

Index

Abstract	12
Chapter 1	
Histamine In The Nervous System	14
1.1 Anatomic Framework	14
1.2 Histaminergic Receptors	15
1.2.1 Histamine H ₁ Receptor	15
1.2.2. Histamine H ₂ Receptor	16
1.2.3 Histamine H ₃ Receptor	16
1.2.4 Histamine H ₄ Receptor	17
1.3 Homeostatic Histaminergic Functions	17
1.3.1 Sleep and Wakefulness	18
1.3.2 Thermoregulation	18
1.3.3 Fluid Balance	18
1.3.4 Feeding and Energy Metabolism	19
Chapter 2	
Cognitive Functions Of Brain Histamine	22
2.1 Recognition Memory	23
2.2 Fear Memory	23
2.3 How to evaluate memory in rodents: most widely used paradigms	24
2.4 The role of central histaminergic system in memory and cognition	25
Chapter 3	
Disorders Associated With Brain Histamine	28
Chapter 4	
Is Histaminergic Neurotransmission Involved in Antidepressant Responses?	30
4.1 Historical background	30
4.2 The modern concept of depression	31
4.3 Neurogenic and neurotrophic theory	31
4.4 Role of CREB in Depression and Antidepressant Treatments	33
4.5 Neurocircuitry of depression	34
4.6 Animal Models used to screen antidepressant compounds	35
4.6.1 Tail Suspension Test (TST)	35

Histaminergic neurotransmission as a gateway for the effects of Oleoylethanolamide	
4.6.2 Forced Swim Test (FST)	36
4.6.3 Chronic Mild Stress (CMS)	36
4.6.4 Learned Helplessness	37
4.6.5 Novelty-suppressed feeding and sucrose preference	37
4.6.6 Neuronal histamine: an insight on depression	37
Chapter 5	
Is Neuronal Histamine Involved In Stress-Related Responses?	40
5.1 Historical Background	40
5.2 Definition and Classification of Stress	41
5.3 Neuroanatomy and Physiology of Stress	41
5.4 Stress: social behaviour, and resilience	42
5.5 Stress impact on memory function	43
5.6 Chronic Stress Paradigm in rodents	44
5.6.1 Chronic Social Defeat Stress	45
5.6.2 Crowding and Isolation	46
5.6.3 Social Instability	46
5.6.4 Chronic Restrain Stress	46
5.7 Neuronal histamine: an insight on stress	47
Chapter 6	
Histamine And The Gut-Brain Axis	48
6.1 Oleoylethanolamide	49
Aim of the Study	53
Results	55
Part I	
Histaminergic Neurotransmission As A Gateway For The Cognitive Effect Of Oleoylethanolamide In Contextual Fear Conditioning	55
1.1 Materials and Methods	55
1.1.1 Animals and Drugs	55
1.1.2 Surgery	55
1.1.3 Infusion Procedure and Experimental Groups	56
1.1.4 Contextual Fear Conditioning	56
1.1.5 Freezing Measurement	56
1.1.6 Histology	57
1.1.7 Statistical Analysis	57
1.2 Results	57
1.2.1 Oleoylethanolamide administration increases freezing time of rats submitted to contextual fear conditioning	57
1.2.2 Histaminergic neurotransmission is required for OEA-freezing enhancements	57

1.2.3 Antagonism of histamine H1 and H2 receptors prevents OEA-induced freezing enhancement	58
1.3 Summary of Results (Part I)	58

Part II

Oleylethanolamide Induces Antidepressant-Related Responses By Targeting PPAR-α And Recruiting The Histaminergic Neurotransmission	61
2.1 Materials and Methods	61
2.1.1 Animals and Drugs	61
2.1.2 Behavioral Experiments	61
2.1.2.1 Tail Suspension Test (TST)	61
2.1.2.2 Open Field test	62
2.1.3 Neurochemical experiments	62
2.1.3.1 Western Blot analysis	62
2.1.4 Statistical Analysis	63
2.2 Results	63
2.2.1 Oleylethanolamide systemic administration exerts antidepressantlike effect by recruiting histaminergic neurotransmission	63
2.2.2 OEA-induced increase in cortical and hippocampal CREB phosphorylation is reduced in HDC-KO mice	64
2.2.3 Oleylethanolamide systemic administration reduced immobility time by targeting PPAR- α	64
2.2.4 OEA-induced increase in cortical and hippocampal CREB phosphorylation is reduced in PPAR-alpha KO mice	64
2.3 Summary of the Results (Part II)	65

Part III

Histaminergic Involvement In Oleylethanolamide Protection On The Cognitive Decline Induced By Chronic Social Stress In Mice	67
3.1 Materials and Methods	67
3.1.1 Animals and Drugs	67
3.1.2 Chronic Social Defeat Stress Paradigm	67
3.1.3 Social Interaction Test	68
3.1.4 Novel object recognition test	68
3.1.5 Statistical analysis	69
3.2 Results (Part III)	69
3.2.1 Chronic Social Defeat Stress induced body weight gain and increased food consumption in OEA or VEH treated mice compared to controls	69
3.2.2 Oleylethanolamide reduces social avoidance induced by social defeat stress	69
3.2.3 Oleylethanolamide improves the performance in the object recognition test of WT stressed mice, but not of HDC-KO mice	70
3.2.4 CSDS did not affect motility of mice tested in the open field	70
3.3 Summary of the Results (Part III)	70

Histaminergic neurotransmission as a gateway for the effects of Oleoylethanolamide

Conclusions And Discussion 73

References 75

Figures 107