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Selective Photothermolysis: Precise Microsurgery by Selective Absorption of Pulsed Radiation

Abstract. *Suitably brief pulses of selectively absorbed optical radiation can cause selective damage to pigmented structures, cells, and organelles in vivo. Precise aiming is unnecessary in this unique form of radiation injury because inherent optical and thermal properties provide target selectivity. A simple, predictive model is presented. Selective damage to cutaneous microvessels and to melanosomes within melanocytes is shown after 577-nanometer (3×10^{-7} second) and 351-nanometer (2×10^{-8} second) pulses, respectively. Hemodynamic, histological, and ultrastructural responses are discussed.*

Many biomedical applications of lasers have been developed (*1, 2*). The first effect of light on tissue is the absorption of photons, which leads either to photochemical reactions or to significant heating. With few exceptions (*3*), biomedical lasers use a variety of thermal effects (*4*). Rapid localized heating causes large thermal transients and shock waves which may propagate, causing mechanical damage. Many enzymes are heat-labile. Above 60° to 70°C, structural proteins including collagens are also denatured (*5*). Above 70° to 80°C, nucleic acids are denatured and membranes become permeable. Thus, essentially any mammalian tissue heated to 70° to 100°C may suffer protein denaturation, leading to "coagulation necrosis." Coagulation necrosis is useful for causing hemostasis due to the denaturation of plasma proteins and the closing of vessels. Above 100°C, vaporization of tissue water with rapid volume expansion followed by carbonization of the dry mass occurs. Rapid vaporization is useful for physically separating or ablating tissues.

Although the mode of damage is important, it is the spatial confinement of heating which mainly dictates which cells or tissues will be affected. Laser "microbeam" microsurgery has produced the most confined thermal damage in biology (*6*). Essentially any structure visualizable under light microscopy can serve as the target and can be selectively damaged. Although a powerful tool for the study of single cells or organelles in vitro, laser microbeams are impractical in cases where millions of cells are embedded in turbid, intact, living tissues. On this larger scale, thermal diffusion occurring during and after exposure and scattering and absorption of laser light within the tissue determine whether damage will be confined to the immediate path of a laser beam. Craters of coagulation necrosis with or without central vaporization have been described and modeled for a great variety of conditions (*7*). If the exposure time is prolonged, there is ample time during exposure for heat to diffuse to surrounding tissue and larger craters are seen. Scar formation is typical of such injuries.

We present here a simple scheme for confining thermally mediated radiation damage to chosen pigmented targets at the ultrastructural, cellular, or tissue structural levels. Experimental verification is shown for two biologically interesting targets—blood vessels and melanocytes. The confinement of damage can be as precise as with microbeam techniques, but millions of targeted structures are damaged simultaneously in vivo without precise aiming. This may be particularly useful in turbid tissues, which unlike the eye, limit the precision with which isolated structures can be exposed. Tissues between targeted structures, including overlying or immediately neighboring cells, are spared, potentially reducing widespread destruction and nonspecific fibrosis. There appear to be few fundamental limitations to applying the approach in various tissues and to a wide range of targets. We call the technique selective photothermolysis (SP).

This technique relies on selective absorption of a brief radiation pulse to generate and confine heat at certain pigmented targets. An absolute requirement is that the targets have greater optical absorption at some wavelength than their surrounding tissues. This requirement can be met either by choosing endogenously pigmented targets, as we do here, or by using staining or dye-labeling techniques. During laser exposure, absorption and radiationless deexcitation convert radiant energy into heat within each target in the exposure field. The targets begin to transfer this heat to their cooler surroundings mainly by thermal diffusion, but this process takes some time and heat is initially confined

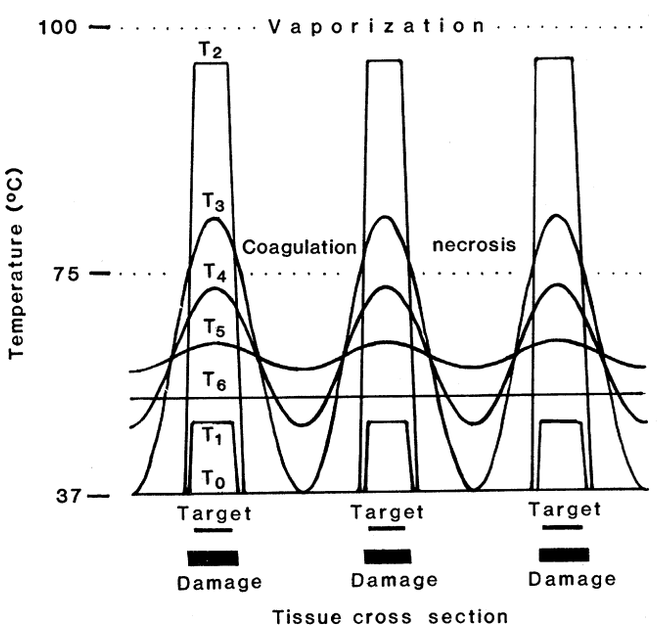

Fig. 1. Schematic temperature profiles during selective photothermolysis: T_0, before laser exposure (uniform body temperature); T_1, during laser exposure (selective rapid target heating); T_2, at the end of laser exposure (targets irreversibly damaged); T_3, one thermal relaxation time after laser pulse (targets cooling, surrounding tissue warming); T_4, two thermal relaxation times after laser pulse; T_5, five thermal relaxation times after laser pulse; and T_6, tissue slowly returing to ambient thermal equilibrium.

to the targets during exposure. At the end of an appropriately brief laser exposure, the temperature of the target may easily have surpassed that required for thermal denaturation while that of the surrounding tissue remains well below this temperature. Immediately after the exposure, thermal diffusion cools the targets and warms the tissue between them but not necessarily to denaturing temperatures. The warmed tissue, with its specifically denatured or otherwise thermally damaged targets, then slowly cools. The sequence of thermal profiles during SP is depicted schematically in Fig. 1.

The primary concern in choosing the laser wavelength for SP is to maximize selective optical absorption in the desired targets. The fraction of energy incident on a target that is absorbed in a single pass through it is roughly

$$A \cong 1 - e^{-\alpha d} \cong 1 - 10^{-\epsilon c d}$$

where α is an absorption coefficient for the target, ϵ is the molar extinction coefficient of the major target chromophore, c is its concentration, and d is an average target size; $\alpha \cong 2.3\ \epsilon c$. Deviations from this relation can occur in highly turbid tissues; A cannot exceed 1.0. For $\epsilon c d \geq 1$, $A \geq 0.9$; hence, there is little to be gained per se from choosing wavelengths or conditions at which $\epsilon c d$ greatly exceeds unity. This fortunately allows some apparently minor target absorption bands to be useful for SP. As the value of αd approaches or exceeds 1.0, the interior of the target is shielded from radiation and hence most of the heat is generated at the periphery of each target. At each point in tissue, the rate of energy absorbed per unit volume is $(\delta E/\delta t) = I\alpha$, where I is the radiation intensity at the site in question. If most of the absorbed energy is dissipated as heat, the ratio of heat input at the boundary of a target to that of its surroundings is simply the ratio of the α values. For excellent specificity in heating targets, the ratio $(\alpha_{target}/\alpha_{tissue})$ should be on the order of 10 or greater, but SP may be achievable with ratios as low as 2.

The wavelength chosen also determines the tissue depths at which SP can occur. Both optical scattering and absorption impede radiation. Scattering by connective tissue varies inversely with optical wavelength, and major tissue chromophores tend to have greater absorption at shorter wavelength (*8, 9*). Thus, in general, SP is possible at greater tissue depths with longer optical wavelengths, until the near-infrared absorption bands of water near 2000 nm are reached. If the targets lie beneath or within a pigmented tissue layer, a wavelength must be chosen to be poorly absorbed by the competing pigment but relatively well absorbed by the targets themselves. This is the case for cutaneous microvessels, which lie beneath the melanin-containing epidermis.

If specific stains or dyes are used to label targets for SP, a wavelength poorly absorbed by the unstained tissue must be chosen. An "optical window" exists for most soft tissues in the red and near-infrared regions, with $\alpha_{tissue} \cong 5\ cm^{-1}$ at 650 to 850 nm (*9*). Thus, a typical blue (red-absorbing) dye with $\epsilon \cong 10^5$ liter mole^{-1} cm^{-1} would require a concentration of about 50 μM in the targets for $\alpha_{target} \cong 10\ cm^{-1}$, that is, for SP to be possible. Dyes have been used to enhance laser-induced damage (*1–3, 6, 10*), but in most studies either photochemical or poorly confined thermal mechanisms account for the responses noted. Apparently dye-labeled antibody targeting of laser damage has not been attempted.

No matter how judiciously one has chosen the laser wavelength, poorly confined damage will result if the exposure duration is too long. During long exposures, heat transfer occurs and the entire tissue is heated relatively uniformly, causing nonspecific coagulation necrosis even though specific pigments are the sites of optical absorption. If, in the other extreme, an instantaneous laser pulse is delivered, extreme temperature differences between a target and its surroundings can be achieved, which might cause vaporization and shock wave damage. Between these two extremes of exposure duration, an interesting continuum with varying degrees of confinement of the thermal damage exists. The transition from specific to nonspecific thermal damage occurs as the laser exposure duration (pulse width) equals and then exceeds the thermal relaxation time (t_r) for the targets. For spheres of diameter d, $t_r \cong (d^2/27\kappa)$, and for long cylinders, $t_r \cong (d^2/16\kappa)$, where t_r is defined as the time required for the central temperature of a gaussian temperature distribution with a width equal to the target's diameter to decrease by 50 percent. For a

Table 1. Data on targets (microvessels and melanosomes) used for selective photothermolysis.

Target	d (μm)	t_r (sec)	Depth in tissue (μm)	Major pigment	c (M)	Absorption spectrum (*9*)
Microvessels	10 to 50, cylindrical	4.8×10^{-5}	150 to 400 (superficial plexus)	Oxyhemoglobin	2.3×10^{-3} (average whole blood)	Maxima at 418, 542, 577 nm
Melanosomes	0.5 to 1.0, ellipsoid	5×10^{-8}	50 to 150 (stratum basali of epidermis)	Melanin	?	Broad absorption at 200 to 1200 nm; decreases with wavelength

Table 2. Target optical data, and estimation of laser exposure dose D_0 for selective photothermolysis (SP).

Major target pigment	Wavelength (nm)	ϵ (liter mole^{-1} cm^{-1})	ϵc (cm^{-1})	$\epsilon c d$*	α_{target} (cm^{-1})	α_{tissue} (cm^{-1})	$\frac{\alpha_{target}}{\alpha_{tissue}}$	f (*8,9*)	Estimated D_0 for SP of target (J cm^{-2})
				Microvessels					
HbO_2	418	5.24×10^5	1200	2.4	2760	~ 30	92	~ 0.1	0.6
	577	6.08×10^4	140	0.28	322	~ 8	40	~ 0.5	1.1
				Melanosomes					
Melanin	351	?	$\sim 10^4$	~ 1	$\sim 2 \times 10^4$	~ 80	~ 250	~ 0.5	0.016
	700	?	$\sim 10^3$	~ 0.1	$\sim 2 \times 10^3$	~ 5	~ 400	~ 0.8	0.1

*d = 20 μm for microvessels and 1 μm for melanosomes.

thermal diffusivity (κ) of 1.3×10^{-3} cm^2 sec^{-1} for both target and surroundings, t_r for spherical targets with diameters of 0.1, 1.0, 10, 100, and 1000 μm has the values 3×10^{-9}, 3×10^{-7}, 3×10^{-5}, 3×10^{-3}, and 3×10^{-1} second, respectively. Thus, SP requires nanosecond-domain or shorter pulses on the subcellular organelle scale, microsecond-domain or shorter pulses on the cell-specific scale, and millisecond-domain or shorter pulses for noncapillary vessels and other small structures. Because of the greater relative heat losses from smaller targets during exposures, it is possible that small targets with t_r smaller than a carefully chosen pulse width would be spared from damage, whereas larger but otherwise similar targets would undergo SP during the same exposure.

If the laser pulse width is suitably brief, thermal diffusion during exposure can be neglected and the incident laser exposure dose required for SP can be easily estimated. The temperature rise (ΔT) of any target volume element is then

$$\Delta T = \Delta E/\rho S$$

where ΔE is the energy input per unit volume, S is the specific heat ($\cong$ 4.2 J g^{-1} °C^{-1}) and ρ is the density ($\cong$ 1.1 g cm^{-3}). In most mammalian tissues, $\Delta T \geq 40$°C should correspond to significant thermal damage. For a target with $\alpha d < 1$,

$$\Delta E \cong f D_0 \alpha$$

where D_0 is the laser exposure dose (in joules per square centimeter) incident on the tissue, and the incident intensity is decreased by a factor f before reaching the targets. Hence the exposure dose necessary for SP is

$$D_0 \cong \frac{\rho S \Delta T}{f\alpha}, \quad \alpha d < 1$$

No correction has been made for the attenuation of radiation within the targets. For cases where $\alpha d > 1$, one can estimate D_0 by assuming that all the energy incident on the cross sectional area of target is absorbed and distributed over the target's volume, giving

$$D_0 \cong \frac{\rho S \Delta T A_t}{f V_t}, \quad \alpha d > 1$$

where A_t is the target area and V_t is the target volume. Because SP invests energy in heating only small targets and not the entire tissue mass, as the pulse width is decreased sufficiently to cause SP one would expect the incident energy necessary for a biologic effect to decrease also. Similar reasoning was invoked by Hayes and Wolbarsht (*11*) to explain the lower retinal damage threshold seen after 30-nsec (0.07 J cm^{-2}) versus 250-μsec (0.7 J cm^{-2}) 694-nm ruby laser pulses (*12*). Damage at the shorter pulse width may have been due to vaporization of melanosomes within the retinal pigment epithelium, whereas the results with the longer pulse width were attributed to the heating of larger volumes of tissue.

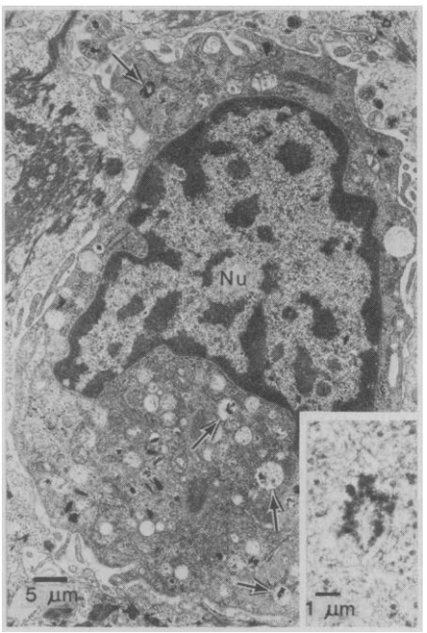

Fig. 2. Transmission electron micrograph (×9,300) of cutaneous melanocyte after in vivo irradiation with 351-nm excimer laser pulse, showing specific disruption of melanosomes (arrows) (inset, ×32,000). *Nu*, nucleus.

We first studied SP of cutaneous microvasculature to develop a specific therapy for hemangiomas (*13*). Tables 1 and 2 give pertinent data for SP of microvessels. Radiation at the 577-nm oxyhemoglobin (HbO_2) absorption band was chosen because this wavelength penetrates skin well (*8, 9*), minimizes absorption by melanin in the overlying epidermis (*9, 13*), and offers excellent selective absorption by blood vessels. For vessels 20 μm in diameter, t_r is about 50 μsec. A dye laser with 0.3-μsec pulse width (Candela model SLL-1100) was used to irradiate uniform 3-mm sites with single pulses ranging from 0.5 to 5 J cm^{-2} on the forearms of eight fair-skinned volunteers. Responses were observed clinically and histologically immediately, 24, and 48 hours after exposure.

Striking vascular changes were noted with little or no damage to the overlying epidermis or structures between vessels. A D_0 of 1.5 to 2 J cm^{-2} consistently produced a pinprick sensation and within a minute the forearm turned purple (purpura), indicating superficial hemorrhage. Twenty-four hours after exposure, a necrotizing vasculitis without epidermal changes was seen histologically. The purpura was an all-or-none response with a threshold of 1.27 ± 0.18 J cm^{-2}. Cooling the skin to 10°C produced a consistent increase in this threshold dose to 1.60 ± 0.11 J cm^{-2} ($P < .05$ by paired t-test), supporting a peak temperature-dependent damage mechanism. The magnitude of this temperature effect is most consistent with microvaporization as the cause for the microhemorrhage leading to purpura.

Hamster cheek pouches were exposed to the same 577-nm dye laser in vivo; this procedure allowed the direct visualization of microvessels. With increasing dose from 0.5 to 2.0 J cm^{-2}, we observed (i) immediate brown discoloration of blood; (ii) a sudden, viscous, decrease in blood flow; (iii) permanent hemostasis (> 15 minutes); and (iv) vessel rupture with hemorrhage. This progression of effects is presumably related to the increasing target temperatures achieved, with the first three effects due to hemoglobin, plasma, and tissue protein denaturations, respectively, whereas the fourth effect may be due to vaporization or shock wave damage.

We also studied SP of cutaneous melanosomes (1-μm pigment granules) and melanin-containing cells (Tables 1 and 2). In the deeply penetrating spectral region around 700 nm, absorption by blood is minimal but melanin has considerable absorption (*9*). We chose a 351-nm XeF excimer laser (Tachisto model 400 XR), however, to maximize absorption by melanized targets at a wavelength that penetrates poorly beyond the epidermal basal cell layer. For 1-μm melanosome-specific photothermolysis, a pulse width of less than 50 nsec is necessary; the excimer laser pulse width was 20 nsec.

Light microscopy of exposure sites 2 mm by 10 mm in six Caucasian subjects biopsied 24 hours after receiving single pulses of excimer laser exposure doses between 0.05 and 0.40 J cm^{-2} revealed highly specific damage to melanin-containing cells. Transmission electron microscopy of representative biopsies showed degenerative changes selectively involving isolated melanocytes and melanin-containing keratinocytes in the basal cell layer after doses of 0.1 to 0.2 J cm^{-2}. Nearly 100 percent of the pigmented basal cells were necrotic after exposures of 0.2 to 0.4 J cm^{-2}, but the less pigmented and immediately neighboring suprabasal keratinocytes were strikingly less affected or normal. There

was no evidence of deep follicular or vascular damage. Electron microscopy showed enlarged, focally disrupted, and centrally electron-lucent melanosomes within affected melanocytes and basal keratinocytes (Fig. 2), whereas organelles of adjacent nonpigmented cells (for example, Langerhans cells) were unaltered. Biopsies taken immediately after exposure disclosed similar changes occurring selectively in melanosomes; these results suggest that these melanin-containing organelles are the primary sites of injury. Grossly acute inflammation for several days was followed by hypopigmentation developing 7 to 10 days after exposure, without gross epidermal sloughing. Exposed sites then gradually repigmented without apparent scarring.

The feasibility of vascular, cellular, and ultrastructurally specific SP is apparent from this work. Whatever usefulness SP of vascular or pigment cell targets may have, the general technique may find many biomedical applications. As a microsurgical technique, cell-specific SP affects large cell numbers without widespread tissue damage. In tissues such as the central nervous system where surgery is hazardous and single cells are the functional operating units, SP may be especially valuable. If tunable lasers and cell-specific dye delivery systems can be used, choice among many targets is possible. The biologic repair of such highly specific damage needs to be understood.

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Brief Deprivation of Vision After Unilateral Lesions of the Frontal Eye Field Prevents Contralateral Inattention

Abstract. *Brief deprivation of vision after unilateral lesions of the frontal eye field prevents the appearance of contralateral inattention to visual, auditory, and somatosensory stimuli. The forced circling that accompanies inattention, however, is not affected. An equivalent preoperative period in the dark only partly reduces inattention symptoms. Visual deprivation does not reduce or prevent inattention resulting from lesions of the superior colliculus.*

In primates a small region of dorsolateral frontal cortex, the frontal eye field, plays a specialized role in eye movements, attention to visual and other sensory stimuli, and spatial alternation and learning (*1–4*). This frontal area is distinguished by a pattern of connections with other brain regions that displays three significant features: (i) polysensory corticofrontal input and a diffuse sensory, visceral, and emotional relay from the dorsomedial nucleus; (ii) motor involvement through projections to the motor and premotor cortex and the neostriatum; and (iii) tectal projections by which retinal input to the superior colliculus may be modulated (*5*). We may thus expect that damage to the frontal eye field will be reflected in each sensory modality and in intermodal association, that a performance disorder will contribute to the attentional and spatial deficits, and that there will be affinities to the symptoms of superior colliculus lesions. Each expectation is borne out experimentally (*2, 6–8*).

There is a similar frontal specialization in the rat. Anatomically, inputs to an anteromedial cortical area from the dorsomedial nucleus and outflow to the striatum and tectum significantly resemble the picture seen in the primate (*9*). Electrical stimulation of this region yields eye movements (*10*), and lesions result in attentional and spatial deficits (*11, 12*).

Unilateral lesions of the frontal eye field produce marked contralateral inattention to polysensory stimuli and forced ipsiversive circling. Monkeys largely recover from these effects in 4 to 6 weeks, rats in about 3 weeks (*2, 3, 11*). Sectioning the corpus callosum after recovery from the cortical lesion reinstates inattention, but recovery again follows (*3*). This recovery from deficits that are initially severe demonstrates the remarkable modifiability of neural systems in response to injury.

Another body of research has established that the conditions attending the lesion may alter its consequences. Preoperative dieting, for example, attenuates the aphagia and sensorimotor deficits produced by lateral hypothalamic destruction, while preoperative fattening exacerbates them. Maintaining animals in the dark pre- or postoperatively minimizes the motor symptoms of lateral hypothalamic lesions (*13*). This research suggests that altering relevant experience in the perisurgical period might modify the symptoms of inattention that follow lesions of the frontal eye field. What experience would be relevant? Anatomical, physiological, and behavioral data on the frontal eye field point to the visual modality. In an earlier experiment on the question (*11*), rats were trained to discriminate patterns before being given unilateral lesions of the anteromedial cortex or, in the case of the controls, of the dorsolateral cortex. One group of animals with anteromedial lesions was kept in darkness except during daily testing; the other group was maintained in the light. The latter group took significantly longer than the controls to make a correct choice, reflecting impaired attention (the impairment was contralateral to the lesion). The response latencies of the visually deprived animals, however, resembled those of controls; thus there was no attentional impairment.

We report here the effects of visual deprivation on symptoms resulting from lesions of the anteromedial cortex or superior colliculus, as determined by sensory tests in visual, auditory, and somatosensory modalities. Male Long-