

TABLE OF CONTENTS

**Abstract**..... iii

**Abbreviations**..... xi

**1. Introduction**..... 1

    1. Regulation of autophagy by insulin and amino acids..... 3

        1.1 Regulation of autophagy by insulin..... 5

        1.2 Regulation of autophagy by amino acids..... 6

    2. Ca<sup>2+</sup>-sensor proteins in the autophagic and endocytic traffic..... 10

        2.1 Involvement of Ca<sup>2+</sup> in the regulation of autophagy..... 13

            2.1.1 Cytosolic Ca<sup>2+</sup> signalling in autophagy..... 13

            2.1.2 Regulation of autophagy by ER-derived Ca<sup>2+</sup> ..... 16

                2.1.2.1 Autophagic response to the inhibition of ER Ca<sup>2+</sup>-ATPases by thapsigargin..... 19

                2.1.2.2 Regulation of autophagy by IP<sub>3</sub>R-dependent Ca<sup>2+</sup> release from the ER..... 20

        2.2 Mitochondrial link between ER derived Ca<sup>2+</sup> and autophagy..... 23

        2.2 Involvement of Ca<sup>2+</sup> in endocytosis..... 25

        2.3 Role of endolysosomal Ca<sup>2+</sup> in autophagy and endocytosis.. 27

            2.3.1 Endolysosomal Ca<sup>2+</sup> channels..... 28

            2.3.2 Ca<sup>2+</sup>-dependent effectors of endolysosomal fusions..... 29

    3. Annexin and copine family..... 32

        3.1 The annexins..... 34

            3.1.1 The origin of the family..... 34

            3.1.2 Structure and function of annexins..... 35

            3.1.3 Tissue distribution and intracellular localization of annexins..... 38

## TABLE OF CONTENTS

3.2 The copines.....	44
3.2.1 The origin of the family.....	44
3.2.2 Structure and function of copines.....	45
3.2.3 Tissue distribution and intracellular localization of copines.....	49
<b>2. Objectives.....</b>	<b>51</b>
<b>3. Results: Chapter 1</b> Identification of proteins associated to lysosomal membranes under different proteolytic conditions.....	<b>55</b>
<b>4. Results: Chapter 2</b> Withdrawal of essential amino acids increases autophagy by a pathway involving Ca <sup>2+</sup> /calmodulindependent kinase kinase-β (CaMKK-β).....	<b>77</b>
<b>5. Appendix to Chapter 2 of Results</b> The effect of intracellular and extracellular pH on Ca <sup>2+</sup> response to amino acids.....	<b>95</b>
<b>6. Results: Chapter 3</b> Annexin A5 stimulates autophagy and inhibits endocytosis.....	<b>105</b>
<b>7. Results: Chapter 4</b> Annexin A1 and mostly copine 1 cooperate with annexin A5 to the enhancement of autophagy and copine 1 promotes endocytosis.....	<b>133</b>
<b>8. General Discussion.....</b>	<b>165</b>
<b>9. Conclusions.....</b>	<b>179</b>
<b>10. References.....</b>	<b>183</b>
<b>11. Appendix 1</b> New Ca(2+)-dependent regulators of autophagosome maturation....	<b>205</b>
<b>12. Appendix 2</b> Materials and Methods.....	<b>215</b>