells	ALA	9
Fibroblasts	SALPC	2
Lymphoma cells	SALPC	16
Myeloma cells	$ZnPcS_2$	10
Pancreatic acinar cells	SALPC	26
Pancreatic acinar cells	PLMGdB	25
Thymocytes	erythrosine B	7

cells, and in all cases a slow, phasic increase in $[Ca^{2+}]_i$ was observed.

In rat pancreatic acini, brief (1 – 2 min) photodynamic action triggered persistent or irreversible oscillations in $[Ca^{2+}]_i$[25,26]. The gadolinium porphyrin-like macrocycle (PLMGd) effect was dose-dependent: these oscillations gradually degenerated into a plateau phase under more intense photodynamic action[25]. SALPC photosensitization triggered similar $[Ca^{2+}]_i$ oscillations[26]. The photodynamically induced oscillations could be completely blocked by a phosphatidylinositol-specific phospholipase C (PI-PLC) inhibitor U73122 (1-{6-[(17β-3-methoxyestra-1,3,5(10)-trien-17-yl) amino] hexyl}-1H-pyrrole-2,5-dione), but not by phosphatidylcholine-specific phospholipase C (PC-PLC) inhibitor D609 (tricyclodecan-9-yl xanthate). Removal of $[Ca^{2+}]_o$ abolished $[Ca^{2+}]_i$ oscillations, which was reversible upon readdition of $[Ca^{2+}]_o$. The newly discovered plasma membrane permeable inositol 1,4,5-trisphosphate (IP_3) receptor inhibitor, 2-aminoethoxydiphenylborate (2-APB)[27-29], also inhibited photodynamic oscillations. Judging from these data, it is concluded that photodynamic action at the plasma membrane transfixes PI-PLC in an active conformation, PI-PLC*. PI-PLC* catalyzes the hydrolysis of phosphatidyl-4,5-bisphosphate (PIP_2) to generate IP_3. IP_3 upon binding to IP_3 receptors (IP_3R) on the internal Ca^{2+} stores, releases Ca^{2+} into the cytosol and hence $[Ca^{2+}]_i$ increases. The amount of Ca^{2+} released into the cytosol was governed by $[Ca^{2+}]_i$ with a bell-shaped response curve (positive regulation with low $[Ca^{2+}]_i$; negative regulation with high $[Ca^{2+}]_i$), and by Ca^{2+} concentration in the internal stores, $[Ca^{2+}]$ (positive regulation). Lowered $[Ca^{2+}]_s$ stimulates Ca^{2+} entry into the cell by the stores operated Ca^{2+} channels (SOCC)[30], to replenish the internal stores, which may involve the Ca^{2+}-ATPase on the internal stores membrane. Fixation of PI-PLC in an active conformation therefore is the sole requirement to trigger this cascade of events, and $[Ca^{2+}]_i$ as a result oscillates.

As a consequence of the $[Ca^{2+}]_i$ increase, the saturated calmodulin in turn modulates a number of intracellular proteins, typically calcium/calmodulin-dependent protein kinase II (Cam kinase II)[31]. Cam kinase II was found to be involved in stimulus-secretion coupling in rat pancreatic acinar cells[32], although its major role in other secretory cells such as the anterior pituitary cells may regulate the L-type voltage-dependent calcium channels[33,34]. Other than Cam kinase II, increased $[Ca^{2+}]_i$ may also directly stimulate the exocytotic process through the v-SNARE synaptotagmin[23].

Ion channels There is no evidence so far to suggest that photodynamic action would have specific membrane targets other than PLC in pancreatic acinar cells. Photodynamic action has been found to modulate specific ion channels. Tarr and Valenzeno found that short periods of rose bengal photodynamic action (2 – 4 s) suppressed all major ion (Na^+, Ca^{2+}, K^+) currents in cardiomyocytes, while longer photodynamic action induced a new, leak current[35]. In the ciliated protozoon *Paramecium caudatum*, the photodynamic action of methylene blue activates both a Ca^{2+} current (in the anterior portion) and a Ca^{2+}-dependent K^+ current (in the posterior portion) resulting in a depolarization and a hyperpolarization, respectively[36]. As to how the relevant ion channel proteins are affected by photodynamic action, will have to await further molecular studies.

Mitochondrion as a site of action *In*

vivo, the photosensitizer protoporphyrin could be synthesized *de novo* from δ-aminolevulinic acid (ALA). Protoporphyrin photodynamic action was found to lead to cell lysis in AR4-2J cells. The fact that mitochondrial benzodiazepine receptor ligands PK11195 [1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline-carboxamide] and Ro 5-4864 [7-chloro-5-(4-chlorophenyl)-1, 3-dihydro-1-methyl-2H-1, 4-benzodiazepin-2-one] attenuated ALA photodynamic effect, combined with the fact that protoporphyrin has high affinity for the mitochondrial benzodiazepine receptor, indicates that the mitochondrion may be an important site of photodynamic action leading to cell death[37].

Nuclear effects The membrane-specific SALPC and the DNA intercalator T4MPyP (a porphine derivative) both induced in golden hamster pancreatic carcinoma line H2T micronucleus formation, and a positive correlation between micronucleus formation and cytotoxicity was found[38].

Photodynamic modulation of cell signalling

Photodynamic action triggers diverse cellular responses in many types of cell. The photodynamically induced cellular responses may be due to modulation of intrinsic cell signalling pathways. In rat pancreatic acinar cells and mouse lymphoma cells, SALPC photodynamic action activates PLA_2[16,24] to liberate arachidonic acid and via cyclooxygenase to stimulate prostaglandin production. This process may play an important role in the initiation of apoptosis[16]. In a human bladder transitional carcinoma cell line T24, hematoporphyrin derivative (photofrin) photodynamic action also stimulates the production of prostaglandin, but prostaglandin here may play the role of protection against further photodynamic insult[39]. In rat pancreatic acinar cells and adrenal chromaffin cells, SALPC and PLMGd photodynamic action irreversibly activates PI-PLC, generating a physiologic form of $[Ca^{2+}]_i$ oscillation[25,26] (Hayashi & Kanno, personal communication). This $[Ca^{2+}]_i$ oscillation may be transformed into a more persistent $[Ca^{2+}]_i$ increase[25] by controlled photodynamic action.

Photofrin photodynamic action has been shown to stimulate the production of intracellular cAMP in the cell line T24, which promotes a protective effect in these incident cells[40]. SALPC photodynamic action stimulates immediate tyrosine phosphorylation of 80-kDa and 55-kDa proteins in mouse lymphoma L5178Y cells, probably via activation of plasma membrane associated *src* family protein tyrosine kinases; the activation of this signalling pathway tends to protect the cells[41]. The photodynamic action by phthalocyanine in CHO cells also stimulates the phosphorylation of MAP kinase and activation of P21-Ras[42]. In cultured murine keratinocytes, benzoporphyrin photodynamic action strongly activates MAP kinases SAP kinase and P38 HOG1; but it has no effect on MAP kinase ERK[43]. There is recent indication that protein kinase C may be involved in photodynamic cell killing[44].

Photodynamic action modulates gene expression. Gomer and associates found that after photodynamic action, expression of the following proteins increased significantly: glucose-regulated protein GRP-78 (with photofrin II as the sensitizer, 1991), heme oxygenase in CHO fibroblasts (photofrin II, 1991), nuclear factor k_B in mouse L1210 cells (photofrin II, 1993), induction of immediate early response genes (*fos*, *jun*, *myc*, *egr*-1) in fibrosarcoma RIF cells (rose bengal, photofrin II, chlorin, 1994), and heat-shock protein HSP-70 in fibrosarcoma RIF cells (chlorin, purpurin, photofrin, 1996)[45]. Similarly, Kick *et al* found that photofrin photodynamic action in human epithelial cells HeLa leads to strong and prolonged induction of *jun* and *fos*[46].

The signalling pathway in the photodynamic triggeration of apoptosis is not well defined. Limited studies indicate that PLC and PLA_2 activation may be involved in photodynamically induced apoptosis in mouse lymphoma cells[16]. Serine/threonine phosphorylation tends to inhibit apoptosis and serine/threonine dephosphorylation promotes apoptosis in some leukemia cell lines[47]. Photodynamic action induced apoptosis may have some common connection with apoptosis induced by other agents in that Bcl-2 expression promotes resistance to apoptosis in CHO fibroblasts[48].

Photodynamic action of all photosensitizers induces the expression of certain stress proteins including the cytosolic and nuclear localized heat-shock protein HSP72, mitochondrion localized GRP75, and endoplasmic reticulum (ER) localized GRP78 and GRP94. In a recent study by Oseroff and coworkers, it was found that the mitochondrial targetting photosensitizer Victoria Blue BO mediated photodynamic action induced GRP78 expression; interestingly, GRP78 overexpression alone could amplify 7-fold the phototoxic effect of Victoria Blue BO, indicating a unique role of GRP78 in mitochondrial targetted photodynamic action[49]. Victoria Blue BO photodynamic action damages the mitochondrial respiratory chain and depolarizes the mitochondrial membrane, which can lead to the opening of the mitochondrial permeability transition pore (MPT)[49]. Sustained opening of MPT appears to play a central role in the effector phase of apoptosis[50]. Specific targetting of mitochondria may therefore prove a promising new approach in photodynamic cancer therapy.

CONCLUSIONS

Photodynamic action of different classes of photosensitizers can modulate the functions of diverse cell types, largely due to a direct modulation of specific cell signalling pathways. Since photodynamic action permanently and specifically transfixes or 'welds' signalling biomacromolecules (such as PLC), locking them permanently in a state to generate an irreversible physiologic process, photosensitization has important implications both as a powerful exploratory tool in cell biology and for practical applications.

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关键词 光化学疗法; 平滑肌; 光敏感剂; 钙; 线粒体; 胰腺; 细胞死亡