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The interplay of electrode- and bio-materials in a redox-cycling-based clozapine sensor

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ABSTRACT

We investigate gold, TiN, and platinum in combination with a chitosan–catechol-based redox-cycling system (RCS) for electrochemical detection of the antipsychotic clozapine. We have previously demonstrated the RCS for detection of clozapine in serum, but challenges remain regarding low signal-to-noise ratios. This can be mitigated by selection of electrode materials with beneficial surface morphologies and/or compositions. We employ cyclic voltammetry to assess the redox current generated by clozapine, and differentiate solely surface-area-based effects from clozapine-specific ones using a standard redox couple. We find that nano- and microstructured platinum greatly amplifies the clozapine signal compared to gold (up to 1490-fold for platinum black). However, the material performs poorly in the presence of chloride ions, and RCS modification provides no further amplification. The RCS combined with atomic-layer-deposited (ALD) TiN, on the other hand, increases the signal by 7.54 times, versus 2.86 times for RCS on gold, with a 9.2-fold lower variability, indicating that the homogenous and chemically inert properties of ALD-TiN may make it an ideal electrode material.

1. Introduction

Electrochemical sensors are appealing due to their ability to directly translate chemical events into electronic signals, which are easily read out [1]. This makes them uniquely versatile and well-suited for miniaturization. A major challenge, especially in clinical samples like blood, is interference from multitudes of other chemical species, many of them redox active [2]. Typical applications, therefore, utilize highly specific recognition elements (e.g. antibodies) or target high-concentration analytes (e.g. glucose) [3,4]. To open up a wider range of targets, however, different electrode modification strategies to confer selectivity are required and have been pursued [5,6]. Particularly when applying biomaterial-based modifications on top of solid-state electrodes, one point of great interest (yet often neglected) is the choice of the underlying electrode material, which fundamentally affects the ability of the sensor to interact with the analyte to produce a signal. Surface morphology, physicochemical interaction with the target analyte, and propensity for fouling or oxidation are all material characteristics that affect sensor performance. Optimization of these systems requires careful investigation into the physicochemical properties of the electrode and its interactions with the analyte and interferents.

In the present work, we specifically consider a biomaterial-based redox-cycling system (RCS) for amplification of electrochemical signals from small molecule analytes [7]. Our RCS comprises an electrodeposited chitosan matrix that facilitates grafting of catechol near the electrode surface. This yields a redox capacitor, allowing for repeated analyte oxidation at the electrode following reduction by catechol, leading to signal amplification. We have previously applied the RCS toward sensing pyocyanin and, more recently, clozapine [8,9]. Clozapine is an antipsychotic drug, the most effective one available for managing treatment-resistant schizophrenia [10–12]. Electrochemical sensing has the potential to greatly decrease the burden associated with

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Table 1
Electrochemical characterization results for the electrode materials studied in this work. The model redox couple ferri/ferrocyanide gives an indication of the effective electrochemical surface area. Toward therapeutic drug monitoring of clozapine, materials were tested with (RCS) and without (bare) further redox-cycling system modification in either PB or PBS. For each group, the relevant gold reference is in *italics*, and relative amplification by more than a factor of five is in bold.

Material	Electrochemical peak current (normalized to bare gold electrode)				
	Ferri/ferrocyanide	Clozapine in PB		Clozapine in PBS	
	Bare	Bare	RCS	Bare	RCS
Au	*1.00 ± 0.02*	*1.00 ± 0.05*	3.04 ± 0.59	*1.00 ± 0.25*	2.86 ± 1.25
TiN	1.05 ± 0.01	0.88 ± 0.07	**6.14 ± 0.86**	1.10 ± 0.15	**7.54 ± 0.36**
Pt-ref	1.40 ± 0.04	**250 ± 56**	**125 ± 19**	**32 ± 11**	–
Pt-black	2.70 ± 0.18	**1490 ± 150**	–	**193 ± 20**	–

required safety and efficacy monitoring (therapeutic range: 1–3 μM) by reducing sample volumes and bringing testing closer to the patient [13]. Like many electrochemical sensors, the use of our RCS has so far been limited to gold electrodes, achieving a detection limit of below 1 μM in human serum [14]. Gold is easily microfabricated and well-characterized; however, it is not as inert as many studies assume, and may not be an optimal choice for a given sensor [15]. Different surface chemistry could specifically reduce the free energy associated with clozapine oxidation ($E \approx +0.38$ V vs. Ag/AgCl 1 M KCl) and different surface morphologies could increase the area for interaction.

In this work, we evaluate gold, TiN, and platinum in combination with the RCS for detection of clozapine. TiN is a conductive ceramic with excellent inertness and stability [16]. In the context of analytical electrochemistry this material has to date only been utilized in the form of thicker and more porous physical or chemical vapor deposition films; we instead utilize atomic layer deposition (ALD) to create a low-defect, homogenous film that allows us to further emphasize its inherent inert properties. By contrast, platinum is a noble metal with well-established catalytic properties. Electroplating allows us to further focus on this aspect by comparing reflective (Pt-ref) and highly textured (Pt-black) surface morphologies [17]. Although this is a relatively common electroanalytical electrode material, it has not been considered as a substrate for further modification, or in the context of clozapine sensing. In our study, we visualize the morphologies of the electrodes using electron microscopy. We employ cyclic voltammetry for the electrochemical characterization, initially with a standard redox couple to assess surface area enhancement. Finally, we quantify the specific clozapine sensing performance of the electrode materials with and without the RCS relative to bare gold electrodes.

2. Materials and methods

2.1. Electrochemical setup

VSP-300 potentiostat (Bio-logic); platinum counter electrode; Ag/AgCl reference electrode (1 M KCl electrolyte; CH Instruments; all potentials are denoted vs. this reference).

2.2. Working electrode fabrication

We fabricated thin-film gold electrodes (5 × 5 mm^2; 200 nm gold on 20 nm chrome adhesion layer) by sputter deposition, photolithography (Shipley 1813), and wet etching on SiO_2. After dicing, the electrodes were cleaned by successive rinsing with acetone, isopropanol, and methanol, 1 min immersion in Piranha solution(1:3 hydrogen peroxide:sulfuric acid), and finally rinsing with deionized water. Pt-ref was subsequently electroplated in 1% chloroplatinic acid, 0.0025% hydrochloric acid solution by applying − 2.500 mA for 5 min. Pt-black was fabricated similarly, with addition of 0.05% lead acetate as a catalyst and a higher current of − 7.500 mA [17]. TiN was coated with ALD (Beneq TFS 500; 400 cycles ≈ 30 nm). RCS films were applied following published procedures after another Piranha cleaning step [9].

2.3. Surface characterization

The effective electrochemical surface area was characterized by cyclic voltammetry (± 0.25 V around open circuit potential, scan speed 100 mV/s) in 10 mM sodium phosphate buffer (PB; pH 7) containing 5 mM ferricyanide, 5 mM ferrocyanide, 100 mM NaCl. Scanning electron microscopy (SEM) relied on a Hitachi SU-70 and a Tescan XEIA.

2.4. Sample solutions

We purchased all chemicals from Sigma-Aldrich, and prepared solutions with deionized water (> 16 MΩ cm). Solutions were based on either 0.1 M PB (pH 7) or 1 × phosphate-buffered saline (PBS; 10 mM PB, 2.7 mM KCl, 137 mM NaCl; pH 7.4). Samples contained either 50 μM hexaammineruthenium(III) chloride alone (reducing mediator required for RCS; negative control), or had an additional 50 μM clozapine.

2.5. Electrochemical testing

We performed cyclic voltammetry (potential range − 0.4 V to + 0.7 V, scan speed 10 mV/s), recording negative controls followed by clozapine samples for each electrode. We present the averages ($N = 3$) of the background-subtracted recordings.

3. Results and discussion

We summarize our results in Table 1, where we report electrochemical signals in terms of the normalized peak current (with bare gold defined as 1.00) and the associated standard deviation (referred to subsequently as variability, and discussed in the text as a percentage of the associated mean) for each solution and all materials investigated. We discuss these results in depth in the following sections.

3.1. Surface area characterization

Initially, we consider the effective electrochemical surface area as determined with the model ferri/ferrocyanide redox couple. This should allow for de-coupling of specific clozapine signal enhancement from pure increases in surface area. TiN shows a minimal 1.05-fold increase, with the effective surface area still defined by the underlying gold due to negligible lateral conductivity in the thin unpatterned TiN film. With Pt-ref, we observe a 1.40-fold gain, indicating that the electroplating process introduces non-negligible surface roughness, in spite of appearing gray and reflective under visual inspection. As expected, Pt-black exhibits the most robust surface area enhancement of 2.70 ×, matched by a deep black color of the film. It also became apparent that manufacturing variability increases disproportionately