Electrochemical interference in a catechol-modified chitosan redox cycling amplification system for clozapine detection

Thomas E. Winkler[1,†], Hadar Ben-Yoav[1,†], Sheryl E. Chocron[1], Eunkyoung Kim[1], Deanna L. Kelly[2], Gregory F. Payne[1], Reza Ghodssi[1,*]
[1]University of Maryland, College Park, Maryland, USA
[2]University of Maryland School of Medicine, Baltimore, Maryland, USA

Clozapine (CLZ) is the most effective antipsychotic drug for schizophrenia treatment [1]. It remains underutilized as frequent blood draws are required to monitor efficacy and adverse side effects. Point-of-care monitoring of drug levels would lower the burden associated with CLZ treatment for patients, enabling wider use of the medication and improving outcomes through personalized medicine.

We have recently demonstrated the application of a biomaterial-based redox cycling system [2] to the detection of CLZ [3]. However, moving toward analysis in a complex biological fluid like human serum, other electroactive species may interact with the system. To evaluate potential interference with CLZ sensing, here we specifically investigate three compounds: the CLZ metabolite norclozapine, a structurally highly similar molecule present in patient blood; the model biological redox species dopamine; and ascorbic acid, abundantly present in blood.

In our redox cycling system, illustrated in Fig. 1, chitosan serves as a matrix to immobilize electroactive catechol (E_0=+0.2 V vs. Ag/AgCl) near the working electrode. We fabricate these by electrodepositing chitosan followed by catechol electrografting. In this system, small redox-active molecules such as CLZ (E_0≈+0.4 V) can diffuse through the film and get oxidized at the electrode. The catechol in close proximity to the electrode allows for subsequent reduction of CLZ. The resulting continuous CLZ redox cycle between the electrode and the catechol improves the signal-to-noise ratio. We determined amplification in the charge transfer by a factor of 3.64 compared to a bare electrode [3]. To recover the redox cycling system to the reduced state, we apply negative potential in the presence of a reducing mediator, e.g. $Ru(NH_3)_6$ ($Ru^{2+/3+}$, E_0=−0.2 V)

In Fig. 2, we show the signal observed with three different oxidizing mediators: CLZ, norclozapine, and dopamine. As can be seen, CLZ and its metabolite both yield oxidation peaks. Importantly, the norclozapine peak position is shifted by 0.11 V. Similarly, dopamine can be clearly distinguished at 0.2 V, demonstrating the ability of our approach to differentiate certain redox-active compounds.

In Fig. 3, we investigate the impact of reducing mediators. The synthetic $Ru(NH_3)_6$ yields approximately 2-fold CLZ signal enhancement over solution without reducing mediator, confirming its function in reducing catechol. Ascorbic acid would present a convenient natural alternative for blood analysis. However, we find that it has neither positive nor negative impact on the CLZ signal. Finally, we observe that even in the absence of a reducing mediator, not applying negative potentials during voltammetry cycles results in diminished currents.

In conclusion, our results demonstrate the feasibility of using the redox cycling system for selective detection of CLZ over other compounds. Moreover, we show that the presence of a suitable reducing mediator is critical for our system's performance.

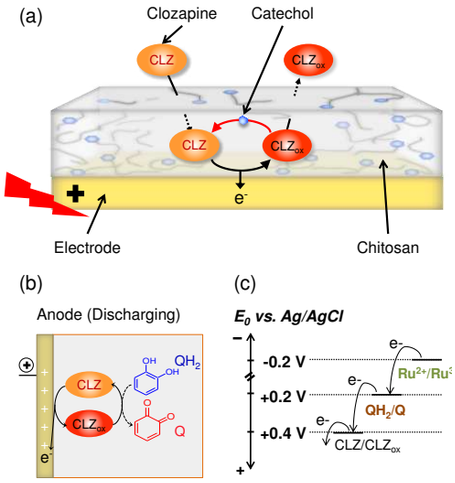

Figure 1. CLZ as an oxidizing mediator in the catechol-modified chitosan system. (a) Schematic of the system with the diffusing CLZ. (b) Continuous oxidation of CLZ in the presence of catechol (Q) reduction. (c) Standard reduction potentials and electron transfers in the system.

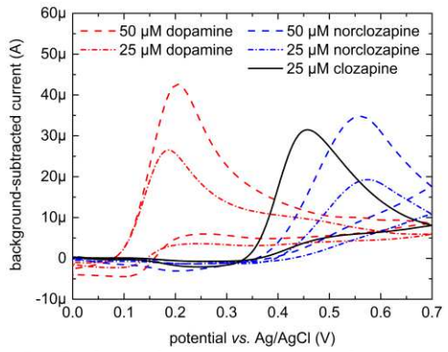

Figure 2. Cyclic voltammetry using phosphate buffer spiked with $Ru(NH_3)_6$ and either CLZ, norclozapine, or dopamine.

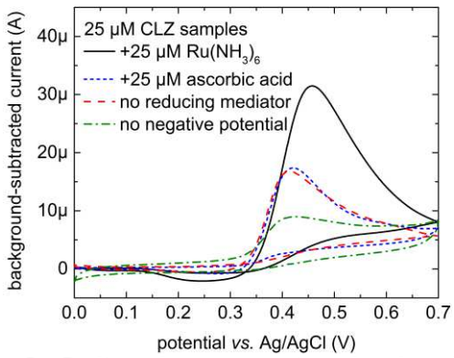

Figure 3. Cyclic voltammetry using phosphate buffer spiked with CLZ and either $Ru(NH_3)_6$, ascorbic acid, or neither. For the latter, a cycle limited to positive potentials is also shown.

References:

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† These authors contributed equally.

* Email: ghodssi@umd.edu