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Letter to the Editor

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# The Putative Role of the Transient Receptor Potential Ion Channel of Vanilloid Type 2 in Red Blood Cell Storage Lesions

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Recently, a review about big data and artificial intelligence was published in "Transfusion Medicine and Hemotherapy," highlighting the importance and chances of quality control of stored red blood cells (RBCs) [1]. RBC quality is decreased over storage time in a donor-dependent manner [2]. Here, we want to emphasize that besides quality control, one has to further think about improving the RBC quality during storage, i.e., addressing storage lesions [3]. A component of the storage lesion is the dissipation of the cation gradients across the RBC membrane [4], i.e., $K^+$ will leak out of the RBC and $Na^+$ enters the cell. So far, the molecular cause of the cation gradient dissipation remains elusive. To this end, we like to present a hypothesis for the involvement of the transient receptor potential channel of vanilloid type 2 (TRPV2) [5]. The hypothesis is based on previously published work [6–9] (in a mostly different context), compiled in Figure 1 and not presented in such a composition before. TRPV2 is a nonspecific cation channel that is part of the transient receptor potential channel family. In a study about RBC transportation modes performed in 2016, we found that the cation gradient dissipation is a $Ca^{2+}$-dependent process ([6], Fig. 1A), enforced by the absence/removal of extracellular $Ca^{2+}$. Later, in 2018, we presented an electrophysiological report about a functional ion channel, abundant in RBCs, which is activated by the removal of $Ca^{2+}$ ([7], Fig. 1B) and might explain the $Ca^{2+}$-dependent cation gradient dissipation. After the initial report of the ion channel TRPV2 in RBCs in 2021 [5], we came up with a commentary about the discovery of TRPV2 and the idea of TRPV2 being the molecular identity of the previously reported ion channel ([8], Fig. 1C). Indeed, the activation of TRPV2 in human RBCs by tetrahydrocannabinol results in a non-selective cation current ([9], Fig. 1D).

This line of argumentation speaks for the involvement of TRPV2 in inducing the cation gradient dissipation as part of the RBC storage lesions. Such TRPV2 appears to be a putative pharmacological target to improve the quality of stored RBCs. In light of the upcoming new EU directive for "Regulation on standards of quality and safety for substances of human origin (SoHO)" (including blood products for transfusion) and the required actions for quality control; therein [11], we believe this letter is valuable information for the transfusion medicine community.

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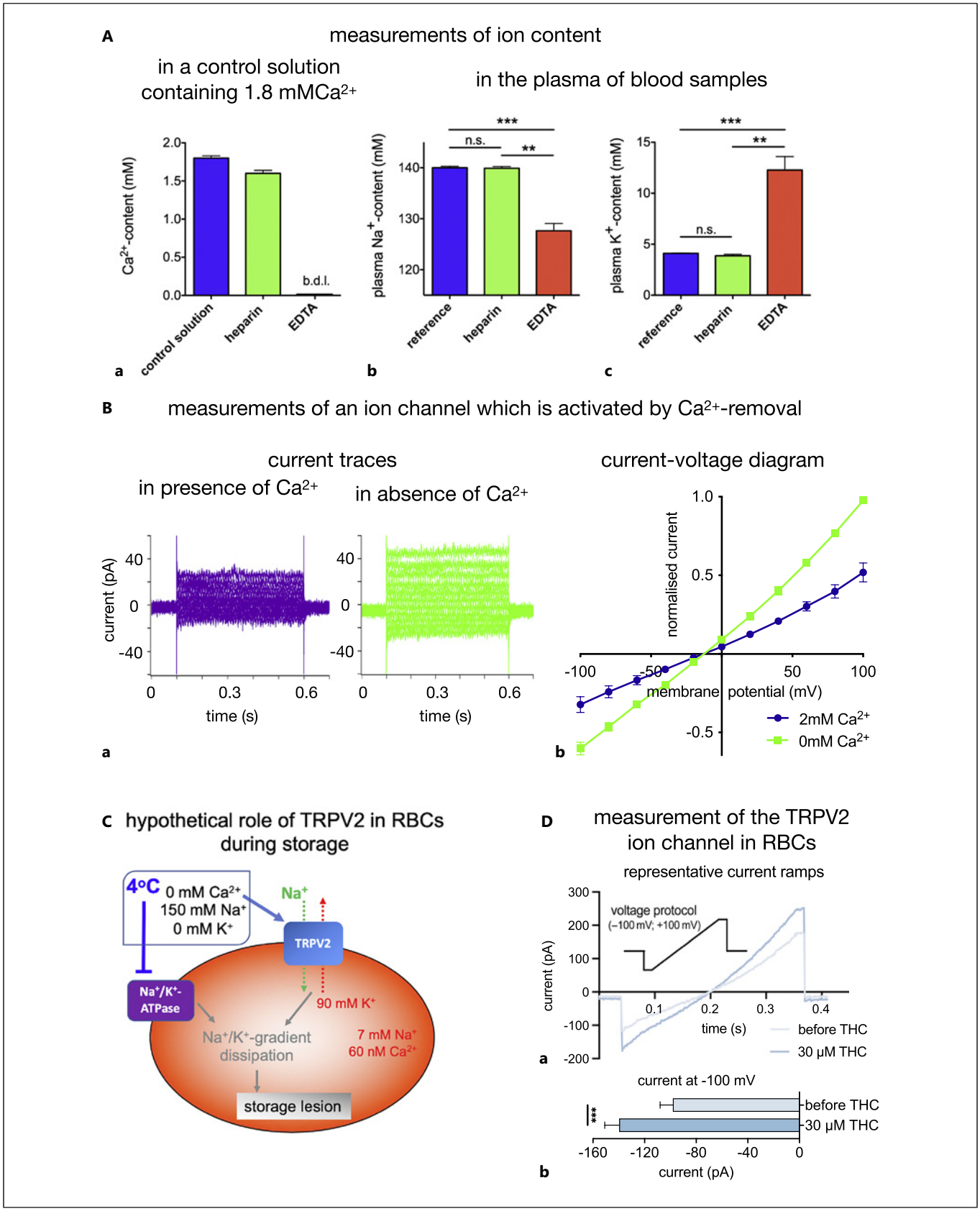


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However, further basic research as well as pharmacological investigations are required to exploit this knowledge in favor of RBC quality.

## Conflict of Interest Statement

N.M. is an employer of Nanion Technologies GmbH, the Patchliner, and the SyncroPatch manufacturer used for data generation presented in this study. L.K. is a shareholder of Cysmic GmbH, the supplier of Erysense, the device used in the measurements of reference [2].


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## Author Contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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**Fig. 1. A** compares the blood plasma ion content of healthy adults with heparin and ethylenediaminetetraacetic acid (EDTA), 1 h after blood withdrawal. **Aa** $Ca^{2+}$ content of a control aqueous non-buffered 1.8 mM $CaCl_2$ solution filled in heparin and EDTA vacutainers. The abbreviation b.d.l. denotes "below the detection limit." **Ab** $Na^+$ plasma content. **Ac** $K^+$ plasma content of blood anticoagulated with heparin and EDTA. Measurements in heparin and EDTA were performed on the blood of healthy adults ($n = 3$) collected in heparin and EDTA vacutainers, respectively, and reference values were taken from Liappis [10]. It is worthwhile to mention that even though the driving force for $Na^+$ to get into the cell was higher in heparin compared with EDTA (due to the additional $Na^+$ coming from the Na-heparin salt itself), it was in EDTA that we detected a higher $Na^+$ influx (lower $Na^+$ plasma content) (**Ab**). Vice versa, even though the driving force for $K^+$ to get out of the cell was lower in EDTA compared with heparin (due to the additional $K^+$ coming from the K3EDTA salt itself), it was in EDTA that we detected a higher $K^+$ outflux (higher $K^+$ plasma content) (**Ac**). This panel was reproduced from data presented by Makhro et al. [6]. **B** shows whole-cell patch clamp recordings in physiological (a $K^+$-based internal and a $Na^+$-based external) solutions. **Ba** Raw current traces from a representative RBC in an external solution containing $Ca^{2+}$ (violet) and in the nominal absence of $Ca^{2+}$ (green). Detailed solutions composition is given in the original publication. **Bb** I/V curves in 2 mM $CaCl_2$ (dark blue) and 0 mM $CaCl_2$ (green) external solutions ($n = 7$). This panel is reproduced from Petkova-Kirova et al. [7]. **C** suggests the TRPV2 channel activity in RBCs during storage. The rectangle next to the RBC describes the main components of typical storage conditions. This panel is reproduced from Egée and Kaestner [8]. **D** shows TRPV2 channel activity in healthy human RBCs induced by the application of THC, for example, current traces of a voltage ramp protocol (**Da**) and the statistical comparison based on 3 healthy donors (**Db**). Detailed solutions composition is given in the original publication. This panel was reproduced from data presented in Flormann et al. [9]. Throughout the entire figure, error bars represent the standard error of the mean (SEM), and stars denote significances as follows: n.s. for not significant, ** for $p < 0.01$, and *** for $p < 0.001$.