Advances in Electrochemical Cortisol Detection: A Comparative Review of Glassy Carbon and Interdigitated Electrode Platforms

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Abstract:

Cortisol, a primary glucocorticoid, serves as a crucial biomarker for stress, adrenal gland function, and various physiological and pathological conditions. Accurate and timely monitoring of cortisol levels is vital for diagnostic, prognostic, and therapeutic purposes. While conventional laboratory-based immunoassays offer high sensitivity, they are often time-consuming, expensive, and require specialized equipment, limiting their utility for point-of-care (POC) applications. Electrochemical biosensors have emerged as a promising alternative, offering advantages such as rapid response, cost-effectiveness, portability, and high sensitivity. This review provides a comprehensive overview of the advancements in electrochemical cortisol detection, with a particular focus on two prominent electrode platforms: glassy carbon electrodes (GCEs) and interdigitated electrodes (IDEs). We discuss various strategies for electrode surface modification, including the integration of nanomaterials (e.g., graphene, carbon nanotubes, metal nanoparticles) and recognition elements (e.g., antibodies, aptamers, molecularly imprinted polymers). The principles of different electrochemical techniques, such as cyclic voltammetry, differential pulse voltammetry, and electrochemical impedance spectroscopy, in the context of cortisol sensing are elucidated. A comparative analysis of GCEs and IDEs highlights their respective merits, challenges, and suitability for specific applications. Finally, the review addresses current limitations, future trends, and the potential for translating these electrochemical platforms into real-world clinical and wearable devices for personalized cortisol monitoring.

Keywords: Cortisol, Electrochemical Sensor, Biosensor, Review, Glassy Carbon Electrode (GCE), Interdigitated Electrode (IDE), Stress Biomarker, Point-of-Care, Nanomaterials, Biosensing.

Introduction

Cortisol, a glucocorticoid steroid hormone produced by the adrenal cortex, is a key component of the hypothalamic-pituitary-adrenal (HPA) axis and plays a crucial role in regulating various physiological processes, including metabolism, immune function, inflammation, and the stress response [1,2]. Its secretion exhibits a pronounced circadian rhythm and responds dynamically to internal and external stressors, necessitating frequent and real-time monitoring for effective diagnosis and management of related disorders [3]. Dysregulation of cortisol levels has been implicated in a spectrum of health conditions, such

as Cushing's syndrome (hypercortisolism), Addison's disease (hypocortisolism), chronic stress, depression, and metabolic syndromes [4–6]. Conventional laboratory-based immunoassays like ELISA, RIA, and CLIA, though highly sensitive, are often hindered by long turnaround times, high costs, complex sample preparation, and the need for skilled personnel and sophisticated equipment [7]. In contrast, electrochemical biosensors offer a compelling alternative by enabling rapid, sensitive, cost-effective, and portable cortisol detection, suitable for point-of-care diagnostics and wearable systems [8]. These sensors function by transducing biochemical interactions between cortisol and a recognition element on the electrode surface into measurable electrical signals, thereby facilitating real-time hormone quantification [9]. This has fueled interest in electrochemical biosensors, which are low-cost, rapid, and miniaturizable alternatives suitable for point-of-care (POC) and wearable applications [10–12].

This review critically examines recent advancements in electrochemical cortisol biosensors, with a focus on two widely used electrode platforms: glassy carbon electrodes (GCEs) and interdigitated electrodes (IDEs). We discuss fabrication strategies, surface modification techniques, electrochemical transduction mechanisms, and performance metrics, followed by a comparative analysis of these platforms.

Fundamentals of Electrochemical Cortisol Sensing

Electrochemical biosensors provide a robust and versatile platform for cortisol detection by transducing biochemical recognition events into quantifiable electrical signals, such as current, potential, or impedance changes [13]. The specificity and sensitivity of these biosensors rely heavily on the immobilization of biorecognition elements—such as antibodies, aptamers, enzymes, and molecularly imprinted polymers (MIPs)—on conductive electrode surfaces [14,15].

Electrochemical Detection Principles

Cortisol, a glucocorticoid hormone, possesses electroactive hydroxyl and ketone functional groups that enable its direct oxidation at high anodic potentials [16]. However, this direct approach is often challenged by high overpotentials, electrode fouling, and limited selectivity. To address these issues, several detection strategies have emerged:

- **Mediated Electron Transfer Systems:** Redox-active mediators (e.g., ferrocene, metal nanoparticles) facilitate efficient electron shuttling between the analyte and electrode, reducing overpotentials and enhancing sensitivity [17].
- **Enzyme-Based Sensors:** Enzymes like 11β-hydroxysteroid dehydrogenase catalyze cortisol into electroactive products, amplifying detection signals [18].
- **Immunosensors:** These utilize antigen–antibody specificity, often incorporating enzymatic or redox labels to enable indirect but highly selective cortisol detection [27].
- **Aptasensors:** Synthetic oligonucleotide aptamers, generated via SELEX, offer high affinity and reusability, enabling stable and selective sensing [15,19].

- **MIP-Based Sensors:** MIPs create template-specific cavities via electropolymerization, offering a biomimetic and stable recognition platform for cortisol detection [15,20].

Electrochemical Techniques

Electrochemical sensors for cortisol commonly employ:

- **Cyclic Voltammetry (CV):** Useful for redox characterization and surface analysis.
- **Differential Pulse Voltammetry (DPV):** Enhances sensitivity by minimizing capacitive currents.
- **Electrochemical Impedance Spectroscopy (EIS):** Provides label-free detection by measuring interfacial resistance changes upon analyte binding [21-23].

For instance, aptamer-based EIS sensors have achieved sub-picogram detection levels in sweat [23], and DPV-enabled ZnO–graphene immunosensors have demonstrated detection limits below 0.2 nM in saliva [27].

Fundamental Components and Biorecognition Elements

A typical electrochemical cortisol biosensor consists of a three-electrode system:

- **Working Electrode:** Commonly a glassy carbon electrode (GCE) or interdigitated electrode (IDE), selected for high conductivity, modifiability, and stability.
- **Reference Electrode:** Usually Ag/AgCl.
- **Counter Electrode:** Typically platinum, used to complete the circuit.

The performance of the sensor is highly dependent on the selection and immobilization of the biorecognition element:

- **Antibodies:** Offer high specificity, but suffer from batch variability and environmental instability [14].
- **Aptamers:** Provide advantages such as chemical stability, low cost, and thermal resistance [15,19].
- **MIPs:** Represent synthetic alternatives with excellent robustness, cost-efficiency, and durability [15,20].

Glassy Carbon Electrodes (GCEs) for Cortisol Detection

Material Properties and Advantages

Glassy carbon electrodes (GCEs) are widely employed in electrochemical biosensors owing to their wide potential window, low background currents, chemical inertness, and excellent electrical conductivity [23]. Their smooth and reproducible surface makes them ideal for further functionalization.

Surface Pre-Treatment and Functionalization

To enhance the sensitivity and selectivity of GCEs for cortisol sensing, the electrode surface is modified using various nanomaterials and recognition elements:

Nanomaterial-Based Enhancement

- **Graphene and Reduced Graphene Oxide (rGO):** Provide high conductivity and surface area. rGO-modified GCEs enhance electron transfer and enable dense bioreceptor loading [24,25].
- **Carbon Nanotubes (CNTs):** Single- or multi-walled CNTs improve conductivity and provide a scaffold for biomolecule immobilization [26].
- **Gold Nanoparticles (AuNPs):** Facilitate stable antibody or aptamer attachment and signal amplification through enhanced conductivity [27].
- **ZnO Nanoparticles:** Biocompatible with high surface area, improving cortisol antibody immobilization and facilitating signal enhancement [28].
- **Metal–Organic and Covalent Organic Frameworks (MOFs/COFs):** Provide high porosity and active sites for cortisol pre-concentration [29].

Recognition Element Immobilization

- **Antibodies:** Antibody-functionalized GCEs enable high-specificity detection via immunoassay principles, often aided by redox or enzymatic tags [27].
- **Aptamers:** Aptamer-functionalized GCEs offer excellent regeneration and stability. A DNAzyme–graphene–gold hybrid system has demonstrated high sensitivity in saliva samples [30].
- **MIPs:** Electropolymerized MIP layers mimic cortisol structure, enabling robust and reusable sensors with strong specificity and selectivity [31].

Performance Characteristics of GCE-Based Sensors

GCE-based electrochemical sensors for cortisol have demonstrated excellent analytical performance across several key metrics. Reported limits of detection (LOD) typically range from picomolar to nanomolar concentrations, which aligns with clinically relevant cortisol levels found in saliva (1–100 nM) and serum (50–700 nM) [32,34,36,37]. These sensors often exhibit broad linear dynamic ranges, spanning multiple orders of magnitude, thus enabling detection across a wide range of physiological and pathological states [35,40,41].

The selectivity of GCE-based sensors is significantly enhanced by the use of specific biorecognition elements such as antibodies, aptamers, and molecularly imprinted polymers (MIPs), allowing for minimal interference from structurally similar steroid hormones [33,37,39,40]. Furthermore, reproducibility and operational stability are generally favorable. Most GCE-based sensors demonstrate consistent signal responses over repeated measurements and maintain functional integrity for several days to weeks under appropriate

storage conditions. Notably, MIP-based platforms have shown superior reusability with minimal signal degradation, even after multiple sensing cycles [33].

Applications and Challenges

GCE-based electrochemical sensors have been effectively applied to the detection of cortisol in biological fluids such as saliva, serum, and sweat, supporting their role in stress monitoring, endocrinology research, and personalized medicine [34,36]. Their compatibility with non-invasive sampling and real-time monitoring makes them particularly attractive for wearable and point-of-care diagnostic platforms.

Despite these advantages, several challenges persist. A primary concern is biofouling, which arises due to the nonspecific adsorption of proteins and other matrix components in complex biological samples. This can significantly reduce sensor performance and lifespan [39]. Additionally, immobilized biorecognition elements may experience denaturation or desorption, leading to reduced sensitivity and compromised stability over time. Furthermore, the fabrication and surface modification processes for GCEs—especially when integrating nanomaterials—require stringent control to ensure batch-to-batch reproducibility [40,41].

To overcome these limitations, future efforts must focus on the development of antifouling surface chemistries, robust and stable biorecognition layers, and scalable, reproducible fabrication protocols that maintain high performance in practical applications.

Interdigitated Electrodes (IDEs) for Cortisol Detection

Interdigitated electrodes (IDEs) are microfabricated planar arrays consisting of two comb-like electrodes interlocked in an alternating finger configuration. This geometry provides a high surface-to-volume ratio and a non-faradaic capacitive interface, which significantly amplifies electrochemical signals in small sample volumes [42]. IDEs are typically fabricated using photolithography, laser scribing, or inkjet printing on substrates such as glass, silicon, or flexible polymers with conductive materials like gold, silver, or carbon [43,44]. The narrow inter-electrode gaps (5–20 μm) enable enhanced redox cycling, reduced diffusion paths, and improved sensitivity [42,43].

For cortisol detection, surface functionalization of IDEs involves techniques such as self-assembled monolayers (SAMs), nanomaterial coatings (e.g., ZnO nanowires, graphene, AuNPs), and immobilization of biorecognition elements like antibodies, aptamers, or molecularly imprinted polymers (MIPs) [44,45]. Dielectrophoresis (DEP) has also been employed to direct the spatial deposition of nanomaterials on IDE surfaces, enhancing signal uniformity and bioreceptor alignment [50]. IDE-based cortisol sensors have demonstrated ultra-low detection limits, often in the sub-picogram range, with rapid response times of less than 5 minutes and excellent reproducibility across saliva, sweat, and serum samples [47,51]. Moreover, their planar configuration allows seamless integration into microfluidic devices and wearable platforms for real-time, non-invasive cortisol monitoring [49,62].

Comparative Analysis of GCEs and IDEs for Cortisol Detection

Both glassy carbon electrodes (GCEs) and IDEs have emerged as effective platforms for electrochemical cortisol biosensing, yet they differ markedly in design, fabrication complexity, and application focus. GCEs offer a cost-effective and chemically stable interface that supports diverse surface modifications with nanomaterials (e.g., CNTs, rGO, ZnO, MOFs) and biorecognition layers [46,48,52]. They are particularly suitable for benchtop assays and fundamental electrochemical investigations due to their straightforward fabrication and ease of use [47]. GCE-based cortisol sensors have demonstrated detection limits in the picomolar range and broad linearity, making them reliable for quantitative analysis in lab-scale applications [48,54].

In contrast, IDEs, owing to their interdigitated geometry, intrinsically promote redox cycling and local electric field enhancement, resulting in superior sensitivity and lower detection limits [42,43,51]. Their miniaturized structure is conducive to integration with flexible substrates and microfluidic systems, which is crucial for developing wearable, real-time diagnostic tools [49,55,62]. Although IDE fabrication requires more sophisticated processes such as lithography or laser scribing [43], they offer unmatched potential for multiplexing and continuous monitoring [42,45]. IDEs are thus particularly advantageous in point-of-care (POC) settings where portability, low sample volume, and high sensitivity are imperative [42,46].

Challenges and Future Perspectives

Despite significant advancements, several challenges remain in translating electrochemical cortisol sensors from laboratory prototypes to widely adopted clinical tools:

- Real-Sample Analysis and Matrix Effects: Biological samples (saliva, sweat, serum) contain numerous interferents (e.g., salts, proteins, other hormones) that can cause signal fouling, non-specific binding, or matrix effects, affecting sensor accuracy and stability [63]. Robust anti-fouling strategies and effective sample preparation are crucial.
- Selectivity: While recognition elements enhance selectivity, cross-reactivity with structurally similar steroids (e.g., corticosterone, progesterone) can still be a concern, requiring careful sensor design and validation [64].
- Long-Term Stability and Shelf-Life: Biosensors, particularly those relying on biological recognition elements (antibodies, enzymes), can suffer from limited shelf-life and stability due to denaturation or degradation. Development of more robust synthetic recognition elements (MIPs, aptamers) or stable immobilization chemistries is vital [63,65].
- Batch-to-Batch Reproducibility: Achieving consistent performance across different batches of sensors, especially those involving complex surface modifications, remains a challenge for manufacturing and quality control [63].

- Calibration and Standardization: Reliable and standardized calibration procedures are needed, particularly for wearable sensors, to account for variations in sample matrix (e.g., sweat rate and composition) and ensure accurate readings [65].
- Cost-Effectiveness for Mass Production: While individual components may be inexpensive, the overall manufacturing process—especially for microfabricated IDEs—needs to be scaled up cost-effectively for widespread adoption [66].
- Clinical Validation: Rigorous clinical validation against established gold-standard methods using a large cohort of patient samples is essential to demonstrate the reliability and clinical utility of these sensors [67].
- Integration into Wearable/Portable Systems: Developing compact, low-power electrochemical instrumentation suitable for seamless integration into wearable devices is a key engineering challenge. This includes robust wireless data transmission, power management, and user-friendly interfaces [68].

Future Directions:

- Multimodal Sensing: Combining electrochemical detection with other sensing modalities (e.g., optical, thermal) to achieve enhanced accuracy and robustness [63].
- Artificial Intelligence (AI) and Machine Learning (ML): Integrating AI/ML algorithms for complex signal processing, noise reduction, personalized calibration, and predictive analysis of cortisol dynamics [64,67].
- Advanced Nanomaterials: Exploring novel 2D materials (e.g., MXenes, transition metal dichalcogenides), quantum dots, and hybrid nanocomposites with superior electrical, catalytic, and biocompatible properties [63].
- Microfluidic Integration: Developing fully integrated lab-on-a-chip systems for automated sample collection, pre-treatment, and multiplexed detection, particularly leveraging IDEs [66].
- Non-Invasive Sample Sources: Further development of highly sensitive sensors for real-time cortisol monitoring in non-invasive biofluids like sweat, tears, and interstitial fluid, moving beyond blood/saliva [67].
- Closed-Loop Systems: Towards personalized medicine, developing feedback systems that can monitor cortisol levels and potentially trigger interventions based on real-time data [68].

Table 1: Key Characteristics and Performance Metrics

Feature/Metric	**Glassy Carbon Electrodes (GCEs)**	**Interdigitated Electrodes (IDEs)**
Material	Glassy carbon [69]	Gold, Silver, Carbon (on glass, Si, flexible polymers) [70,71]
Fabrication	Polishing, electrochemistry, simple functionalization [72]	Photolithography, laser scribing, inkjet printing [73,74]

Geometry	Disk, plate, rod (single surface) [69]	Interlocked comb-like fingers (planar, high edge density) [70,75]
Surface Area	High, enhanced by nanomaterial modification [76,77]	High effective area due to finger geometry [75]
Signal Amplification	Nanomaterials, redox mediators [78,79]	Intrinsic redox cycling, enhanced local electric fields [80,81]
Sensitivity (LOD)	Picomolar to nanomolar range [82,83]	Sub-picogram to picomolar range [84,85]
Response Time	Typically minutes [86]	Faster (<5 min) due to short diffusion paths [87]
Sample Volume	Larger drops/volumes typically [88]	Small volumes (microliters) [89]
Integration Potential	Benchtop, lab-on-chip [90]	Wearable, flexible, microfluidic integration [91,92]
Cost (per unit)	Relatively low for basic GCEs [72]	Higher initial cost, but scalable for mass production [93]
Robustness	Excellent chemical/mechanical stability [69]	Good, can be flexible substrates, microstructures more fragile [94]
Fouling Susceptibility	Requires anti-fouling strategies [95]	Also susceptible, similar countermeasures needed [96]
Applications	Fundamental research, diagnostics, lab sensors [97]	POC diagnostics, wearables, real-time monitoring [98,99]

Table 2: Comparison of Cortisol Detection Strategies on GCE versus IDE Platforms

Strategy	**GCE Examples (Refs)**	**IDE Examples (Refs)**	**Shared Advantages**	**Specific Challenges (Platform-Dependent)**
Immunosensors	GCE/rGO/AuNPs-Ab (Saliva, nM LOD) [100]	IDE/ZnO NWs-Ab (Sweat, pM LOD) [101]	High specificity, established biorecognition	Antibody stability, batch variability (GCE); complex fabrication and alignment (IDE) [102]
Aptasensors	GCE/Graphene-Aptamer (Saliva, sub-nM LOD) [103]	Flexible IDE/AuNPs-Aptamer (Sweat, sub-pg LOD) [104]	High stability, reusability, cost-effective	Aptamer selection, nonspecific adsorption [105]
MIP-based Sensors	GCE/MIP (Serum, nM LOD) [106]	IDE/MIP (Various samples, pM LOD) [107]	High robustness, low cost, reusability	Imprinting selectivity, cross-reactivity with other

				steroids [108]
Mediated Systems	GCE/Ferrocene-nanocomposite (Enhanced sensitivity) [109]	IDE-integrated redox mediators [110]	Reduced overpotential, amplified signals	Mediator leaching, biocompatibility, long-term stability [111]

Conclusion

Electrochemical biosensors have emerged as powerful tools for the rapid, sensitive, and cost-effective detection of cortisol, with glassy carbon electrodes (GCEs) and interdigitated electrodes (IDEs) representing two leading platforms. GCEs offer robustness, ease of modification, and suitability for fundamental electrochemical research, while IDEs provide superior signal amplification, miniaturization, and seamless integration into wearable and point-of-care systems. Together, these platforms support a wide range of cortisol sensing applications, from benchtop assays to real-time monitoring in biofluids. However, challenges such as matrix interference, biorecognition element stability, and scalable fabrication must be addressed to enable clinical translation. Continued innovation in nanomaterials, surface functionalization, microfabrication, and integration with flexible electronics and AI-based analytics will be crucial in advancing electrochemical cortisol biosensing toward next-generation, personalized healthcare solutions for stress monitoring and endocrine diagnostics.

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