A novel drug delivery method for neuropharmacological research, using liposomes and lasers

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Neurotransmission is a key process for communication between neurons. Mimicking neurotransmitter release with precise control in timing and dosage would provide a powerful tool to investigate brain functions and mechanisms. We developed a novel method to mimic neurotransmitter release with sub-second control using liposome stimulated by femtosecond lasers. Liposomes have the capability to encapsulate various types of drugs, making them useful for a wide range of research applications, including treatment of neurological diseases. Here, we compare this technique to other of drug delivery currently used in neuroscience applications.

Keywords: neurotransmitter release; liposome; sub-second drug application; hollow gold nanoshells; ultrafast; femtosecond laser

Table 1. Comparison of drug application systems

<table>
<thead>
<tr>
<th></th>
<th>Liposome</th>
<th>Caged compound</th>
<th>Electrical stimulation</th>
<th>Optogenetics (channelrhodopsin)</th>
<th>Pressure application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stimulation</strong></td>
<td>NIR laser</td>
<td>femtosecond</td>
<td>Electric current through electrode</td>
<td>Visible light</td>
<td>Pressure pipette through</td>
</tr>
<tr>
<td><strong>Classes of compounds that may be delivered</strong></td>
<td>Wide range of drugs</td>
<td>Limited</td>
<td>Only intrinsic neurotransmitters</td>
<td>Only intrinsic neurotransmitters</td>
<td>All types</td>
</tr>
<tr>
<td><strong>Target cell specificity</strong></td>
<td>Possible</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Toxicity</strong></td>
<td>Little or no</td>
<td>Little or no</td>
<td>Invasive</td>
<td>Gene recombination</td>
<td>Invasive</td>
</tr>
<tr>
<td><strong>Arbitrary temporal control</strong></td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
<td>Possible</td>
<td>No</td>
</tr>
<tr>
<td><strong>Arbitrary concentration control</strong></td>
<td>Possible</td>
<td>Difficult</td>
<td>Difficult</td>
<td>Possible</td>
<td>No</td>
</tr>
<tr>
<td><strong>Repeatability</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

diffusion. The time-profile and the quantity of the released dopamine can be both independently controlled via the laser power and the stimulation time. Moreover, it is possible to release drug from liposomes repeatedly without destroying them.

An alternate technique uses caged compounds that are able to bind target chemicals such as calcium, and release them following optical stimulation [10]. It is possible to exercise sub-second temporal control and arbitrary spatial control with lasers. UV irradiation is used for most caged compounds, but UV is phototoxic to neurons. The variety of compounds that can be caged is limited; thus many drugs cannot be delivered by such means. Above all, caged compound techniques only allow one-time delivery and the caged compounds are destroyed by the optical stimulation. Optogenetics uses gene modification [11, 12], whereby light-gated ion channels are expressed in specific types of cells. These can be harnessed to modulate neural activity and induce neurotransmitter release from neurons by optical stimulation. It is also possible to control release amplitude. Since optogenetic techniques stimulate living cells, they are restricted to delivering intrinsic neurotransmitters. Another way to induce neurotransmitter release from living cells is electrical stimulation via electrodes rather than optical stimulation [13, 14]. But electrodes must be inserted into the target tissue and there is essentially no cellular target specificity. It is easy to control stimulation timing, but not amplitude. Pressure application of drugs via pipettes is convenient [15], and while it is possible to deliver any drug, it is invasive and precise temporal control is difficult.

In conclusion, femtosecond laser stimulated liposome enable controlled, pulsatile delivery with unprecedented temporal resolution. Moreover, since liposomes can encapsulate a wide range of drugs and even proteins [16, 17], this method offers a wide range of applications, including delivery of selective agonists, antagonists and inhibitors. This new tool has great promise for neuroscience research.

![Figure 1. The optical/experimental setup.](image-url)
References


