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Study on the mechanism of potential response of a ketamine-sensitive membrane electrode

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The response mechanism of a simple device for the rapid detection of ketamine with 'in the field' capabilities is investigated. The mechanism is a membranous ketamine ionic selective electrode (ISE) with partly carboxylated PVC as matrix and *ortho*-nitrophenyloctyl ether (o-NPOE) as plasticizer. The experimental results reveal that the inclusion of the plasticizer in the membrane significantly increased the response. A mechanism is proposed where the infiltration of a target species into the membrane is capable of producing a superior response. This response process is non-selective for species with similar molecular structure and size. This new research addresses some omissions and misapprehension in the literature where the mechanism was reported as an ion-exchange-induced response. In this research the ion-exchange-induced response was measurable after the elimination of the infiltration-induced response extending to lower concentration ranges and thus providing the potential for better sensitivity and selectivity. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: ketamine; ionic selective electrode; potential response; infiltration; ion exchange

Introduction

Ketamine hydrochloride (KH) is a medical analgesic and a rapid-acting anesthetic.[1] It has been used for premedication, sedation, induction, as a general anaesthesic in clinical and veterinary practices, as well illegally for recreational use. Effective screening and confirmation methods for KH are in great demand.[2] To date, many KH determination methods have been reported, including UV–vis spectrophotometry,[3–5] gas chromatography-mass spectrometry (GC-MS),[6–8] high performance liquid chromatography (HPLC),[9–12] polarography,[13] and capillary electrophoresis.[14–15] For the purpose of narcotics administration and public security, however, these laboratory technologies do not satisfy the demands for portable and rapid 'in the field' use.

Alizadeh[16] reported an ionic selective electrode (ISE) based on KH-embedded carboxylated PVC as the potential response membrane to determine KH and to study its interaction with bovine serum albumin. For the distinct advantages of this approach – sensitivity, portable instrumentation, economic viability, facile operation etc. – the selectivity of the ISE is an important feature that needs to be improved with further research and development.

As defined by IUPAC, the selectivity of ISE is evaluated with selective coefficient ($K^{Pot}_{i,j}$). Here 'i' denotes the target analyte and 'j' denotes interferential species. Its value equals to the concentration ratio of target to interferential species which resulted in equal potential response. The smaller the selective coefficient, the better the selectivity. Generally the value at centesimal, even millesimal, level is expected for excellent selectivity.

Selective coefficients from 0.24 to 0.87 for some analogous drugs such as triflupromazine, antazoline, prometazine, atropine, naphazoline, and propranol hydrochloride have been reported together with the low selectivity of the ketamine ISE. Although the ion-exchange-induced response has been proposed, it is difficult to agree these findings in respect of the data.

The purpose of this paper is to study the potential response mechanism of KH on this membrane in order to understand why there was such low selectivity. Based on our results, we found that the plasticizer (*ortho*-nitrophenyloctyl ether o-NPOE) in the membrane played an important role in increasing the response. The response is potentialized through greater infiltration of ketamine ions understood as an ion-exchange-induced response in previous literature. Moreover this research explains why the selectivity of the previous methodology was very low.

Experimental

Reagents and materials

PVC (containing 1.8% of carboxylated PVC) was purchased from Fluka (St. Louis, MO, USA). o-nitrophenyloctyl ether (o-NPOE, 98%) was purchased from Alfa (Heysham, Lancs, UK). Sodium tetraphenylborate (NaTPB), sodium chloride and tetrahydrofuran (THF) were purchased from Chemical Reagent Co. Ltd, Sinochem Group (Shanghai, P.R. China). Ketamine hydrochloride injection was purchased from Jiangsu Hengrui Medicine Co. Ltd (Lianyungang, P.R. China). All chemicals were analytical grade and used without further purification. Distilled water was used throughout the experiments.

Apparatus

The potential measurements were accomplished by the use of a CHI400A electrochemical quartz crystal microbalance (Shanghai

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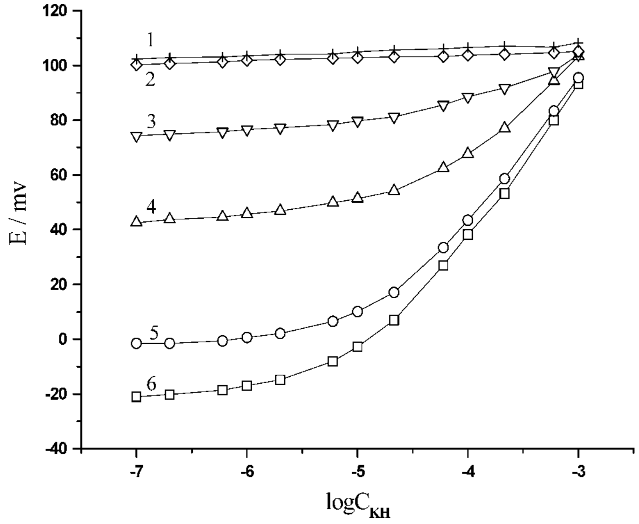


Figure 1. The potentiometric response of membrane electrodes upon KH with different o-NPOE content of (1)0 (2)20% (3)33% (4)50% (5)60% (6)66% for w/w.

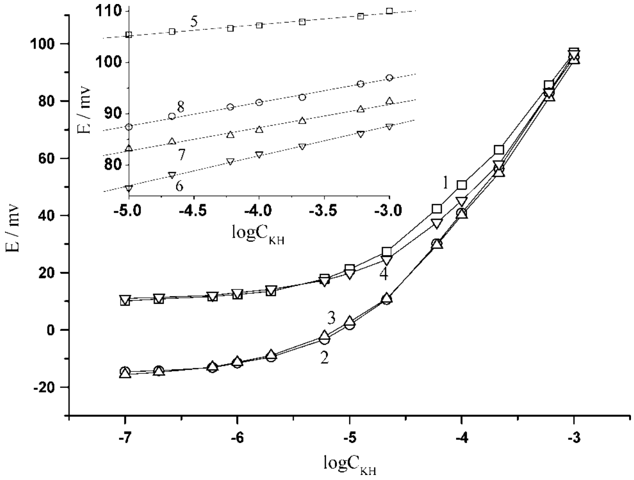


Figure 2. The potentiometric response of the membrane electrodes with different KH content in the membrane. Here 1 to 4 are for higher content of o-NPOE and 5 to 8 are for lower content of o-NPOE.

Chenhua Instrument Co. Ltd, Shanghai, China). All determinations were performed at 27 ± 0.1 °C in a thermostatic bath. A saturated calomel electrode (SCE) acted as the reference electrode.

Preparation of electrode

For the preparation of the sensitive membrane, the carboxylated PVC-KH complex was prepared according to Alizadeh[16] with different concentrated KH solutions (0.00M, 0.02M, 0.04M, 0.08M, named as PVC-KH(0) to PVC-KH(3), respectively). The casting of the sensitive membrane and the construction of the final ISE was conducted according to Alizadeh[16] with an Ag/AgCl electrode as the internal reference electrode and 1×10^{-3} M KH - 0.01M NaCl as the internal reference solution.

Results and Discussion

The potential response upon the composition of membrane

The sensitive membranes were constituted with different compositions of PVC (partly carboxylated), plasticizer, KH, and NaTPB. Here the NaTPB was used to form the ion-association complex dispersed in the PVC. The PVC dispersal does not influence the potential response. Ignoring the NaTPB, the other membrane components are all responsible for producing the potential. Their contents in the membrane significantly influenced the response, and even the mechanism.

The content of o-NPOE

From the experiments, it was evident that without KH in the membrane the potential response of the sensitive membrane was still active and the response was noticeably altered with the different content of plasticizer, as shown in Figure 1 and Table 1.

For membranes without KH, the potential response increased along with different o-NPOE contents from 0 to 66% (w/w). In cases of more than 60% (w/w) of plasticizer content, there was an adequate Nernstian response.

Effect of KH content for the PVC-KH membrane electrodes

Various constituted membranes were prepared to investigate the response for KH. Figure 2 and Table 2 show the responses of the PVC-KH membrane with 60% or *c*. 21% of o-NPOE with different KH content.

As can be seen in Table 2, with 60% w/w of o-NPOE in the membrane (No. 1 to 4), the potential responses were higher than membranes (No. 5 to 8) with lower o-NPOE content (*c*. 21% w/w). More notably the response was affected by the content of the KH rather than the volume of the plasticizer. The results clearly revealed that the responding slopes of KH membranes were greater than non-KH membranes and the membrane marked as

Table 1. The composition and response of the PVC membrane electrodes

	Composition (mg, % w/w)							
	PVC		o-NPOE		NaTPB			
Membrane no.	Mg	w/w%	mg	w/w%	mg	w/w%	Slope mV/decade	r
1	19	95%	0	–	1	5%	1.59	0.9817
2	19	76%	5	20%	1	4%	1.44	0.9866
3	19	63%	10	33%	1	4%	14.2	0.9815
4	19	47.5%	20	50%	1	2.5%	33.9	0.9938
5	19	38%	30	60%	1	2%	47.6	0.9955
6	19	32%	40	66%	1	2%	51.9	0.9973

Table 2. The composition and response of the PVC-KH membrane electrodes

		Composition (mg, % w/w)							
		PVC-KH complex		o-NPOE		NaTPB			
Membrane no.		mg	% w/w	mg	% w/w	mg	% w/w	Slope mV/decade	r
1	PVC-KH(0)	19	38%	30	60%	1	2%	42.0	0.9945
2	PVC-KH(1)	19	38%	30	60%	1	2%	51.1	0.9974
3	PVC-KH(2)	19	38%	30	60%	1	2%	50.1	0.9963
4	PVC-KH(3)	19	38%	30	60%	1	2%	43.5	0.9859
5	PVC-KH(0)	18	75%	5	20.8%	1	4.2%	2.22	0.9850
6	PVC-KH(1)	18	75%	5	20.8%	1	4.2%	5.84	0.9973
7	PVC-KH(2)	18	75%	5	20.8%	1	4.2%	4.52	0.9896
8	PVC-KH(3)	18	75%	5	20.8%	1	4.2%	4.59	0.9954

PVC-KH (1) had the greatest slope for both cases of plasticizer content (electrode 2 or 6 in Figure 2).

The function of carboxylated PVC

At lower plasticizer content and with no KH, the membrane exhibited a relatively low potential response towards KH as 1.5 to 2 mV for one order of magnitude. In comparison there was zero response from the pure PVC membrane under the same experimental conditions. The response in the 'carboxylated PVC only' experiment may be attributed to -COOH functional groups of carboxylated PVC in the membrane causing the ion exchange between -COOH in membrane and ketamine ions in solution.

The deductive mechanism of potential response

In these experiments, three main components of the membrane all affected the response of resulting ISE. It is very important to distinguish the principal components that resulted in low selectivity.

The inclusion of KH in the membrane causes a definite selective ion-exchange response. Neglecting the small response from the carboxylated PVC, it could be concluded that the plasticizer-induced response was non-selective for those analogous drugs. Such may be attributed to the higher infiltration for constituents at high content of plasticizer in the membrane.[17]

The o-NPOE, used as the plasticizer has high electric permeability and hydrophobicity,[18] increasing the migration ability of ions in the membrane phase. Therefore, we can conclude that the potential response of non-KH membrane was not caused by the ion exchange of carboxylated PVC-KH complexes (PVC-COO-K) but by the infiltration of ketamine ions passing through the membrane which depend specifically on the plasticizer content. The plasticizer content acts as the primary factor in generating a greater but unselective response.

Based on this discussion, it is shown that the infiltration caused the greater mechanism in the response. After comparing the responses of those membranes, the best results were obtained from the PVC-KH membranes (1). For higher or lower plasticizer content membrane, the increasing ratios of response are approximately 21.7% and 163.1% from the ion exchange, respectively. The plasticizer effect decreases with its volume enabling the emergence of the ion-exchange-induced response. The results indicated that the construction of PVC-KH (1) was the best composition for the highest ion-exchange-induced response regardless of the volume of the plasticizer content. From Figure 2, it was also observed that the different response (infiltration or ion-exchange) was superior with different concentration ranges of KH. While KH was concentrated at 5×10^{-6} mol/L, the response was determined primarily by infiltration. With lower concentrations of KH, the ion-exchange-induced response emerged. In this case, the limit of detection was 5.56×10^{-8} mol/L. Such results underpin the possibility of developing a more sensitive and selective method for the determination of KH.

Detailed discussion on response mechanism of the sensitive membrane

In the recent literature, similar membranous ISE were presented. For example, with an ion pair of amiloride-sodium tetraphenyl phthalate, an amiloride ISE was developed based on a PVC matrix.[19] It is indicated in the case of the membrane without a carrier, that it displayed insignificant selectivity towards amiloride and the response was not reliable. It was also reported that the plasticizers such as DOP ($\varepsilon = 5.0$, ε is the dielectric constant) and DBP ($\varepsilon = 6.42$) with lower polarity showed better selectivity than higher polar plasticizer o-NPOE ($\varepsilon = 24$); however, the literature does not explain the cause. The results of this study report that the response was also induced by the infiltration.

The use of partly carboxylated PVC as matrix is discussed by Lindner *et al.*[20] who reported that the -COOH content in the membrane decreased the selectivity. Considering the dissociation of H^+ from −COOH and the different charging situation (positive or negative) of the plasticizer, the acidity of the detection solution is an important factor in membrane performance. From previous literature, we found that there was insufficient discussion regarding the influence of acidity in the performance of the response mechanism.

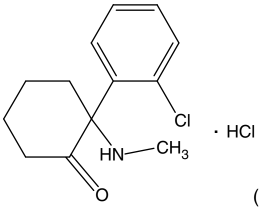
Based on observations, the best ion-exchange-induced response was obtained with PVC-KH (1) without higher KH content in membrane; it clearly indicated that the formation of carboxylated PVC-KH complex was an equilibrium process. The following reaction of carboxylated PVC with KH has reached equilibrium in the membrane phase[21].

$$\text{PVC-COO}^-\text{H}^+ + \text{KH}^+ \rightleftharpoons \text{PVC-COO}^-\text{KH}^+ + \text{H}^+$$

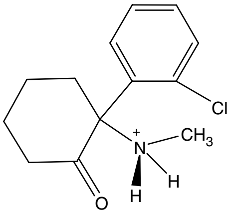
The response mechanism of the PVC-KH membrane towards KH contained an exchange of KH^+ ions between the membrane phase and the aqueous phase besides the plasticizer-induced infiltration.

Concurring with the literature,[16] the potential response of the sensitive membrane is related to the pH of the test solution. The literature demonstrated the reason for the observed potential drift at the higher pH than 8.5 as the deprotonation of KH. However, the reason for the potential change at lower pH could not be explained.

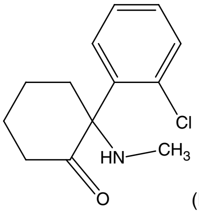
Ketamine (K) has a pKa of 7.5,[22] and therefore it has two main existing forms along with the pH of the solution.[23] For pH $\leq$ pKa, the KH$^+$ cation[24] was formed by protonation of the imino group, while pH $\geq$ pKa, it mainly exists in the uncharged form.



(K·HCl)



(KH$^+$)



(K)

The response remains approximately constant over pH range 4.0–8.5. At higher pH values, in accordance with previous research, the response decreased due to the deprotonation of ketamine, causing the termination of ion-exchange. The infiltration-induced response disappeared as the ketamine was in an uncharged form. On the other hand, at lower pH range, the increased response could naturally be attributed to increasing protonated content of ketamine. The literature does not uncover such abnormalities because, in previous research[25], the interferential test species were too dissimilar from the molecular structure of the target. From our research, it is tenable that the infiltration-induced response phenomenon is not an isolated case. While the literature has reported the effect of plasticizer in similar studies, there have not been any explanations of that response.

Conclusions

With reference to the literature, this paper studies the potential response of PVC-KH membrane electrodes to KH. Based on the investigation of the potential responses of different membrane compositions, we propose that the potential response of ketamine-sensitive membrane included three aspects of infiltration, ion-exchange with PVC-COOK, and PVC-COOH. Plasticizer (o-NPOE) played an important role in the function of the membrane. The potential response of the membrane was primarily caused by the infiltration it induces. While this response was eliminated by decreasing the content of plasticizer, the membrane exhibited a smaller response. This could be attributed to the ion exchange of the PVC-COOK membrane. Finally, a very low response occurred from the ion exchange of ketamine with PVC-COOH after the elimination of the two abovementioned responses. This research has proved that the current literature has overlooked the response mechanism of this sensitive membrane. The research also explains why the membrane had very low selectivity. The study outlines potential approaches for a more sensitive and selective detection method based on the ion-exchange-induced response in lower concentration ranges.

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