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Ingestible roasted barley for contrast-enhanced photoacoustic imaging in animal and human subjects

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ABSTRACT

Photoacoustic computed tomography (PACT) is an emerging imaging modality. While many contrast agents have been developed for PACT, these typically cannot immediately be used in humans due to the lengthy regulatory process. We screened two hundred types of ingestible foodstuff samples for photoacoustic contrast with 1064 nm pulse laser excitation, and identified roasted barley as a promising candidate. Twenty brands of roasted barley were further screened to identify the one with the strongest contrast, presumably based on complex chemical modifications incurred during the roasting process. Individual roasted barley particles could be detected through 3.5 cm of chicken-breast tissue and through the whole hand of healthy human volunteers. With PACT, but not ultrasound imaging, a single grain of roasted barley was detected in a field of hundreds of non-roasted particles. Upon oral administration, roasted barley enabled imaging of the gut and peristalsis in mice. Prepared roasted barley tea could be detected through 2.5 cm chicken breast tissue. When barley tea was administered to humans, photoacoustic imaging visualized swallowing dynamics in healthy volunteers. Thus, roasted barley represents an edible foodstuff that should be considered for photoacoustic contrast imaging of swallowing and gut processes, with immediate potential for clinical translation.

1. Introduction

As a hybrid imaging modality that combines acoustic detection with optical excitation, photoacoustic computed tomograph (PACT) has proven capable of multiscale imaging with endogenous or exogenous contrasts, making it a valuable imaging tool in biomedical research [1,2]. The most commonly used endogenous contrast agent is hemoglobin, which provides anatomic [3,4], functional [5] and metabolic [6] information about blood vessels. Numerous exogenous agents for PACT have been demonstrated to enhance imaging contrast, including metallic nanoparticles [7–14], carbon nanotubes and graphene [15,16], organic semiconducting polymer nanoparticles [17–21], tetrapyrrole nanoparticles [22–24], dyes [25–29], proteins [30–32], and many others [33–36]. Compared to endogenous contrast agents, exogenous contrast agents can be designed to improve photoacoustic detection sensitivity or to reveal functional and molecular information such as intestine motility [37], glucose uptake [38], or calcium activity [39]. Unfortunately, with the exception of dyes such as indocyanine green, which are already approved for human use by health regulatory agencies, the majority of these novel contrast agents will not be tested in humans until passing through a lengthy and expensive regulatory process. A readily available and safe exogenous contrast agent that is already consumable would be attractive for improving immediate clinical applications of contrast-enhanced PACT. One imaging application for a consumable PACT contrast agent is swallowing imaging. Swallowing is a complex movement which is completed through coordination of nerves and muscles in the tongue, palate, pharynx, larynx, and esophagus. Swallowing disorders in humans can result in serious health issues. So far, swallowing testing in human has been performed through magnetic resonance imaging (MRI) [40], X ray [41], and ultrasound

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imaging [42]. However, MRI is high in cost, X-ray is radiative and not suitable for long-term imaging, and ultrasound has difficulty in differentiating small amount of swallowed materials from tissues. PACT is low cost, non-radiative and sensitive to optical absorption contrast. With a consumable and absorptive contrast agent, PACT might be used as a new screening and/or diagnostic tool for swallowing disorders.

In this work, we examine foods as potential photoacoustic (PA) contrast agents. Roasted barley was identified through screening of already human-consumed, edible products and is demonstrated to be a viable contrast for PA imaging in animal and human subjects. This technique allowed swallowing processes to be characterized through PACT safely and non-invasively in humans for the first time. The wavelength we chose for imaging was 1064 nm, which is advantageous for deep tissue imaging for the following reasons: low optical scattering [43], homogeneous contrast from background tissue [44], high wall-plug laser output efficiency based on current laser technology, and high maximum permissible exposure value as defined by the American National Standards Institute (ANSI) [45].

2. Materials and methods

2.1. Photoacoustic computed tomography (PACT) system configuration

All experiments were performed with our customized PACT system that utilizes an Nd:YAG laser (Continuum) as an excitation source, whose output is 1064 nm light with 10 Hz pulse repletion rate and 10 ns pulse duration (Fig. 1a). As the imaged subjects varied in different experiments, selection of optical fiber bundles for light delivery and transducers for PA signal detection were carefully considered. Configurations of PACT system in all experiments are as follows: 1) PACT system equipped with L7-4 (ATL/Philips, linear transducer array with 128-element and 5 MHz center frequency) and bifurcated fiber bundle (one circular input and two linear outputs) was used in experiments of preliminary sample pool screening, agar phantom scan and mouse intestines mapping (Fig. 1, Fig. S1a); 2) PACT system equipped with L7-4 and circular fiber (both input and output were circular) was used in depth imaging through chicken breast tissue and human hand, and dynamics intestine imaging; 3) PACT system equipped with ring fiber and three-quarter-ring transducer array (custom-made, 128-element, 5 MHz center frequency) was used solely in final sample pool screening (Fig. S1b); 4) PACT system equipped with C5-2 (Philips C5-2, 128-element, center frequency 3 MHz) and bifurcated fiber was used only in human swallowing imaging (Fig. 1b). The coupling efficiency for all three aforementioned fibers is approximately 50%. The maximum light intensities at the object surface varied from 20 to 30 mJ/cm^2 in different experiments, but all are well below the ANSI safety limit (100 mJ/cm^2) at 1064 nm [45]. Signals detected by transducers were amplified and digitized by a 128-channel ultrasound data acquisition (DAQ) system (Vantage, Verasonics) with 20 MHz sampling rate and 54 dB gain (24 dB low noise amplifier + 30 dB programmable gain amplifier). After each laser pulse, the raw channel data was reconstructed using the universal back-projection algorithm [46] and was displayed in real-time during experiments.

2.2. Preliminary sample pool screening

In order to identify the potential candidates for PA imaging, 200 types of ingestible foodstuff samples were scanned with our PACT system (Fig. S1a). For scanning, we used a 96-well plate as a sample container. The plate is made of transparent plastic to ensure maximum light illumination to all samples. In each well, 50 mg of foodstuff was weighed and ~360 μL of water was added to achieve a concentration of 139 mg/mL. The plate was then sealed with a transparent plastic tape. To ensure illumination for the sample, neighboring wells were kept empty. The 1064 nm light of the laser was routed to the imaging region through a bifurcated optical fiber bundle. The light intensity at the surface of the plate surface was around 30 mJ/cm [2], which is below the ANSI safety limitation at 1064 nm. The plate was placed underneath a water tank with a bottom window, which was sealed with an optical and ultrasound transparent silicon film. Ultrasonic gel was applied as a coupling medium between plate surface and film. PA signal of the sample was acquired by a L7-4 transducer array, which was scanned with a 0.1 mm step size from the first to the final row of the plate. Because the width of the transducer array is 38 mm, only four columns of the well-plate can be imaged in one scan. Three scans were needed to image the whole plate.

2.3. Final sample pool screening

Final sample pool screening among 20 different roasted barleys was performed with our PACT system using a three-quarter ring transducer array (Fig. S1b). For each barley, 6 mL solution with

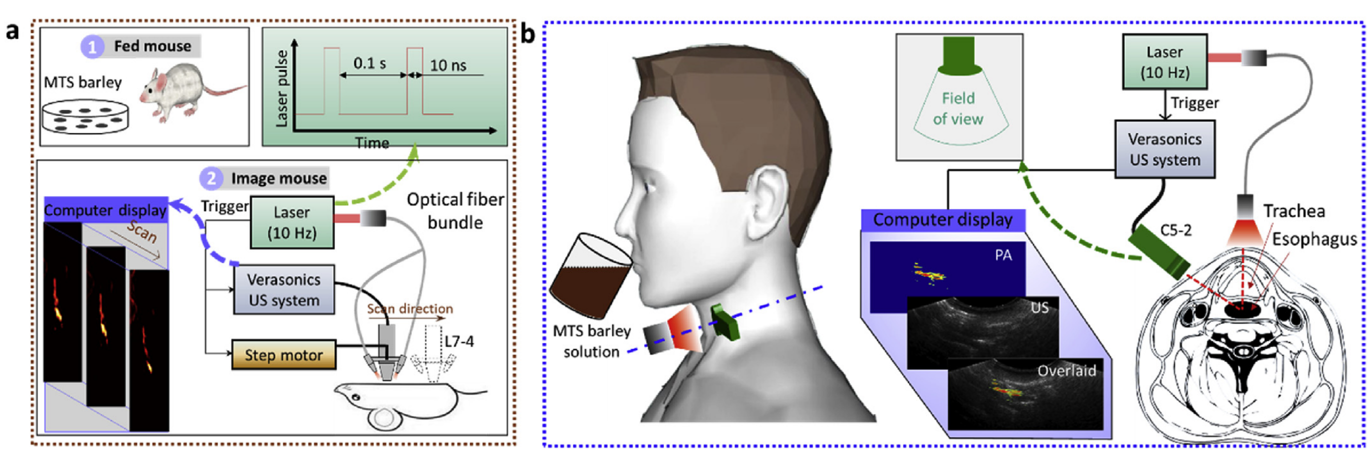

Fig. 1. PA imaging systems. (**a**). Schematic drawing of the setup used in mouse intestine imaging. The animal was fed with roasted barley before imaging. The transducer moved along the scan direction to acquire three-dimensional images. Trigger signals from the laser enabled synchronization among laser, DAQ and translation stage (driven by step motor). (**b**) Schematic drawing of the set up used for human swallowing imaging. Field of view of the C5-2 transducer is shown in the gray region.