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SUBEROYLANILIDE HYDROXAMIC ACID: A MINI-REVIEW

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ABSTRACT
Histones are the basic proteins that complex with DNA to form the nucleosome core. The human genome consists of repetitive units of nucleosomes arranged in a compact and co-ordinated manner. Histones can be either in acetylated or deacetylated form and the equilibrium between two is regulated by the corresponding enzymes, histone acetylases and histones deacetylases (HDACs). These enzymes play an important role in regulating gene expression and chromatin assembly. Thus, Inhibition of HDACs represents a new strategy to treat several diseases. In this report, we will discuss the role of HDACs in metabolism with special reference to Suberoylanilide hydroxamic acid (SAHA).

Keywords:
suberoylanilide hydroxamic acid

INTRODUCTION

The critical balance between the histone acetylation and deacetylation is maintained by histone acetylases (HATs) and histone deacetylases (HDACs). They regulate the survival, proliferation and differentiation of cells through chromatin remodelling and change in gene expression patterns. The role of histone deacetylases (HDAC) and the potential of these enzymes as therapeutic targets for cancer, inflammatory, neurodegenerative diseases and a number of other disorders is an area of rapidly expanding the investigation. In humans, 18 HDAC's are present, and they are not redundant in function. They are classified by homology to yeast HDACs: Class I include HDACs 1, 2, 3, and 8; Class IIA includes HDACs 4, 5, 7, and 9; Class IIB, HDACs 6 and 10; and Class IV, HDAC11. HDAC inhibitors are the chemical compounds that inhibit Zn^{2+}dependent HDAC enzymes. Over the last ten years, almost 490 clinical trials have been carried out with the HDAC inhibitors [1-3].

HDACs and glucose homeostasis

The glucose homeostasis is achieved through stringent regulation of glucose production in the liver and uptake of glucose in the peripheral tissues. The recent studies have revealed that the maintenance of glucose homeostasis is linked with the epigenetic mechanisms. The post-transcriptional modifications by histones play a significant role in gene transcription. The acetylation of histones and non-histone proteins, in particular, provides a critical mechanism for controlling gene expression. The reports have also shown that the HDACs regulate acetylation of histones that are involved in glucose homeostasis and thereby play critical role in regulating glucose metabolism. In summary, HDACs downregulate the expression levels of GLUT4 and lead to insulin resistance in muscle cells and adipocytes. HDACs play a role in the regulation of gluconeogenesis; class IIa HDACs are dephosphorylated and translocated towards the nucleus where they recruit HDAC3, which deacetylates FOXO1 and FOXO3 and eventually enhances FOXO-DNA binding to promote gluconeogenic gene expression. The recent studies have also shown the role of HDAC6 in glucocorticoid receptor-mediated effects on glucose metabolism and its potential as a drug target for production of glucocorticoid-induced diabetes. The HDAC1 is also involved in silencing PDX1 leading to failure in β-cell development and function. HDACs also mediate STAT3-mediated gluconeogenesis [4].

HDAC inhibitors and inflammation

The anti-inflammatory properties of HDAC inhibitors were reported from a number of animal and cellular inflammatory models. The molecular function of HDACs was restricted to histone acetylation, but recent reports have shown that they regulate the activity of non-histone proteins. Though the treatment of cancer was the original theme of HDAC inhibition, but it is now being evaluated for neurodegenerative diseases, inflammatory diseases and even diabetes. This is further substantiated by the findings of 3600 acetylation sites on 1750 proteins including only cytoplasmic proteins. Acetylation is now known to regulate nuclear factor kappa beta (NF-κB), the master regulator of inflammatory pathways. As the activation of NFκB is a critical event in IL-1β–induced β-cell death, these findings led to the investigation and demonstration of the protective effects of HDAC inhibition in inflammatory processes [5].

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HDAC inhibitors and Diabetes mellitus

The HDAC inhibitors have shown characteristics in the treatment of Diabetes. In addition to regulating glucose metabolism by enhancing insulin secretion, improving insulin resistance and maintaining the process of gluconeogenesis, the HDAC inhibition has also shown to treat diabetic complications including Diabetic retinopathy (DR) and Diabetic nephropathy (DN). Taken together, this provides a strong rationale to carry preclinical studies using HDAC inhibitors for metabolic disorders [6].

HDAC inhibitors and adipogenesis

Adipogenesis is an intricate process accompanied by coordinated alterations in gene expression patterns. The studies showing the relation between the regulation of HDAC expression and adipogenesis suggest that adipogenesis might be regulated by HDAC inhibitors [7]. Treatment of 3T3-L1 cells with HDAC inhibitors such as apicidin, Trichostatin A and Suberoylanilide hydroxamic acid inhibited adipocyte differentiation and downregulated the adipogenic marker genes such as FAS, PPAR-γ, SREBP-1c, aP2 indicating the role of HDAC inhibition in regulating adipogenesis. Since adipogenesis is a crucial process that contributes to weight gain and obesity and the inhibition by HDAC inhibitors implicate the relevance of therapeutic application of HDAC inhibitors for the treatment of obesity [8].

Suberoylanilide hydroxamic acid:

SAHA is an inhibitor of histone deacetylases (HDAC's), including HDACs 1, 2, 3, and 8, class II HDACs, HDACs 6 and 10 and HDAC11. HDAC's alter the structure and function of many target proteins including histone and non-histone proteins, components of transcriptional factors controlling gene expression and the proteins that regulate cell proliferation, migration and death. HDAC inhibitors are emerging as a promising class of chemotherapeutic agents against cancer. However, reports indicate that the majority of HDAC inhibitors block adipogenesis through down-regulation of adipogenic gene expression and concomitantly induce the de-differentiation of adipogenesis in 3T3L1 cell line, thereby implying a novel therapeutic role that HDAC inhibitors may play in controlling obesity. Reports have also revealed the anti-inflammatory effects of SAHA on the activation, proliferation; cytokine secretion and apoptosis of Concanavalin A activated murine lymphocytes [9,10].

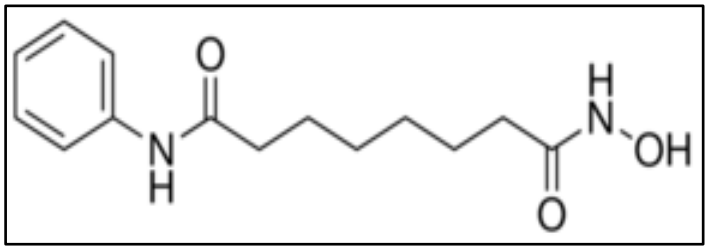

Fig 1.9: Structure of Suberoylanilide hydroxamic acid (SAHA).

The inhibitory effect of SAHA for reducing pro-inflammatory cytokines appears to be effective at lower doses relative to the doses used for inhibition of tumours. The *in vitro* concentrations of SAHA that inhibited proliferation of tumour cell lines were 1–5 μM whereas at nanomolar concentrations (50–200 nM), a 50%–85% reductions in LPS-induced secretion of Tumor Necrosis Factor-α, Interleukin-1β, Interferon-γ, and Interleukin -12 in freshly isolated human PBMCs (Peripheral blood mononuclear cells) was observed. Thus, the anti-inflammatory effect of SAHA is evident at concentrations lower than those needed to suppress tumour cell growth *in vitro* and *in vivo*. The treatment with SAHA also causes reduction in secretion of mature IL-1β from PBMCs and the level of circulating IL-1β in LPS-injected mice. SAHA reduced the secretion of TNF-α and IFN-γ as well as their mRNA levels from the same cultures. Therefore, the reduction in IL-1β by SAHA appears to be primarily at the degree of secretion of mature IL-1β. Although the pathway(s) for secretion of IL-1β remain unclear [11].

CONCLUSION

The present report discusses the role of HDAC's in different disorders like Diabetes Mellitus, inflammation, adipogenesis and glucose homeostasis. One of the widely used HDAC inhibitor is Suberoylanilide hydroxamic acid. The use of SAHA in different experiments has also been discussed.

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