A Simple Fluorescent Aptasensing Platform Based on Graphene Oxide for Dopamine Determination

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Abstract
Dopamine (DA) is a catecholamine neurotransmitter playing an important role in different biological functions including central nervous, renal, cardiovascular, and hormonal systems. The sensitive and selective detection of this neurotransmitter plays a key role in the early diagnosis of various diseases related to abnormal levels of dopamine. Therefore, it is of great importance to explore rapid, simple, and accurate methods for detection of dopamine with high sensitivity and specificity. We propose in this work a fluorescent aptasensor based on graphene oxide (GO) as a quencher, for the rapid determination of dopamine. The principle of this aptasensor is based on fluorescence resonance energy transfer (FRET), where GO was used as energy donor, and a carboxy fluorescein (FAM)-labeled aptamer as acceptor. In the absence of DA, FAM-aptamer was adsorbed on the surface of GO through π-π stacking interactions between nucleotide bases and the carbon network, leading to a weak FRET and a quenching of the FAM fluorescence. However, by adding the target, the aptamer undergoes a conformational change to bind to DA with high affinity, resulting in a fluorescence recovery. Under the optimal experimental conditions, the fluorescence recovery was linearly proportional to the concentration of DA in the range of 3–1680 nM, with a limit of detection of 0.031 nM and a limit of quantification of 0.1 nM. Moreover, the developed assay exhibited minor response in the presence of various interferents and it revealed a satisfactory applicability in human serum samples.

Keywords Dopamine · Aptamer · Fluorescence resonance energy transfer · Graphene oxide · Fluorescence quenching

Introduction
Dopamine (DA) is an important neurotransmitter that has a potential vital role in regulating functional activities such as the central nervous, renal, hormonal, and cardiovascular systems [1]. In addition, DA has an important effect on stress, behavior, attention, and other cognitive functions. It has been reported that high dopamine levels induce...
cardiotoxicity leading to rapid heart rates, hypertension, heart failure, and drug addiction [2]. In parallel, a low dopamine level may be considered a major cause of psychiatric disorders such as Parkinson, schizophrenia, and depression [3]. Therefore, the accurate and rapid measurement of DA is crucially required for the diagnosis of these diseases. Dopamine analysis is usually based on enzyme assays, liquid chromatography, mass spectroscopy, and capillary electrophoresis [4]. However, most of these techniques are time consuming and involve sophisticated pre-treatment process, expensive instruments, and expertise for operation, thus limiting their applications in routine detection of DA [5]. Great efforts are devoted to developing simple, accurate, and inexpensive methods for detecting DA in biological samples with high sensitivity and selectivity.

Among the different technologies, fluorescence resonance energy transfer (FRET) constitutes a promising technique promoting diagnostics. It is a non-radiative energy transfer process that occurs through dipole-dipole interaction between an emitter (donor) and an absorber molecule (acceptor) often called the “FRET pair” [6]. FRET can only occur when the intermolecular distance between donors and acceptors is smaller than 10 nm, which allows the detection of interaction between molecules, thus providing accurate information at the nanoscale [7]. This phenomenon is based on the excitation of a donor fluorophore accompanied with an emission spectrum that overlaps the excitation spectrum of an acceptor, in very close proximity [8]. In this context, fluorescently labeled aptamers can be used as bioreceptors to develop several aptasensors using FRET as a detection method. Based on this principle, the target amount is measured by monitoring the fluorescence change induced by the modification of the aptamer conformation [9].

Aptamers are short sequences of DNA or RNA, characterized with high affinity and specificity for their targets. They are selected in vitro by the exponential enrichment process named SELEX (systematic evolution of the ligand by the exponential enrichment process). As compared to antibodies, aptamers are more stable and economical because they are chemically synthesized [10]. In addition, aptamers can be functionalized with different probes including chemical groups, enzymes, and fluorophores. Aptamer functionalization with a fluorescent probe provides a fundamental advantage in FRET to control the distance between acceptor and donor molecules [11]. Theoretically, any known aptamer can be engineered into a molecular aptamer beacon (MBA) that shows a FRET in response to a specific biomarker [12]. Traditional MBA are composed of a fluorophore and a quencher, each attached at the end of hairpin-structured oligonucleotides. The fluorescence is quenched as a result of the proximity between the fluorophore and its quencher. Then, it will be recovered once the optimal distance between the FRET couple is broken [8]. However, traditional MBs suffer from some limitations, such as false-positive signals, high-cost synthesis, and difficult selection of dye-quencher pair in certain cases. Therefore, new types of MBs based on various kinds of nanomaterials have been developed as promising candidates for biosensor design [13].

To date, gold nanoparticles (AuNPs), quantum dots (QDs), graphene oxide (GO), and carbon nanotubes (CNTs) have been utilized as a fluorescent quencher to detect different types of target. However, most of fluorescent biosensors using AuNPs as quencher suffer from the interference of deep background, the limited surface, and the instability. As a result, they should be coupled with other nanoparticles like Ag and Cu to enhance the sensing properties which make them more complex, time consuming, and expensive [14]. Moreover, QDs stand out as an efficient FRET donor or acceptors owing to their high absorption coefficients and characteristic absorption spectra. However, the toxic nature of these nanoparticles is the major challenge for biological applications [15]. In addition,
QD-based FRET methods suffer from background noise, due to their excitation energy occurring in the spectral range of biological autofluorescence [16].

Due to its unique properties, GO has emerged as one of the most extensively studied nanomaterials. It is a two-dimensional (2-D)-layered material synthesized by the oxidation of graphene [17]. GO has excellent electronic, thermal, mechanical, and photophysical properties. It has a great potential of applications ranging from molecular electronics to ultrasensitive biosensing. It has been shown that GO has the ability to quench fluorescence of the adsorbed dyes. This is mainly due to the large conjugated structure of GO which makes it an excellent electron acceptor during energy transfer processes [18]. These characteristics offer very interesting opportunities to construct a variety of biosensors, in particular aptasensors for the detection of different targets such as glucose and pathogens [19]. However, most of the fluorescent methods developed for dopamine aptasensing are mainly based on quantum dots, nanoclusters, or nanoparticles [20]. The synthesis of such materials involves relatively complicated and time-consuming processes. In this work, we develop a simple fluorescent aptasensor based on a non-reduced graphene oxide as a quencher for DA detection. The principle of this aptasensor is based on FRET by using the FAM-labeled aptamer as a donor and GO as an acceptor. First, DA-aptamer was adsorbed onto the surface of GO where the fluorescence was efficiently quenched. After the target binding, the aptamer changes its conformation, thus recovering the fluorescence that is theoretically proportional to the analyte concentration [21]. This homogeneous fluorescent assay exhibited a high specificity toward DA with a detection limit of 0.031 nM and a quantification limit of 0.1 nM. Besides, the application of this sensing system was demonstrated by detecting the DA levels in human serum. Compared with conventional methods, this sensing platform is simpler and faster and shows comprehensible quantitative results. Moreover, it avoids expensive dual labeling of aptamer required in conventional molecular beacon-based platforms.

**Material and Methods**

**Reagents**

The fluorescein amidite (FAM)-labeled dopamine aptamer with a sequence 5′-FAM-GTC TCT GTG TGC GCC AGA GAA CAC TGG GGC AGA TAT GGG CCA GCA CAG AAT GAG GCC C-3′ was synthesized by Microsynth company (Balgach, Switzerland, www.microsynth.ch). Graphene oxide (GO) solution, magnesium chloride (MgCl2), sodium chloride (NaCl), hydrochloric acid (HCl), tris-hydroxymethyl-methane (Tris), glycine, glucose, lactic acid, and dopamine (DA) were purchased from Sigma-Aldrich (https://www.sigma-aldrich.com). Cysteine was purchased from Biochem (https://www.biochemopharma.fr/). Human serum was obtained from a local biological analysis laboratory. The stock solution of GO (4mg/ml) was used to prepare a homogeneous GO aqueous solution of different concentrations (0, 2, 3, 4, 5 µg/µl) using Tris-HCl buffer (5 mM MgCl2, 0.5 M NaCl, and 50 mM Tris-HCl, pH 7.4), and they were stored at room temperature prior to use. The stock aptamer solution (2µM) was prepared with Tris-HCl buffer (5 mM MgCl2, 0.5 M NaCl, and 50 mM Tris-HCl, pH 7.4), and stored at −20°C before use. The stock solution of DA (100µM) was also prepared using the same Tris-HCl buffer and stored at −4°C. Purified water was used to prepare all the other solutions. All reagents are of analytical grade.
Apparatus

All fluorescence measurements were recorded with a microplate reader, employing a 96-well black microplate. Aptamer pre-heating was occurred using a thermocycler (Bio-Rad).

Fluorescent detection of dopamine

The FAM-labeled aptamer (400 nM) was dissolved in Tris-HCl buffer (5 mM MgCl2, 0.5 M NaCl, and 50 mM Tris-HCl, pH 7.4), and then heated to 90°C for 5 min. After cooling at room temperature, 25 µl of FAM-labeled aptamer was incubated with 25 µl of different concentrations of DA for 25 min under vortex mixing to make sure that dopamine and DA-aptamer interacted with each other sufficiently. Then, 25 µl of GO (3 µg/ml) was added to the above solution, and the volume was completed to 200 µl using the Tris-HCl buffer. The mixed solution was allowed to settle under a quit stirring for 30 min at room temperature. Finally, the fluorescence intensity was measured under the excitation and emission wavelengths of 485 and 538 nm, respectively. All experiments were repeated three times and carried out under the optimized sensing conditions.

Interference studies

Aiming to confirm the specificity of the proposed technique for dopamine detection, some interfering compounds (glycine, cysteine, glucose, lactic acid) were tested. The selectivity assay was conducted under the same procedure as for DA detection. In brief, 25 µl of FAM-labeled aptamer (400 nM) dissolved in Tris-HCl buffer was added to 25 µl of each interferent. Then, the mixture solution was incubated for 25 min at room temperature; after that, 25 µl of GO (3 µg/ml) was introduced to the solution. Finally, the fluorescence was measured after 30 min of quit stirring at room temperature.

Detection of DA in real samples

In order to confirm the response of the sensor in real samples, human serum samples were diluted 10 times with Tris-HCl buffer. Then, the samples were spiked with different known concentrations of DA (3, 7, 280, 1120 nM). The fluorescence detection of DA in human serum sample was performed under the same procedure mentioned above.

Results and Discussion

Mechanism of sensing detection

Figure 1 illustrates the sensing strategy for the DA detection based on the fluorescence resonance energy transfer (FRET) between aptamer and GO. In the absence of target molecule (DA), FAM-modified aptamer is adsorbed onto the surface of GO via hydrophobic and π-π stacking interaction between the nucleotide bases and the sp2 honeycomb network of carbon [22]. Therefore, these interactions induce the formation of a stable complex that
will lead to quench the fluorescence of FAM easily through energy transfer from the FAM to GO [23]. However, in the presence of target molecule (DA), the conformation of DA-aptamer is altered (target-induced allosteric effect), and switched from a random coil to rigid stem–loop structure-DA that have a weak affinity to GO and keep the dyes away from graphene surface [24]. Consequently, the FRET process will be hindered, and the FAM fluorescence is recovered and measured as a function of DA. In the experimental mixture, the fluorescence recovery increases by increasing DA concentrations and the fluorescence will be proportional to the concentration of dopamine [25]. On the other hand, the addition of interferents could not change the conformation of DA-aptamer, so as it cannot be released from GO surface, resulting in non-emission of fluorescence due to the quenching effect of GO.

Based on ssDNA-GO interactions, Ye and collaborators [25] demonstrated the generation of a versatile molecular beacon-like probe as a multiplex sensing platform. This probe has been effectively applied as an example of a fluorescent biosensor-based FRET method to detect a specific target, for instance, specific sequence of DNA, as well as thrombin, metal ions such as Ag⁺ and Hg²⁺, and amino acids such as cysteine, with detection limits of 5 nM, 20 nM, 5.7 nM, and 60 nM, respectively.

**Selection of material**

GO is a universal quencher that has been used as an ideal acceptor surface in many energy transfer-based applications [26]. Its ease of synthesis, lower price, a high detection signal-to-background ratio, large surface area, and good water solubilities make GO a very suitable quencher for simple and quick one-pot applications [27]. Due to these particular
properties, GO has been used as quencher to develop this simple fluorescent assay for DA detection.

**Optimization of assay conditions**

Aptamer and quencher concentrations and incubation time are experimental variables that play an important role in the fabrication of sensitive and selective aptasensing platforms based on FRET principle. In this context, different experiments have been realized to optimize aptamer and quencher concentrations, as well as incubation time.

**GO concentration**

The choice of GO concentration is a critical factor because it may affect the performance of the sensing system. Optimizations were carried out by varying GO concentrations between 0 and 5 µg/ml where the aptamer concentration was fixed at 400 nM. The quenching efficiency was defined by $100\% \times (F - F_0)/F$, where $F_0$ and $F$ are the fluorescence intensities of the aptamer solution with and without GO, respectively. As shown in Fig. 2, the quenching of fluorescence increased dramatically with the increasing amounts of GO, indicating that aptamers are still free in the solution. Then, the fluorescence quenching efficiency (~75 %) stabilized when the GO concentration was higher than 3 μg/ml, indicating that the FAM-labeled aptamer was almost completely adsorbed onto the surface of GO. Since higher concentrations of GO have not shown an enhanced quenching efficiency, a concentration of 3 µg/ml was selected as the GO amount generating the optimum quenching. Thus, it has been used in the next experiments.

![Fig. 2 Effect of GO concentration (0–5 µg/ml) on the quenching efficiency toward FAM-modified aptamer in the absence of DA at the emission wavelength of 538 nm. The aptamer concentration was fixed at 400 nM. n=3](image-url)
The effect of reaction time between the aptamer and GO on the fluorescence quenching of FAM probe was also investigated. In this context, different incubation times have been tested ranging from 0 to 30 min. As we can see from Fig. 3, the quenching efficiency increased by increasing the reaction time, indicating that the FAM-aptamer was adsorbed onto the surface of GO. After 10 min of incubation, the signal reached the maximum of 75% of quenching and stabilized. Therefore, 10 min was chosen to be the optimal incubation time for GO and FAM-aptamer.

**Fig. 3** FAM-labeled aptamer quenching kinetic behaviors with respect to the reaction time in the presence of 400 nM FAM-aptamer, and 3 µg/ml GO in Tris-HCl buffer (5 mM MgCl$_2$, 0.5 M NaCl, and 50 mM Tris-HCl, pH 7.4) in the absence of DA at the emission wavelength of 538 nm. $n=3$

**Fig. 4** Effect of aptamer concentrations (200–800 nM) on the fluorescence intensity at the emission wavelength of 538 nm. $n=3$

**GO quenching time**

The effect of reaction time between the aptamer and GO on the fluorescence quenching of FAM probe was also investigated. In this context, different incubation times have been tested ranging from 0 to 30 min. As we can see from Fig. 3, the quenching efficiency increased by increasing the reaction time, indicating that the FAM-aptamer was adsorbed onto the surface of GO. After 10 min of incubation, the signal reached the maximum of 75% of quenching and stabilized. Therefore, 10 min was chosen to be the optimal incubation time for GO and FAM-aptamer.
Aptamer concentration

To obtain the maximum sensitivity of biosensing, four different concentrations of aptamer (200, 400, 600, and 800 nM) were tested. According to the results presented in Fig. 4, the change of fluorescence intensity kept increasing gradually with increasing aptamer concentrations. The optimal concentration is determined according to the sensitivity of the proposed aptasensor. It should be noted that a high concentration of FAM-aptamer provides a better fluorescence signal. However, a high concentration of FAM-aptamer may influence the assay sensitivity leading to an erroneous results [28]. Therefore, the aptamer concentration of 400 nM was adopted to perform the next experiments.

Detection of DA

The sensitivity of any detection method is considered a key factor to determine its applicability. It was investigated by monitoring the fluorescence intensity of increasing concentrations of DA at the emission wavelength of 538 nm. The fluorescence intensity was quantified by calculating the percentage of fluorescence \[\frac{(F-F_0)}{F_0} \times 100\], where \(F\) is the fluorescence intensity in different dopamine concentrations and \(F_0\) is the fluorescence intensity in the absence of dopamine. The calibration curve presenting the fluorescent recovery percentages as function of DA concentrations ranging from 3 to 1680 nM is illustrated in Fig. 5. It was revealed that with increasing the concentration of DA, the fluorescence recovery increased gradually with a good linear relationship (regression coefficient \(R^2= 0.997\)), indicating the growth of the number of FAM-aptamer attached to the DA target even at low concentrations (3 nM). The detection limit was estimated to be 0.031 nM based on 3\(\delta\)/S calculation and the limit of quantification (LoQ) was calculated to be 0.10 nM using the equation: 10\(\delta\)/S (\(\delta\) is the standard deviation for the blank solution, and S is the slope of the calibration curve).

The performance of our technique was compared to other electrochemical and optical aptasensors, previously reported in the literature for dopamine detection. It has been noted that the LOD achieved in this new approach is much lower than those of these techniques (Table 1). The high sensitivity of our aptasensor could be attributed to the high affinity

![Fig. 5](image-url)
of the aptamer toward DA, and the ultra-high fluorescence quenching ability of GO. The change of the conformation of the aptamer upon the addition of target molecules enhanced the distance between FAM-labeled signal probe and the surface of GO, inducing a higher fluorescence restoration. Moreover, since this assay was performed in a homogenous solution, it avoided the need for time-consuming immobilization, coating, and washing steps usually required in common heterogeneous assays [29]. Several research groups have studied the use of aptamers as the recognition elements for the diagnostic of DA. For example, a label-free fluorescent aptasensor for DA detection has been developed. Wherein, CQDs and AuNPs were served as fluorescent donor-quencher pair, and aptamer was DA recognition element. The developed sensing platform was also tested in a human serum samples; however, the LOD was 10 nM which is higher than the LOD developed in this work [30]. In addition, Guo and co-workers have developed a dual-signal ratio-metric electrochemical biosensor based on a split aptamer using two competitive redox-labeled aptamer strands labeled with methylene blue (MB) and anthraquinone (AQ). The developed biosensor has been tested in the human serum samples and show a high accuracy. Apart from the LOD (10000nM) which is much higher than our developed biosensor, labeling, splitting aptamers, and immobilizations make this sensing platform more complex [31]. Compared to the previous works, our biosensor provides a simple and rapid detection of DA since it is based on monitoring the fluorescence change due to the target binding. These features, as well as its other merits, such as low cost and fluorescence background, make it a promising tool for a rapid label-free detection of DA.

Table 1: Comparison between this method and other reported techniques for detection of dopamine

| Detection method   | Detection range    | LOD  | Principle                                                                 | Refs       |
|--------------------|--------------------|------|---------------------------------------------------------------------------|------------|
| Electrochemical    | $5 \times 10^3$–$75 \times 10^3$ | $3.36 \times 10^3$ | DNA aptamer/AuNPs/rGO/modified glassy carbon electrode (GCE)             | [32]       |
|                    | 5–300              | 2.1  | Au electrode/AuNPs/PEI/CNTs                                              | [33]       |
|                    | 5–150              | 1    | MB/MCH/DNA/Au electrode                                                  | [34]       |
|                    | 1–1000             | 0.75 | Aptamer/GCSC-GO/GCE                                                      | [35]       |
|                    | 5–5×$10^2$         | 1.8  | aptamer/AuNPs/GCE                                                        | [36]       |
| Colorimetric       | 300–3130           | 65.2 | Aptamer/AuNPs                                                            | [37]       |
|                    | 540–5400           | 360  | Aptamer/unmodified AuNPs                                                 | [38]       |
|                    | 200–1100           | 70   | AHMT/AuNPs                                                               | [39]       |
| Fluorescence       | 26–2.90 $\times 10^3$ | 2    | DNA/rhodamine B/AuNPs                                                   | [40]       |
|                    | 0.1–10.0           | 0.08 | tDNA/cDNA/aptamer/dopamine/hDNA/Exo III                                  | [29]       |
|                    | 50–2.5×$10^5$      | 10   | CQDs/AuNPs/aptamer                                                       | [30]       |
|                    | $5 \times 10^4$–$10^6$ | $10^4$ | CB/Fe$^{2+}$/DNA                                                          | [41]       |
|                    | 3–1680             | 0.031| GO/DNA                                                                   | This work  |

Selectivity of the sensing system

Selectivity is another important feature of a good sensing system as though the presence of many interferents in the real sample would affect the accuracy of the detection mechanism. In this regard, the selectivity of the aptamer-GO sensing platform was studied by monitoring the fluorescence recovery percentage for different interferential substances
including glycine, cysteine, glucose, and lactic acid. For that, we set the concentration of DA and the other interferents at 1120 nM, and then, each one was incubated with 25 µl of FAM-aptamer. After 25 min, 25 µl of GO was added to the mixture, and the fluorescence recovery was measured after 30 min of incubation. As shown in Fig. 6, under the same experimental conditions, the fluorescence recoveries of the sensing system in the presence of DA are highly significant, whereas a minor fluorescence was observed in the presence of the tested interferents. Furthermore, it can be seen that the fluorescence enhancement in the presence of the target was more than 4-fold as compared to the other interferents. These results indicate that glycine, cysteine, glucose, and lactic acid are not recognized by DA-aptamer. Consequently, the aptamer remains adsorbed on the GO surface inducing the fluorescence quenching. In particular, the aptamer was strongly bound to dopamine, thus inducing the fluorescence recovery. Therefore, this confirms that the label-free fluorescent aptasensor based on GO exhibited an excellent specificity for the DA detection, thus indicating its potential application in complex matrices.

**Determination of DA in human serum**

In order to investigate the applicability of the method, our biosensor was tested in human serum samples. For that, the samples free of DA were collected from a local biomedical analysis laboratory. Then, they were diluted 10 times and spiked with 3, 7, 280, and 1200 nM of DA. After incubation with the aptamer, 25 µl of GO was added and the fluorescence recovery was measured. As it is shown in Fig. 7, the fluorescent recovery percentages of human serum and Tris-buffer were almost the same. This latter conclusion is confirmed by the analytical results for the samples spiked with DA presented in Table 2. As illustrated in this table, the developed aptasensor exhibited good recoveries ranging from 89 to 103%, with RSD between 0.61 and 2.09 %. These experimental results confirm the good reliability and applicability of the proposed method for DA detection in complex biological samples.
Conclusion

This work describes the first label-free fluorescent aptasensor for DA detection using GO as a quencher. The developed aptasensor showed a linear relationship between the fluorescence recovery and DA concentration in the range of 3–1680 nM. In addition, the present sensing platform exhibited an excellent selectivity and sensitivity. Moreover, the applicability of this sensing platform was confirmed by detecting DA in complex biological matrices, with a prominent accuracy. By comparing the present technique to that previously reported in the literature, our results have shown a high accuracy and reliability for rapid analysis of dopamine. Furthermore, the developed device does not require any surface functionalization, thus simplifying the fabrication process as well as the analysis. Therefore, the ssDNA-GO platform could be an excellent alternative to universal molecular beacons in constructing sensing systems. It could be potentially applied in biomedical diagnostics for dopamine monitoring as well as other biomarkers.

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Data Availability Not applicable

Code Availability Not applicable
Declarations

Conflict of Interest  The authors declare no competing interests.

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