

Influence of common antidepressants on MMP-2 and MMP-9

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Common antidepressants modulates MMP-2 and MMP-9 activity, suggesting a potential mechanism in neuroplasticity and therapeutic response.

INTRODUCTION

Depression is a recognized independent risk factor for Alzheimer's disease (AD), and antidepressants are widely prescribed in patients with AD and related dementias (1,2). Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are implicated in extracellular matrix remodeling and vascular integrity in AD. Dysregulation of these enzymes has been linked to basal lamina degradation and cerebrovascular dysfunction, both being key features of AD pathology (2). Although antidepressants are known to modulate neuroplasticity and inflammatory signaling, it remains unclear whether they can directly affect MMP enzymatic activity independently of cellular or inflammatory mechanisms (3). Therefore, this study aimed to evaluate the direct effects of common antidepressants regularly used in the clinical management of AD on the enzymatic activity of MMP-2 and MMP-9.

METHODS

1

Screening panel of 23 antidepressants and their metabolites (SSRIs, SNRIs, TCAs, NDRIs, NaSSaS, MAOIs and NMDA mechanisms) using therapeutically effective drug concentrations (Consensus guidelines for therapeutic monitoring in neuropsychopharmacology, 2017)

2

Enzyme-specific FRET Substrate
Commercial inhibitors specifically targeting MMP-2 and MMP-9, respectively

Recombinant human MMP-2
Recombinant human MMP-9

3

[Enzyme MMP-2 / MMP-9]
[Single Antidepressants]
[Commercial MMP Inhibitor]
[FRET Substrate]

4

INTACT SUBSTRATE
Donor Acceptor
Binding
Quenched Emission (Low Fluorescence)
Enzyme Cleavage
Separated Donor and Acceptor
Donor Emission (High Fluorescence)
CLEAVED PRODUCTS

MMP Inhibition Data
Control (Active MMP - No Drug)
Commercial Inhibitor (Full Inhibition)
Antidepressant Compound A (Partial Inhibition)
Antidepressant Compound B (Moderate Inhibition)

Microplate reader

5

Antidepressant showing inhibition

Dose-response profiles of antidepressants identified as MMP-2 / MMP-9 inhibitors via screening

RESULTS

(A)

MMP-2 MMP-9

control
inhibitor
Agomelatine
Amitriptyline (hydrochloride)
Bupropion (hydrochloride)
Citalopram
Clomipramine (hydrochloride)
Desipramin
Desvenlafaxine (succinate hydrate)
(S)-Duloxetine (hydrochloride)
Escitalopram
Fluoxetine (hydrochloride)
Imipramide (hydrochloride)
Ketamin
Mianserin
Mirtazapine
Moclobemide
Norfluoxetine (hydrochloride)
Nortriptyline (hydrochloride)
Paroxetine (hydrochloride)
Sertraline (hydrochloride)
Tianeptine (sodium salt)
Tranylcypromine (hydrochloride)
Trimipramine (maleate)
Venlafaxine (hydrochloride)

Active metabolite of Fluoxetine
Active metabolite of Amitriptyline

(B)

MMP-2 Relative activity (%)
MMP-2 Relative activity (%)
MMP-2 Relative activity (%)
MMP-2 Relative activity (%)
MMP-9 Relative activity (%)

Agomelatine [ng/mL]
Paroxetine [ng/mL]
Norfluoxetine [ng/mL]
Nortriptyline [ng/mL]
Norfluoxetine [ng/mL]

CONCLUSIONS

This screening demonstrated that a subset of antidepressants directly inhibits MMP-2 (Agomelatine, Nortriptyline, and Paroxetine), with Norfluoxetine also reducing MMP-9 activity. Notably, dose-response evaluations indicated that this moderate enzyme inhibition remains sustained across all tested concentrations, suggesting a plateau effect achieved even at the lowest therapeutic doses. While the precise molecular mechanisms of these direct interactions remain to be fully characterized, these findings provide insights into how specific antidepressants might influence ECM remodeling. Given the roles of MMP-2 and MMP-9 in AD pathology, further investigation in cellular and *in vivo* models is required to determine whether this enzymatic inhibition translates into relevant wanted or unwanted side-effects in patients.

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