ministration of anti-ADM antibodies. Further, dosing may be critical when applying ADM or anti-ADM antibodies.

For other diseases blocking of ADM may be beneficial to a certain extent. However, it might also be detrimental if ADM is totally neutralized as a certain amount of ADM may be required for several physiological functions. In many reports it was emphasized that the administration of ADM may be beneficial in certain diseases. In contrast thereto in other reports ADM was reported as being life threatening when administered in certain conditions. The disadvantage of the prior art may be overcome with the anti-ADM antibodies or anti-ADM antibody fragments or anti-ADM non-Ig scaffolds provided by the present invention.

Summary

In a first aspect, there is provided anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament, wherein said antibody ~~or said fragment or said scaffold is a non-neutralizing antibody~~ or fragment or scaffold binds to the N-terminal part, aa 1-21, of adrenomedullin: YRQSMNNFQGLRSFGCRFGTC; SEQ ID No. 23.

In a second aspect, there is provided the use of anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin in the manufacture of a medicament, wherein said antibody ~~or said fragment or said scaffold is a non-neutralizing antibody~~ or fragment or scaffold binds to the N-terminal part, aa 1-21, of adrenomedullin: YRQSMNNFQGLRSFGCRFGTC; SEQ ID No. 23.

In a third aspect, there is provided a pharmaceutical composition comprising an anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin as disclosed herein for use as a medicament.

In a fourth aspect, there is provided the use of a pharmaceutical composition comprising an anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin as disclosed herein in the manufacture of a medicament. ~~In a fourth aspect, there is provided anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin, wherein said antibody or said fragment or said scaffold binds to the~~

~~N-terminal part (aa 1-21) of adrenomedullin and wherein said antibody or fragment or scaffold would neither bind N-terminal extended nor N-terminal modified adrenomedullin nor N-terminal degraded adrenomedullin.~~

~~In a fifth aspect, there is provided a pharmaceutical composition comprising an anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin as disclosed in the fourth aspect.~~

Description of the invention

Subject matter of the invention is an anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin for use as a medicament, wherein said antibody or said fragment or said scaffold is a non-neutralizing antibody or fragment or scaffold.

Throughout the specification the "antibodies", or "antibody fragments" or "non-Ig scaffolds" in accordance with the invention are capable to bind ADM, and thus are directed against ADM, and thus can be referred to as "anti-ADM antibodies", "anti-ADM antibody fragments", or "anti-ADM non-Ig scaffolds".

In another embodiment of the invention the anti-ADM antibodies, anti-ADM antibody fragments, or anti-ADM non-Ig scaffolds provided by the invention are capable to bind circulating ADM, and thus are directed against circulating ADM.

In a specific embodiment said anti-ADM antibody, anti-ADM antibody fragment or anti-ADM non-Ig scaffold is a non-neutralizing antibody, fragment or non-Ig scaffold. A neutralizing anti-ADM antibody, anti-ADM antibody fragment or anti-ADM non-Ig scaffold would block the bioactivity of ADM to nearly 100%, to at least more than 90%, preferably to at least more than 95%.

In contrast, a non-neutralizing anti-ADM antibody, or anti-ADM antibody fragment or anti-ADM non-Ig scaffold blocks the bioactivity of ADM less than 100%, preferably to less than 95%, preferably to less than 90%, more preferred to less than 80% and even more preferred to less than 50 % (baseline value). This means that the residual bioactivity of ADM bound to the non-neutralizing anti-ADM antibody, or anti-ADM antibody fragment or anti-ADM non-Ig

CLAIMS

1. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament, wherein said antibody or ~~said fragment or said scaffold is a non-neutralizing antibody or~~ fragment or scaffold binds to the N-terminal part, aa 1-21, of adrenomedullin:

   YRQSMNNFQGLRSFGCRFGTC; SEQ ID No. 23.

2. Use of anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin in the manufacture of a medicament, wherein said antibody or ~~said fragment or said scaffold is a non-neutralizing antibody or~~ fragment or scaffold binds to the N-terminal part, aa 1-21, of adrenomedullin:

   YRQSMNNFQGLRSFGCRFGTC; SEQ ID No. 23.

3. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament according to claim 1 or the use according to claim 2, wherein said antibody or fragment or scaffold is monospecific.

4. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament or the use according to any of claims 1 to 3, wherein said antibody or fragment or scaffold exhibits a binding affinitity to ADM of at least 10^{-7} M.

5. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament or the use according to any of claims 1 to 4, wherein said antibody or fragment or scaffold is not ADM-binding-Protein-1 (complement factor H).

~~6. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin for use as a medicament or the use according to any of claims 1 to 5, wherein said antibody or antibody fragment or non-Ig scaffold binds to a region of preferably at least 4 or at least 5 amino acids within the sequence of aa 1-42 of mature human ADM:~~
~~YRQSMNNFQGLRSFGCRFGTCTVQKLAHQIYQFTDKDKDNVA~~
~~SEQ ID No. 24.~~

~~7. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin for use as~~

~~a medicament or the use according to any of claims 1 to 6, wherein said antibody or fragment or scaffold binds to the N-terminal part (aa 1-21) of mature human ADM:~~

~~YRQSMNNFQGLRSFGCRFGTC~~
~~SEQ ID No. 23.~~

~~8.~~6. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament or the use according to any of claims 1 to ~~7~~5, wherein said antibody or said fragment or said scaffold according to any of claims 1 to ~~7~~5 binds to an epitope containing the N-terminal end (aa 1) of adrenomedullin.

~~9. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-scaffold binding to adrenomedullin for use as a medicament or the use according to any of claims 1 to 8, wherein said antibody or said fragment or said scaffold binds to the N-terminal part (aa 1-21) of adrenomedullin and wherein said antibody or fragment or scaffold would neither bind N-terminal extended nor N-terminal modified adrenomedullin nor N-terminal degraded adrenomedullin.~~

~~10.~~7. Anti-Adrenomedullin (ADM) antibody or an anti-ADM antibody fragment binding to adrenomedullin or anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament or the use according to any of the claims 1 to ~~9~~6, characterized in that said antibody, antibody fragment or non-Ig-protein scaffold does not bind to the C-terminal portion of ADM, being it aa 43-52 of ADM
PRSKISPQGY-NH2
(SEQ ID NO: 25).

~~11.~~8. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament or the use according to any of claims 1 to ~~10~~7, wherein said antibody or said fragment or said scaffold is an ADM stabilizing antibody or fragment or scaffold that enhances the half life ($t_{1/2}$ half retention time) of adrenomedullin in serum, blood, plasma at least 10 %, or at least 50 %, or >50 %, or 100 % and/or wherein said antibody or fragment or scaffold blocks the circulating ADM bioactivity ~~not more than 80 %, or~~ not more than 50 %, as determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

~~12.~~9. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin for use as a medicament or the use according to any of claims 1 to ~~11~~8, wherein said antibody or said fragment or said scaffold is a modulating anti-ADM antibody or fragment or scaffold that enhances the half life ($t_{1/2}$ half retention time) of adrenomedullin in serum, blood, plasma at least 10 %, or at least, 50 %, or >50 %, or 100 % and that blocks the bioactivity of ADM to ~~not more than 80 %, or~~ not more than 50 %, as determined in a human recombinant Adrenomedullin receptor cAMP functional assay.

~~13.~~10. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin for use as a medicament or the use according to any of claims 1 to ~~12~~9, wherein said antibody or fragment is a monospecific antibody or monospecific antibody fragment that binds to ADM or an antibody fragment thereof, binding to ADM wherein the heavy chain comprises the sequences:
SEQ ID NO: 1
GYTFSRYW

SEQ ID NO: 2
ILPGSGST

SEQ ID NO: 3
TEGYEYDGFDY

and wherein the light chain comprises the sequences
SEQ ID NO:4
QSIVYSNGNTY

SEQ ID NO: 5
RVS

SEQ ID NO: 6
FQGSHIPYT.

~~14.~~11. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin for use as a medicament or the use according to claim ~~13~~10, wherein said antibody or fragment

QESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 13 (AM-VL1)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLNWFQQRPGQSPRRLIYRVSNRDSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 14 (AM-VL2-E40)

DVVMTQSPLSLPVTLGQPASISCRSSQSIVYSNGNTYLEWFQQRPGQSPRRLIYRVSNRDSG
VPDRFSGSGSGTDFTLKISRVEAEDVGVYYCFQGSHIPYTFGQGTKLEIKRTVAAPSVFIFPP
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

~~15.~~12. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin or the use according to any of claims 1 to ~~14~~11, wherein the medicament is to be used in combination with a vasopressor e.g. catecholamine.

~~16.~~13. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin or the use according to any of claims 1 to ~~14~~11, wherein the medicament is to be used in combination with an intravenous fluid.

~~17.~~14. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin or the use according to any of claims 1 to ~~14~~11, wherein the medicament is to be used in combination with a TNF-alpha-antibody.

~~18.~~15. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin or the use according to any of claims 1 to ~~14~~11, wherein the medicament is to be used in combination with antibiotics.

~~19.~~16. Pharmaceutical composition comprising an anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig-protein scaffold binding to adrenomedullin according to any of claims 1 to ~~18~~15 for use as a medicament.

~~20. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin, wherein said antibody or said fragment or said scaffold binds to the N-terminal part (aa 1-21) of adrenomedullin and wherein said antibody or fragment or scaffold would neither bind N-terminal extended nor N-terminal modified adrenomedullin nor N-terminal degraded adrenomedullin.~~

~~21. Anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin according to claim 20, wherein said antibody or said fragment or said scaffold binds to the N-terminal end (aa 1) of adrenomedullin.~~

~~22. Pharmaceutical composition comprising an anti-adrenomedullin antibody or an anti-ADM antibody fragment binding to adrenomedullin or an anti-ADM non-Ig scaffold binding to adrenomedullin according to any of claims 20 or 21.~~

17. Use of a pharmaceutical composition according to claim 16 in the manufacture of a medicament.

18. The use according to any one of claims 2-17, wherein the medicament is used for reducing the risk of mortality during a chronic or acute disease of a patient, for stabilizing the circulation, for regulating the fluid balance in said patient, for preventing or reducing edema in said patient, wherein said chronic or acute disease is selected from the group comprising sepsis, diabetes, cancer, acute and chronic vascular diseases, organ failure, kidney failure, heart failure, shock, septic shock, organ dysfunction and kidney dysfunction.