Scientific Research Publishing

Pharmacology & Pharmacy, 2025, 16(6), 174-185
https://www.scirp.org/journal/pp
ISSN Online: 2157-9431
ISSN Print: 2157-9423

Melanocortin Receptors as Anti-Inflammatory and Analgesic Targets in Sickle Cell Disease: A Comparative Study in Congolese Patients

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How to cite this paper: Berge, T.N., Loubano-Voumbi, G., Samoukamat, L.D., Tchatchouang, D.G.N., Angounda, B.M., Gokaba, T.L.O., Martial, M.L., Moukassa, D. and Abena, A.A. (2025) Melanocortin Receptors as Anti-Inflammatory and Analgesic Targets in Sickle Cell Disease: A Comparative Study in Congolese Patients. *Pharmacology & Pharmacy*, **16**, 174-185.
https://doi.org/10.4236/pp.2025.166012

Received: May 17, 2025
Accepted: June 22, 2025
Published: June 25, 2025

Abstract

Introduction: Sickle cell disease is an autosomal recessive inherited hemoglobinopathy, leading to the formation of an abnormal hemoglobin, hemoglobin S (HbS). CVO is the most frequent and disabling clinical manifestation of sickle cell disease, representing the main cause of hospitalization, school or work absenteeism, and reduced quality of life in SS homozygous patients. These painful attacks are the result of a complex pathogenic process combining HbS polymerization, systemic inflammation, vascular endothelial activation and tissue ischemia. Despite therapeutic advances, management of CVO-related pain remains limited and unsatisfactory, particularly in sub-Saharan Africa. Commonly used treatments include opioids (such as morphine), which are effective in the short term but associated with significant side effects, including tolerance, constipation, sedation, and above all the risk of dependence and abuse. These therapeutic limitations underline the pressing need to develop new, targeted approaches that are more effective and better tolerated, based on a thorough understanding of the pathophysiological mechanisms of sickle cell pain. MCRs, activated by pro-opiomelanocortin (POMC) peptides such as melanotropic hormone (α-MSH) and corticotropic hormone (ACTH), are involved in a variety of biological processes including regulation of im-

munity, stress response, energy homeostasis and nociception. The MC3R, MC4R and MC5R receptors appear to be strategic biological targets in the study of sickle cell pain, due to their shared involvement in inflammatory and nociceptive signaling pathways, their potential as biomarkers of severity, and their suitability as pharmacological targets in the development of new treatments. For the first time in the Congolese context, this study examines the correlations between MC3R, MC4R and MC5R receptor expression levels and CVO clinical parameters in homozygous sickle cell patients followed in Brazzaville. **Methodology**: A prospective observational study was carried out on 85 patients (2 - 62 years). Pain intensity was assessed using a validated scale. Biomarkers (haemogram, CRP, IL-6, MC3R, MCR4R and MC5R) were measured by turbidimetry and ELISA. Data were statistically analyzed using specific tools. **Results**: 45.88% or 39 of patients were in CVO, while severe pain was reported frequently in more than 14 patients during attacks. WBC, CRP and MC5R showed significantly higher concentrations during CVO ($p = 0.018$ for WBC; $p < 0.0001$ for CRP and $p < 0.003$ for MC5R), while the other markers measured (GR, PLT, IL6, MC3R, MC4R) showed no statistically significant difference. Although a weak positive correlation was observed between CRP levels and MC5R expression ($r = 0.23$, $p = 0.07$), this did not reach statistical significance. **Conclusion**: These results suggest that MC5R may be considered a promising biomarker for assessing inflammatory pain during CVO and its potential usefulness in therapeutic pain monitoring in sickle cell crisis patients, although further studies are needed to confirm its clinical role. Also, CRP/MC5R correlation results may suggest a complex regulatory mechanism of melanocortin receptors during sickle cell inflammation.

Keywords

Sickle Cell Disease, Vaso-Occlusive Crisis, Melanocortin, Inflammation

1. Introduction

Sickle cell disease is an autosomal recessive inherited hemoglobinopathy characterized by a point mutation in the HBB gene, leading to the substitution of valine for glutamic acid in position 6 of the β-globin chain (Glu6Val), and the formation of an abnormal hemoglobin, hemoglobin S (HbS) [1] [2]. This mutation alters the structure and function of red blood cells, inducing cell rigidity, abnormal adhesion to the endothelium and an increased tendency to intravascular hemolysis, leading to severe clinical complications, notably vaso-occlusive crises (CVO) [3].

CVO is the most frequent and disabling clinical manifestation of sickle cell disease, representing the main cause of hospitalization, school or work absenteeism, and reduced quality of life in SS homozygous patients [3]. These painful attacks are the result of a complex pathogenic process combining HbS polymerization, systemic inflammation, vascular endothelial activation and tissue ischemia [4].

Despite therapeutic advances, management of CVO-related pain remains lim-

ited and unsatisfactory, particularly in sub-Saharan Africa. Commonly used treatments include opioids (such as morphine), which are effective in the short term but associated with significant side effects, including tolerance, constipation, sedation, and above all the risk of dependence and abuse [5]. As a complement, non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used, although their efficacy in CVO is modest, and their chronic use limited by their gastrointestinal, renal and cardiovascular adverse effects [6]. These therapeutic limitations underline the pressing need to develop new, more effective and better-tolerated targeted approaches, based on a thorough understanding of the pathophysiological mechanisms of sickle cell pain.

Melanocortin receptors (MCRs), a family of G protein-coupled receptors, are attracting increasing attention. MCRs, activated by pro-opiomelanocortin (POMC) peptides such as melanotropic hormone (α-MSH) and corticotropic hormone (ACTH), are involved in a variety of biological processes including regulation of immunity, stress response, energy homeostasis and nociception [7]. Of the five known subtypes (MC1R to MC5R), the MC3R, MC4R and MC5R receptors have been particularly associated with the modulation of pain and inflammation [7], motivating their exploration in the context of CVOs.

The MC3R receptor, expressed in both the central nervous system and peripheral macrophages, plays a key role in controlling inflammatory responses and pro-inflammatory cytokines such as tumor necrosis factor (TNF)= $-\alpha$, Interleukin 6 and 1β (IL-6 and IL-1β) [8]. Its activation by α-MSH has also been shown to reduce inflammation and chronic pain in mouse models of rheumatoid arthritis and neuropathy [9].

The MC4R receptor is widely expressed in the central nervous system, notably in the hypothalamus, thalamus and spinal nuclei. It is directly involved in the neural circuits of pain, nociceptive perception and top-down pain modulation [10]. Studies have shown that MC4R agonists possess analgesic properties comparable to opioids but without inducing dependence, making them a promising therapeutic target for chronic pain [11].

MC5R, although less studied, is expressed in several peripheral tissues, including leukocytes, sweat glands and liver. It is involved in the peripheral inflammatory response, promoting resolution of inflammation and regulating the expression of cell adhesion molecules [12]. It also plays a role in post-inflammatory tissue regeneration [13], which is particularly relevant in the context of vaso-occlusive crises with tissue damage.

Thus, the MC3R, MC4R and MC5R receptors appear as strategic biological targets in the study of sickle cell pain, through their common involvement in inflammatory and nociceptive signaling pathways, their potential as biomarkers of severity, and their ability to serve as pharmacological targets in the development of new treatments.

Our study proposes, for the first time in the Congolese context, to examine correlations between expression levels of MC3R, MC4R and MC5R receptors and

clinical parameters of CVO in homozygous sickle cell patients followed in Brazzaville. This approach aims to identify relevant prognostic biomarkers, gain a better understanding of the molecular mechanisms underlying inflammatory pain, and open prospects for innovative targeted therapies in a public health context with a high unmet therapeutic need.

2. Materials and Methods

This prospective observational study took place over a four-month period, between January and December 2024. Subjects were recruited at the National Reference Centre for Sickle Cell Disease (CNRDr) in Brazzaville, during scheduled consultations or day hospitalizations. Analytical investigation was carried out at the TRIOS laboratory, the research laboratory of the Faculty of Health Sciences (FSSA), and at the National Blood Transfusion Centre (CNTS).

Sampling was exhaustive and non-probabilistic, including 85 homozygous sickle cell patients aged from 2 to 62 years. The data collection strategy was based on three complementary axes: an epidemiological survey via a structured questionnaire, a clinical evaluation documenting the history and frequency of CVO and a biological exploration based on inflammatory and endothelial markers. Inclusion criteria included patients hospitalized in the acute vaso-occlusive crisis (CVO) phase, before any administration of analgesic treatment and patients in the inter-critical phase, having received no blood transfusion in the previous three months, with no hospitalization episode within 72 hours, and having given informed consent. For minors, approval was obtained from their legal representatives. Cases presenting inadequate biological samples for the planned analyses were excluded. Clinical assessment was carried out by CNRDr physicians, and pain intensity was quantified using a visual analog scale from 1 to 10. Biological sampling involved whole blood collected in EDTA and dry tubes (5 ml each), for the determination of targeted inflammatory and vascular biomarkers: C-reactive protein (CRP), measured by turbidimetry (**Figure 1**) and interleukin-6 (IL-6), MC3R, MC4R and MC5R receptors determined by ELISA method (**Figures 2-5**). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and received a favourable opinion from the Brazzaville Health Sciences Research Ethics Committee
(Ref N˚056-40/MESRSIT/DGRST/CERSSA/-23).

Statistical analysis was performed using GraphPad Prism software version 5.0 (GraphPad Software Inc., La Jolla, CA, USA), after initial data entry on Microsoft Excel 2021. The significance level was set at $p < 0.05$. The normality of quantitative variables was tested beforehand using the Shapiro-Wilk test. In the case of a normal distribution, data were expressed as mean ± standard deviation and compared between groups using Student's t-test for independent samples; in the case of a non-Gaussian distribution, data were described as median [interquartile range] and compared using the Mann-Whitney test. Categorical variables (gender, presence of vaso-occlusive crisis) were compared using Pearson's Chi^2 test, or Fisher's

exact test when theoretical numbers were <5. Hematological parameters (WBC, RBC, Hb, PLT) were analyzed using Student's t-test. Concentrations of CRP and IL-6, as well as those of MC3R, MC4R and MC5R receptors, were compared using the Mann-Whitney test, due to their non-normal distribution. Correlations between quantitative variables were assessed using Spearman's coefficient, particularly for the analysis of the relationship between CRP and MC5R, due to the asymmetric distribution of the data.

3. Results

The study included 85 homozygous sickle cell patients aged from 2 to 62 years. The demographic and clinical characteristics of the cohort showed a mean age of 18.70 ± 9.30 years. The overall sex ratio was 1.02 (43 men or 50.59% and 42 women or 49.41%). The age distribution of sickle cell patients was non-significant with p = 0.490 (Table 1). The frequency of CVO in the overall cohort was 45.88% (39 patients) and the distribution of CVO by age showed a predominance in children (57.14% of patients aged 2 - 11 years were in crisis at the time of the study) although no significant difference was found between age groups after analysis by the Chi^2 test (p = 0.362) (Table 2). These CVOs involved 20 men (46.51%) and 19 women (45.24%), with no significant difference by Chi^2 test (p = 0.906) (Table 3). Pain was assessed using the visual analog scale (VAS) graduated from 0 to 10. In this study, severe pain was defined as a VAS score ≥ 6, in line with clinical recommendations in the context of sickle cell disease. Pain presented 45.88% of patients (n = 39) in CVO phase at the time of the study. This high proportion reflects the high prevalence of acute painful episodes in this population. The absence of statistically significant differences according to gender (p = 0.906) or age (p = 0.362) suggests that the occurrence of CVOs is globally distributed, independently of these demographic variables (Figure 6). The results of the blood count showed a statistically significant higher difference in the CVO group (p = 0.018) between the White Blood Cells (WBC) of two groups, suggesting an increased inflammatory response during attacks; however, there was no significant difference in the Red Blood Cells (RBC)/Hemoglobin (Hb) and Platelets (PLT) parameters of the two groups (p values > 0.05) (Table 4). CRP is a sensitive marker of acute inflammation. It was measured to compare the systemic inflammatory status of patients according to their clinical status. Our data showed a significant elevation of CRP in CVO patients compared with those in the inter-critical phase (p < 0.0001). This result confirms the major involvement of systemic inflammation in painful cell crises, positioning CRP as a relevant biomarker in the assessment of CVO severity (Figure 1). IL6, on the other hand, is a pro-inflammatory cytokine involved in the early stages of inflammation. Its measurement in this study enabled us to assess immune dynamics in sickle cell patients. Although Figure 2 shows an increase in IL-6 concentrations in CVO patients, the difference did not reach statistical significance (p = 0.06). This trend, though close to significance, suggests a modulated or transient immune activation, requiring further studies to confirm its clinical

utility (Figure 2). MC3R was explored for its putative involvement in regulating inflammatory responses and modulating pain. As shown in Figure 3, no significant difference in MC3R concentration was observed between patients in the CVO phase and those in the inter-critical phase ($p = 0.34$). These data suggest that MC3R is not actively involved in CVO-related acute inflammatory responses in this population (Figure 3). MC4R is recognized for its central role in the neurogenic modulation of pain. However, its involvement in sickle cell disease has not yet been elucidated in our study. This result shows a total absence of difference between groups in MC4R concentration ($p = 0.94$). This observation suggests that contrary to data from certain animal models, MC4R does not appear to be significantly activated in the context of human sickle cell inflammation (Figure 4). MC5R is involved in the peripheral regulation of inflammation and the innate immune response. Its potential role in CVO was therefore specifically investigated. This figure reveals a significant increase in MC5R concentration in CVO patients compared to those in the inter-critical phase ($p < 0.003$). This result strongly suggests that MC5R may play an active role in the inflammatory mechanisms associated with acute pain in sickle cell patients, positioning it as a candidate biomarker and therapeutic target of interest (Figure 5). To explore a potential link between systemic inflammation and MC5R receptor activation, a correlation analysis was performed between CRP and MC5R levels in patients in crisis. This figure shows a moderate positive correlation between CRP and MC5R ($r = 0.23$), but this relationship does not reach statistical significance ($p = 0.07$). This trend, although not significant, could reflect an indirect regulatory interaction between these two markers during sickle cell inflammation. It merits further exploration with a larger sample and a longitudinal approach (Figure 7).

Table 1. Patient distribution by age and gender.

Age groups (years)	Gender		Total n (%)	p-value
	Male n (%)	Female n (%)		
[2 - 11]	8 (57, 14)	6 (42, 86)	14 (100)	p = 0.490
[12 - 17]	16 (57, 14)	12 (42, 86)	28 (100)	
[18+]	19 (44, 19)	24 (55, 81)	43 (100)	
Total	43 (50, 59)	42 (49, 41)	85 (100)	

Table 2. Distribution of CVO occurrence according to age.

Age groups (years)	CVO		Total n (%)	p-value
	Yes n (%)	No n (%)		
[2 - 11]	8 (57, 14)	6 (42, 86)	14 (100)	P = 0.362
[12 - 17]	10 (35, 71)	18 (64, 29)	28 (100)	

Continued

[18+]	21 (48, 84)	22 (51, 16)	43 (100)
Total	39 (45, 88)	46 (54, 12)	85 (100)

Table 3. Distribution of CVO occurrence by gender.

Gender	CVO		Total n (%)	p-value
	Yes n (%)	No n (%)		
Male	20 (46, 51)	23 (53, 49)	43 (100)	
Female	19 (45, 24)	23 (54, 76)	42 (100)	p = 0.906
Total	39 (45, 88)	46 (54, 12)	85 (100)	

Table 4. Comparison of hematological parameters between CVO and PCI groups.

Parameters	CVO group (n = 38)	PCI group (n = 38)	p-value
GR (10^{12}/L)	2.74 ± 0.64	2.82 ± 0.79	0.62
Hb (g/dL)	7.44 ± 1.44	7.62 ± 1.31	0.55
GB (10^3/µL)	15.17 ± 5.50	12.36 ± 4.21	**0.**018*
PLT (10^3/µL)	340.15 ± 135.96	391.58 ± 147.22	0.11

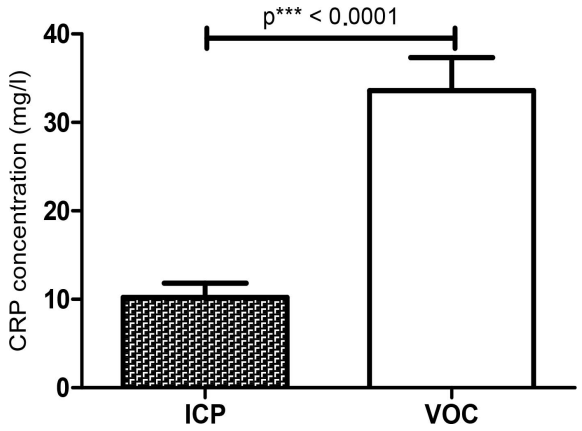

Figure 1. CRP concentration in homozygous sickle cell subjects.

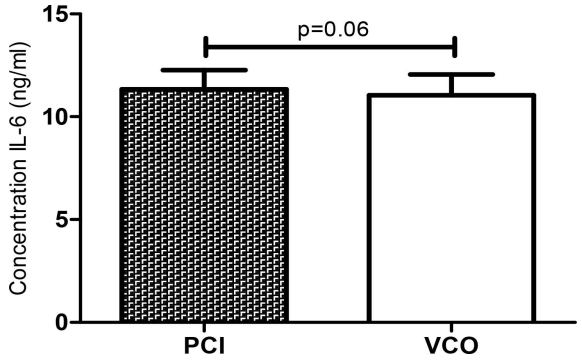

Figure 2. IL-6 concentration in homozygous sickle cell subjects.

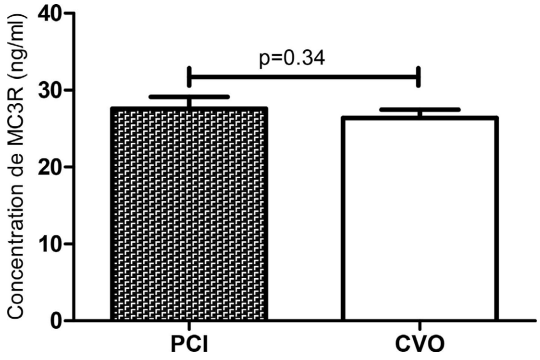

Figure 3. MC3R concentration in homozygous sickle cell subjects.

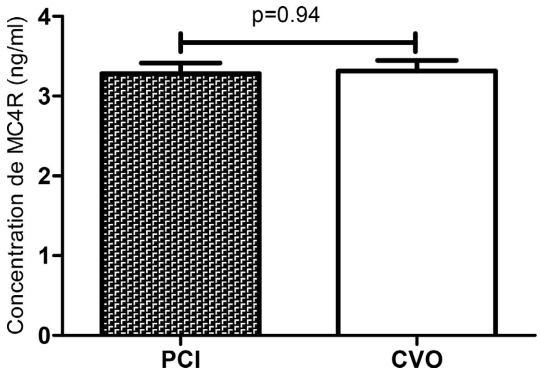

Figure 4. MC4R concentration in homozygous sickle cell subjects.

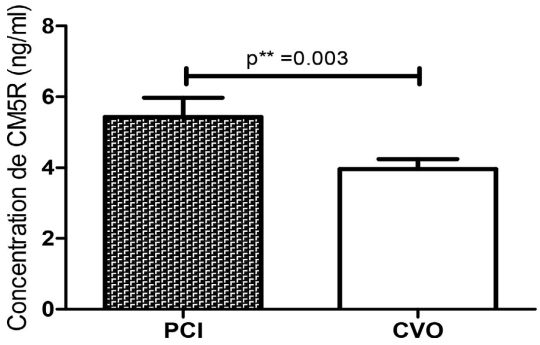

Figure 5. MC5R concentration in homozygous sickle cell subjects.

Figure 6. Pain score and assessment.

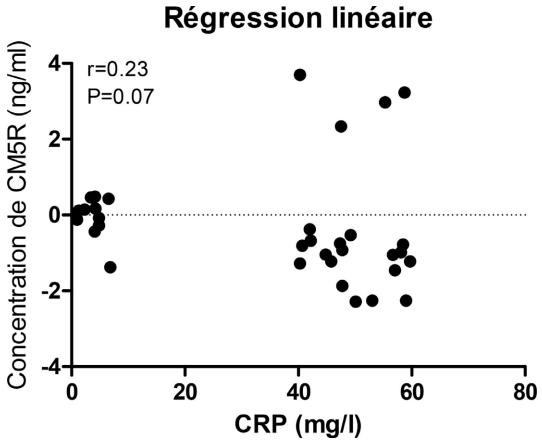

Figure 7. Correlation between CRP and MC5R during CVO.

4. Discussion

Our study aimed to explore the sociodemographic, clinical and molecular characteristics of homozygous sickle cell patients in the context of vaso-occlusive crises (CVO) in Brazzaville, with a particular focus on the role of melanocortin receptors (MC3R, MC4R, MC5R) as potential biomarkers of inflammation and pain.

We observed that patients aged 18 and over were the most represented (50.59%), with a mean age of 18.70 ± 9.30 years, ranging from 2 to 62 years. This predominance of young adults among sickle cell subjects is in line with observations by Shah *et al.* [14] in the USA and Diop *et al.* [15] in Senegal. This overrepresentation could be linked to better survival in this population, but also to a higher frequency of hospitalizations in this age group due to recurrent attacks. Early mortality among children with sickle cell disease in resource-limited countries often limits access to adulthood, in the absence of ongoing management [16].

The sex distribution in our cohort shows a slight male predominance, with an M/F sex ratio of 1.02. This result, consistent with the work of Diagne *et al.* [17] in Senegal and Mounkaila *et al.* [18] in Niger, is explained by the autosomal recessive mode of transmission of the disease, independent of sex.

Clinically, 45.88% of patients were in the CVO phase at the time of the study, with a predominance of severe bone pain (84.62%), in line with the findings of Mekone Nkwele and *al* [19] in Cameroon. Osteoarticular crises were the most frequently reported type of CVO, followed by hand-foot syndrome and abdominal pain. The high frequency of CVO could reflect poor compliance with hygienic and dietary measures, often linked to a feeling of social exclusion and the constraints imposed by a chronic pathology [20].

Next, our results highlighted a significant elevation of CRP and MC5R in CVO patients, while MC3R, MC4R and IL-6 receptors showed no significant variations between the two groups.

CRP, a well-known marker of acute inflammation, was found to be significantly increased ($p < 0.0001$), in line with the work of Nanitelamio *et al.* [20]. Conversely, IL-6, although slightly elevated, did not achieve a statistically significant difference

($p = 0.06$), which could be explained by its earlier kinetics in the inflammatory process [21].

The involvement of the MC5R receptor was particularly notable, with significantly higher concentrations in the crisis phase ($p < 0.003$). A weak positive correlation was observed between CRP and MC5R levels ($r = 0.23$; $p = 0.07$), suggesting a potential link between systemic inflammation and melanocortin receptor regulation. Although this correlation fails to reach significance, it raises the hypothesis of cross-interaction. CRP, produced by hepatocytes under IL-6 stimulation, could influence MC5R expression via inflammatory signaling pathways such as NF-κB. Conversely, MC5R could play an anti-inflammatory role by inhibiting pro-inflammatory cytokines, as suggested by the work of Brzoska *et al.* [12] and Ng *et al.* [22] in experimental models.

Our results showed no statistically significant difference in MC3R ($p = 0.34$) and MC4R ($p = 0.94$) receptors in homozygous sickle cell patients, either in crisis or inter-critical phase. Therapeutically, however, the melanocortin receptor system appears to be a promising avenue. The Agonists of MC4R and MC5R have shown analgesic effects comparable to those of opioids, without inducing dependence [11].

Thus, MC5R could represent an innovative therapeutic target in the management of sickle cell pain, in a context where current options remain limited. However, this study has several limitations. The relatively small sample size ($n = 85$) reduces the statistical power and scope of the conclusions. The absence of a healthy control group makes it impossible to establish a reference level for the markers studied. In addition, assays were performed at a single time point, without longitudinal follow-up, which limits the dynamic interpretation of biomarkers. Finally, the response to analgesic treatments was not analyzed, although it may influence the expression of the markers studied.

Despite these limitations, this study represents a first step towards understanding the interactions between inflammation, pain and melanocortin receptors in sickle cell disease in Central Africa. It highlights the potential of MC5R as a biomarker of inflammatory pain and as a therapeutic target. Further, larger-scale, multicenter studies are needed to confirm these results.

5. Conclusion

Sickle cell disease, in its homozygous phenotype, is an inflammatory disease. Studying therapeutic avenues for the management of CVO related to this disease could improve the management of patients suffering from this pathology. Our study highlighted the involvement of melanocortin receptors as inflammatory biomarkers associated with pain in CVO in homozygous sickle cell patients in the inter-critical and critical phases. In conclusion, our results show the involvement of MC5R as an anti-inflammatory target and CRP as a biomarker associated with inflammation and pain during CVO in homozygous sickle cell patients.

Acknowledgements

We would like to thank the doctoral program at the Faculty of Health Sciences for giving us the opportunity to write both these scientific articles (with submission and publication). Our thanks also go to all the research centers that enabled us to collect and process samples, namely the CNDr in Brazzaville, the CNTS in Brazzaville, the research laboratory of the Faculty of Health Sciences and the TRIOS Medical Analysis Laboratory.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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