Effect of Antidepressants on Radiolabeled Metaiodobenzylguanidine (MIBG) Uptake

Rudolf A. Werner, Ryohei Kobayashi, Hiroshi Wakabayashi, Constantin Lapa, Andreas Menke, Takahiro Higuchi

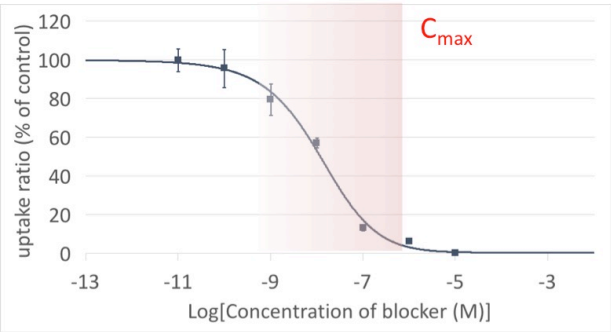
Background: Radiolabeled metaiodobenzylguanidine (MIBG) scintigraphy had been widely available not only for risk stratification of heart failure patients, but also for differential diagnosis of dementia with lewy bodies. Depression is one of the most common co-morbidities in such dementia patients. Pharmacological interference on cardiac ^{123}I-MIBG uptake with conventional tricyclic antidepressants (TCA) via inhibiting norepinephrine transport is well recognized, but influence of the newly introduced antidepressants are not yet determined.

Methods: *In-vitro* cell uptake assay using human neuroblastoma cells overexpressing NET (SK-N-SH cells ($2*10^5$ cells/well)) was conducted. Cells were incubated for 60 min at 37°C with ^{131}I-MIBG together with three different antidepressants {desipramine (TCA), escitalopram (SSRI), venlafaxine (SNRI) or bupropion (NDRI)}. Dose-response curves were plotted to determine IC_{50} and % inhibition at C_{max} (maximum concentrations determined at clinical trials). In healthy New Zealand White rabbits, in-vivo planar 10min ^{123}I-MIBG scans were performed 2.5 hours after intravenous ^{123}I-MIBG administration (50MBq per animal). Imaging was conducted using 3 different pharmacological pretreatments 10min before tracer administration: 1) desipramine (1.5mg/kg weight IV), 2) escitalopram (2.5 or 15 mg/kg weight IV) and 3) saline-treated controls. Heart-to-mediastinum ratios (HMR) were calculated by dividing the count mediastinal ROI.

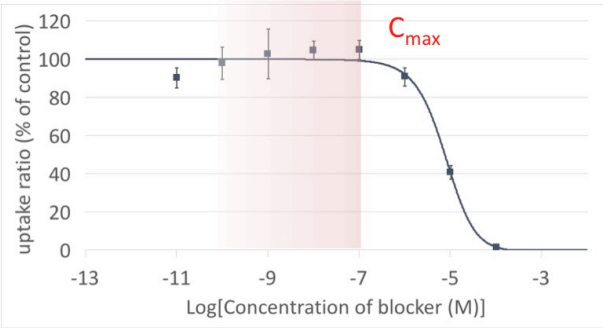
Results: The IC_{50} value of desipramine, escitalopram, venlafaxine and bupropion on ^{131}I-MIBG uptake were 12 nM, 7.5 uM, 4.9 uM, and 13 uM, respectively. The inhibition rates of ^{131}I-MIBG uptake were calculated as 90 % for desipramine, 0.7 % for escitalopram, 26 % for venlafaxine, and 12 % for bupropion at C_{max}. Consisted with cell uptake study, desipramine pretreatment led to a marked reduction of the cardiac ^{123}I-MIBG uptake *in-vivo* (HMR: 1.94 ± 0.22 vs. 1.23 ± 0.13, $p<0.01$), while there was no significant pharmacological influence of escitalopram, even in blood concentrations

being considerably higher than in clinical practice (escitalopram 2.5 mg/kg, HMR: 2.01 ± 0.13, escitalopram 15 mg/kg, HMR: 2.05 ± 0.19, n.s. vs. controls).

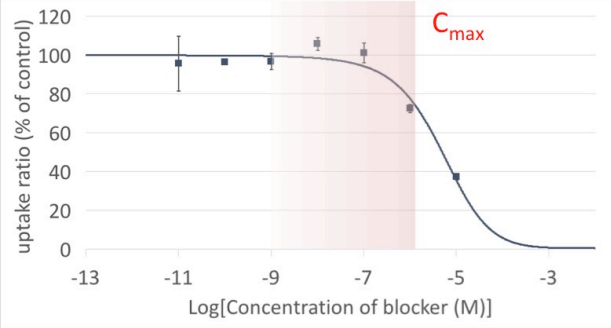
Conclusions: In the present *in-vitro* binding assay and *in-vivo* rabbit study, we demonstrated that serotonin selective antidepressant escitalopram (SSRI) has no major interference on neuronal ^{123}I-MIBG uptake, while other types of antidepressants lead to a significant decrease.



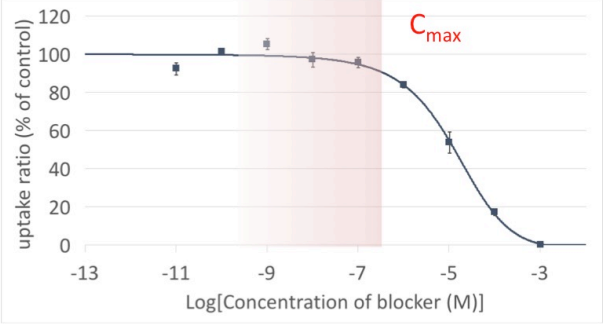
Desipramine (TCA)



Escitalopram (SSRI)



Venlafaxine (SNRI)



Bupropion (NDRI)

Research Support: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 701983.