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An Integrated Analytical Framework for Calcium-Dependent MC4R Function

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A structured workflow linking biochemical measurements, receptor mechanism and computational verification

Why calcium matters to MC4R

MC4R is a class A GPCR involved in central appetite regulation and energy expenditure.

MC4R signalling

α-MSH activates MC4R, connecting melanocortin signalling with energy homeostasis.

Calcium cofactor

Structural studies identify Ca^{2+} in the extracellular ligand-binding pocket, associated with agonist recognition.

Clinical relevance

Disruption of MC4R can contribute to obesity; BMI alone cannot reveal the underlying receptor mechanism.

Central question: how can biochemical data and molecular modelling be integrated without overstating what each dataset proves?

Aims and analytical objectives

The paper evaluates the numerical components available in the source project and organises them into a traceable framework.

- Summarise resting and peak calcium values across 50 records.
- Assess linear relationships between BMI and calcium measurements.
- Interpret a separate eight-condition MC4R comparison table while preserving uncertainty and assay limitations.
- Review synthetic computational demonstrations as numerical checks—not as receptor simulations.
- Define the experimental and computational evidence needed for receptor-specific validation.

Three evidence streams were kept separate

The source material contains distinct components; they were not assumed to share participants, constructs or experimental runs.

A | Calcium dataset

50 records
BMI, sex and group labels
Resting and peak calcium
Descriptive statistics + Pearson correlation

B | Receptor table

Eight MC4R conditions
Binding parameter, Bmax and cAMP EC_{50}
Ratios calculated against calcium-replete WT

C | Synthetic tests

Assigned docking-score ordering
Abstract coordinate RMSD/RMSF tests
Independent Ca–O distance markers

Important: these evidence streams are analytically integrated, not treated as one experimentally linked dataset.

Calcium distribution in the 50-record dataset

Mean ± sample SD, except SS (n = 1). Concentrations are reported in nM.

Group	n	Resting Ca^{2+}	Peak Ca^{2+}
All	50	96.6 ± 14.0	305.9 ± 55.7
AA	40	97.4 ± 13.6	298.7 ± 56.6
AS	9	93.2 ± 16.9	325.4 ± 33.2
SS	1	96.5	418.0

BMI mean

29.52 ± 5.20 kg/m²

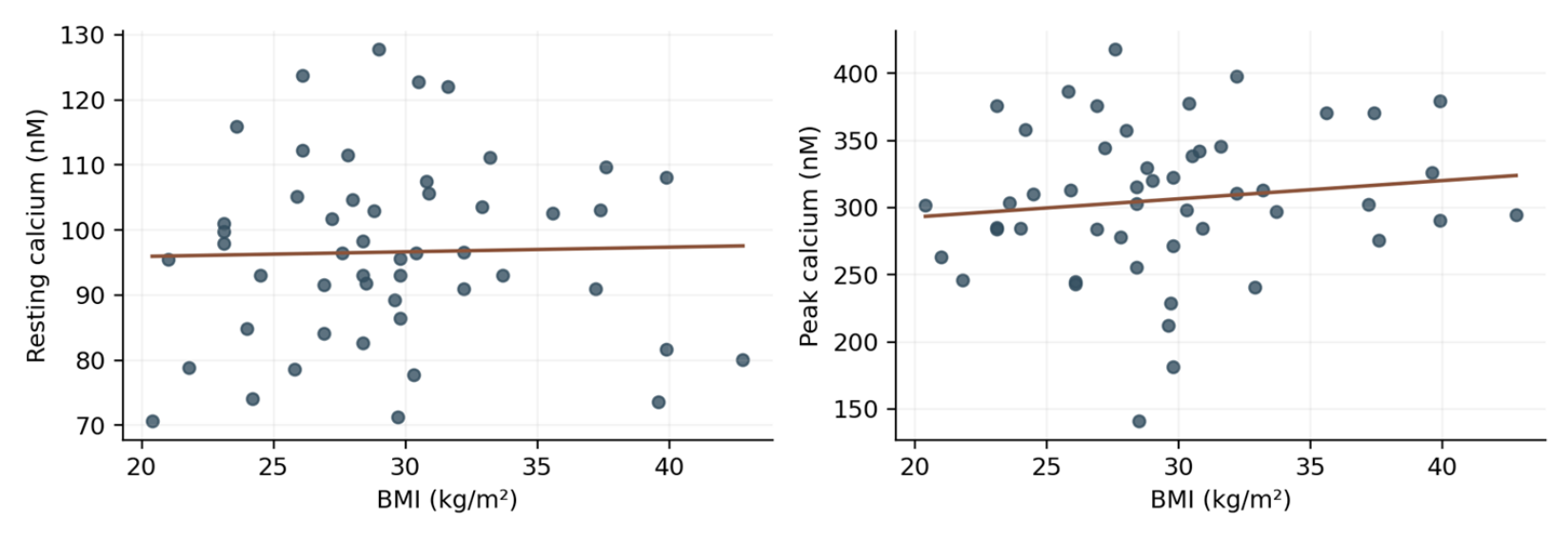
Recorded sex labels

37 female | 13 male

Peak calcium exceeded resting calcium in all 50 records. Resting range: 70.6–127.8 nM; peak range: 140.8–418.0 nM.

BMI showed weak linear associations with calcium

Neither Pearson correlation met the nominal $p < 0.05$ threshold.



Resting calcium

r = 0.027
p = 0.855

Peak calcium

r = 0.127
p = 0.380

Interpretation: the supplied data show little linear association. This does not establish that calcium signalling is unrelated to adiposity.

Supplementary participant comparisons

Source-reported analyses; age and ABO record-level inputs were not available for independent recalculation.

Sex and BMI

Female: 29.11 ± 4.90
Male: 30.70 ± 6.03
Welch p = 0.402

Group comparison

AA vs AS: p = 0.918
ABO: p = 0.365
Holm-adjusted p = 1.000

Age and BMI

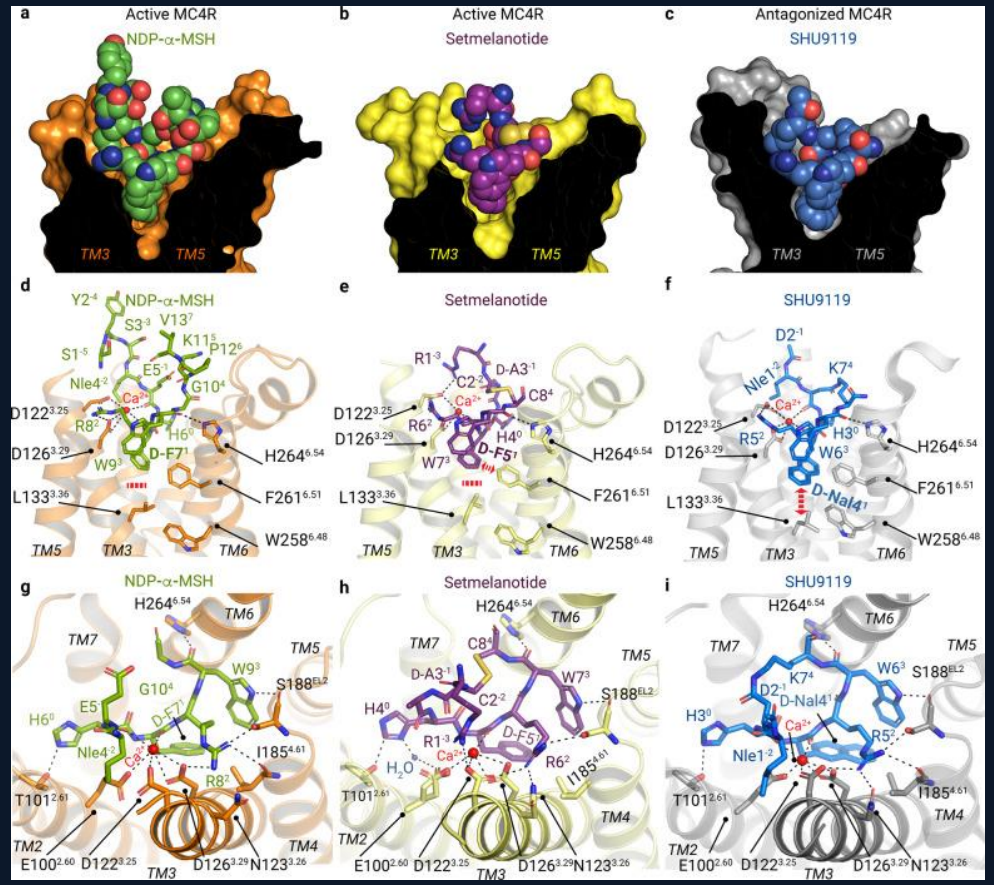
r = 0.275
p = 0.053
Adjusted p = 0.214

No adjusted comparison met p < 0.05. AA/AS/SS labels are not MC4R alleles; SS included only one record.

The source applied Holm correction across four exploratory tests: sex, AA versus AS, ABO and age.

Calcium sits within the extracellular ligand-binding pocket

Published MC4R structures show ligand-dependent interactions involving Ca^{2+} and acidic receptor residues.



Key acidic region

Glu100 • Asp122 • Asp126

Ligand context

Agonist-bound structures include NDP-α-MSH and setmelanotide; SHU9119 is shown as an antagonist.

Structural figures reproduced from Heyder et al. (2021), Cell Research, under CC BY 4.0; they are published evidence, not outputs of this study.

The separate receptor table suggests distinct endpoint patterns

Values are source-reported; assay provenance, replicate numbers and meaning of ± remain unspecified.

Condition	Binding parameter	Bmax (% WT)	cAMP EC_{50}
WT, 1.2 mM Ca^{2+}	1.2 ± 0.3	100	2.1 ± 0.4
WT, 0 mM + EGTA	45.0 ± 8.5	~25–35	>350
V103I	1.1 ± 0.2	98 ± 5	1.9 ± 0.3
E100K	>1,000	<5	>5,000
D126Y	820 ± 110	12 ± 3	2,100 ± 340
R165W	1.4 ± 0.3	18 ± 4	>1,000

Calcium depletion

45.0 / 1.2 = 37.5-fold binding-parameter ratio

Interpret cautiously

Binding, capacity and potency are different endpoints. Lower Bmax complicates affinity-only interpretation.

The binding endpoint is labelled Kd/IC_{50} without a defined assay; it is therefore described as an unspecified binding parameter.

The computational tests checked calculations—not MC4R dynamics

No receptor topology, force-field trajectory, saved docking pose or converged free-energy calculation was supplied.

Scenario	Mean RMSD (nm)	Mean RMSF (nm)	Mean Ca–O (Å)	Below 2.8 Å
A	0.398	0.361	2.354	100.0%
B	0.795	0.729	2.552	100.0%
C	1.375	1.249	2.884	20.8%

Docking-score set

Assigned values: −8.4 to −6.8
Ordering check only

Meaning

Increasing RMSD/RMSF followed prescribed perturbation scales; distance tests were independent.

The 2.8 Å fraction is a geometric threshold result—not validated MC4R calcium-coordination occupancy.

A traceable validation workflow is the next step

The framework separates extracellular coordination, intracellular response and serum calcium measurements.

1 | Experimental

Sequence-verified WT and mutant constructs
Matched extracellular calcium conditions
Vehicle and receptor-negative controls
Calibrated Fura-2 recordings
Binding + cAMP assays

2 | Computational

Document receptor structure and state
Use comparable WT/mutant preparation
Retain docking parameters, logs and poses
Run replicated, converged MD trajectories
Analyse ion–donor distances and persistence

3 | Integration

Measure receptor expression
Separate availability from recognition
Distinguish binding from signalling potency
Report uncertainty and provenance
Avoid inferring receptor effects from BMI alone

Intracellular calcium is downstream of many processes; serum calcium cannot substitute for receptor coordination or intact-cell fluorescence.

The contribution is an integrated analytical framework

The available evidence supports a workflow—not validated variant-specific clinical effects or binding free energies.

- Across 50 records, BMI had weak associations with resting calcium (r = 0.027) and peak calcium (r = 0.127).
- The separate receptor table illustrates different patterns in binding parameter, relative binding capacity and cAMP potency.
- Synthetic tests demonstrate numerical consistency checks only; they are not molecular-dynamics trajectories.
- Sequence-defined experiments, calibrated recordings and reproducible molecular trajectories are required for receptor-specific conclusions.

SELECTED REFERENCES

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