Didesmethyl-Cariprazine, the Major Active Human Metabolite of Cariprazine With Greater Dopamine D_3 vs D_2 Receptor Selectivity, Increases Dopamine Release in the Rat Medial Prefrontal Cortex

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OBJECTIVE

To evaluate whether there are any differences in the neurochemical effects of cariprazine (CAR) in comparison with didesmethyl-CAR (DDCAR) to provide potential mechanism(s) that can account for the unique clinical profile of CAR

CONCLUSIONS

DDCAR produced a significant increase in the level of dopamine (DA) and DA metabolites in the medial prefrontal cortex (mPFC), whereas CAR did not show any significant effects on these parameters with a trend towards a decrease at the lower dose tested

These data suggest that DDCAR's greater D_3 receptor affinity and selectivity over D_2 receptor compared to CAR may contribute to the increase in DA neurotransmission in the mPFC, supporting the notion that the increasing D_3 vs D_2 selectivity of compounds produces more benefit for ameliorating negative and cognitive symptoms

DDCAR treatment did not have any impact on acetylcholine (ACh) and histamine (HA) levels, whereas CAR resulted in a significant decrease in these neurotransmitters, which may be due to the CAR's greater D_2 receptor activity compared to DDCAR

Collectively, these results demonstrate a differential neurochemical profile of DDCAR in comparison to CAR, indicating that the predominance of this metabolite following stable dosing of CAR may contribute to the unique clinical profile of CAR therapy in various psychiatric symptoms

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INTRODUCTION

Cariprazine

- Cariprazine (CAR) is a dopamine (DA) D_3-preferring D_3/D_2 and serotonin 5-HT_{1A} receptor partial agonist approved by the US Food and Drug Administration to treat adults with schizophrenia, manic, mixed, and depressive episodes associated with bipolar I disorder as well as adjunctive treatment for major depressive disorder (MDD)
- CAR is metabolized to desmethyl-CAR (DCAR) and ultimately to didesmethyl-CAR (DDCAR) with DDCAR being the prominent moiety (~ 70% of total) at steady state in humans[1]
- Although in general, DDCAR displays comparable in vitro binding receptor profile and has a similar antipsychotic-like activity as CAR, this metabolite has greater D3 receptor (D_3R) affinity and selectivity compared to the parent[2]

Study Objective

- To evaluate whether there are any differences in the neurochemical effects of CAR in comparison with DDCAR, which is more D_3 receptor-preferring, to provide potential mechanism(s) that can account for the unique clinical profile of CAR

Rationale for Analysis

- Neurochemical effects of CAR and DDCAR were evaluated in rats using microdialysis probing in the mPFC, a brain area of importance with dysregulated function in various psychiatric and cognitive disorders. The negative and/or cognitive symptoms of schizophrenia may be due to reduced dopaminergic and/or cholinergic tone in cortical brain areas[3,4]
- Alteration in the function of dopamine D_3 receptors may play a role in this cortical hypofunctionality and underlie the deficits in social behaviors and cognitive functions in various mood disorders[5,6]

METHODS

Analysis

- Neurochemical effects of CAR and DDCAR were evaluated in rats (male Sprague-Dawley rats weighing 300–320 g, N = 49) using microdialysis probing in the mPFC
- Seven days before the microdialysis experiment, the rats were pretreated with buprenorphine and carprofen, anesthetized with isoflurane, and the guide cannulas were stereotaxically implanted into the mPFC. On the day of experiment, the separate groups of awake rats were treated with CAR and DDCAR, and the samples were collected in 20-minute intervals for the following 4 hours
- Microdialysis samples concentrations of neurotransmitters DA, norepinephrine (NE), 5-HT, ACh, HA, glutamate (Glu), gamma-aminobutyric acid (GABA), glycine (Gly), as well as the levels of D-serine (D-Ser) and the monoamine metabolites, 3-methoxy-4-hydroxyphenylglycol (MHPG), 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) were measured by ultra high-performance liquid chromatography with electrospray tandem mass spectroscopy (UHPLC-MS/MS) following their derivatization with benzoyl chloride except for ACh which was measured by a separate UHPLC-MS/MS method. Concentrations of D-Ser were measured by UHPLC-MS/MS using a chiral separation column. Concentrations of CAR and DDCAR in the remaining volumes of the microdialysates were measured by UHPLC-MS/MS

Statistical Analysis

- The values were presented as mean ± standard error of mean (SEM) and differences were considered statistically significant at the $P < .05$ level
- The data was expressed as percentage of the basal concentrations and as relative area-under-the curve $AUC_{(0\text{-}240\ min)}$ values
- The mean basal levels in the control and treated groups and the relative $AUC_{(0\text{-}240\ min)}$ values were compared by use of one-way analysis of variance (ANOVA) followed by Tukey's and Dunnett's multiple comparison test, respectively
- Differences between the groups and treatments were analyzed by repeated measures two-way ANOVA followed by Bonferroni's posttest

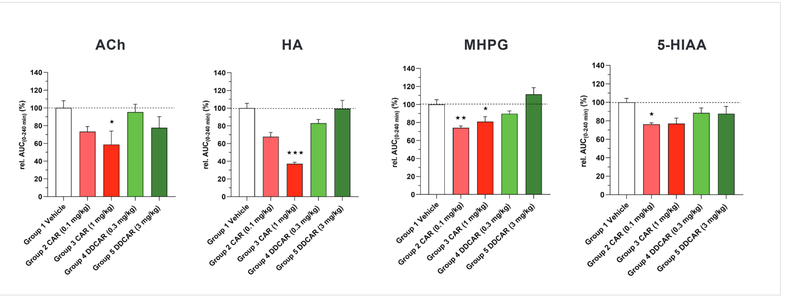
RESULTS

Basal Levels[a] of Neurotransmitters, Neuromodulators and Monoamine Metabolites in the mPFC of Awake Rats

	Group 1 Vehicle	Group 2 CAR 0.1 mg/kg	Group 3 CAR 1 mg/kg	Group 4 DDCAR 0.3 mg/kg	Group 5 DDCAR 3 mg/kg
DA	0.287 ± 0.0203	0.305 ± 0.0495	0.336 ± 0.0747	0.414 ± 0.0241	0.083 ± 0.0431*
NE	0.675 ± 0.0872	0.455 ± 0.0487	0.493 ± 0.1196	0.773 ± 0.0997	0.468 ± 0.1671
5-HT	1.304 ± 0.3596	0.472 ± 0.0635	0.521 ± 0.0749	0.91 ± 0.2649	0.438 ± 0.0275
ACh	3.682 ± 0.5321	3.483 ± 0.4804	4.505 ± 0.9361	3.722 ± 0.3429	3.245 ± 0.8793
HA	5.844 ± 0.3934	13.30 ± 4.681	6.131 ± 1.06	66.60 ± 22.72**	12.39 ± 2.694
Glu	353.5 ± 69.5	955.4 ± 244.5	1199 ± 418.1	523.6 ± 93.7	1196 ± 422.5
GABA	28.80 ± 6.91	42.56 ± 11.08	47.12 ± 5.01	54.39 ± 3.68	54.86 ± 11.56
Gly	3305 ± 1305	4098 ± 1416	7139 ± 1183	2408 ± 589	4611 ± 1093
D-Ser	2152 ± 168.9	2123 ± 160.4	1873 ± 155.5	1798 ± 304.7	2300 ± 95.5
MHPG	20.48 ± 2.821	27.26 ± 4.096	31.72 ± 4.073	23.09 ± 2.635	32.21 ± 4.585
DOPAC	43.17 ± 7.418	30.99 ± 3.948	58.29 ± 11.78	39.48 ± 7.938	52.19 ± 6.850
HVA	24.83 ± 4.162	26.85 ± 3.543	98.48 ± 37.18*	59.53 ± 10.99	111.5 ± 11.35*
5-HIAA	174.6 ± 35.45	212.8 ± 56.22	295.9 ± 81.69	171.2 ± 20.28	338.4 ± 45.71

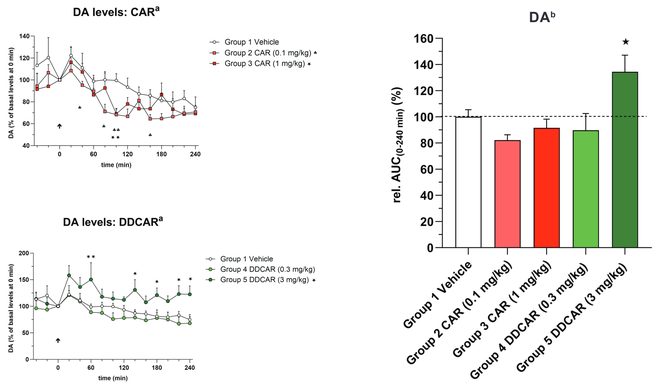
[a] The basal levels were calculated as a mean of 3 basal levels (-60 to 0 min) of each rat, thereafter as the mean ± SEM of these levels for each group and the analyte. The concentrations are expressed in nmol/L (nM). One-way ANOVA followed by Dunnett´s multiple comparison test, (*) $P < .05$; (**) $P < .01$ as compared to the vehicle group.
5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; ACh, acetylcholine; CAR, cariprazine; DA, dopamine; DDCAR, didesmethyl-CAR; DOPAC, 3,4-dihydroxyphenylacetic acid; D-Ser, D-serine; GABA, gamma-aminobutyric acid; Glu, glutamate; Gly, glycine; HA, histamine; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; mPFC, medial prefrontal cortex; NE, norepinephrine.

CAR Caused Significant Decreases in the Neurotransmitters, ACh and HA, and Monoamine Metabolites, MHPG and 5-HIAA, Levels[a] in the mPFC



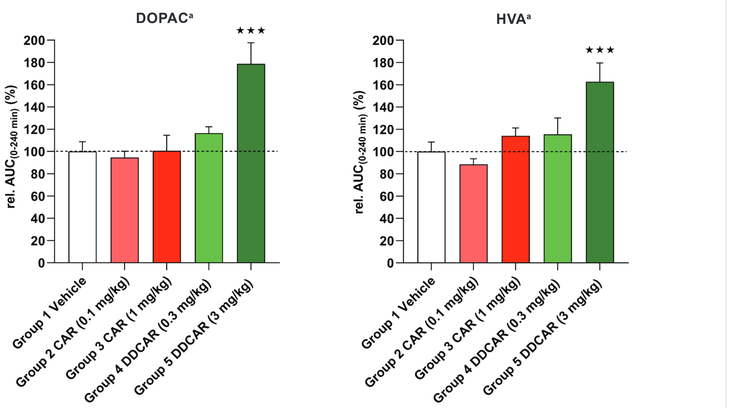
[a] Extracellular levels (Mean ± SEM) of ACh, HA, MHPG, and 5-HIAA in the mPFC of awake rats; one-way ANOVA followed by Dunnett´s multiple comparisons test; (*) $P < .05$; (**) $P < .01$; (***) $P < .001$.
5-HIAA, 5-hydroxyindoleacetic acid; ACh, acetylcholine; AUC, area under the curve; CAR, cariprazine; DDCAR, didesmethyl-CAR; HA, histamine; MHPG, 3-methoxy-4-hydroxyphenylglycol; mPFC, medial prefrontal cortex.

DDCAR but not CAR Significantly Increased the $AUC_{(0\text{-}240min)}$ Levels of DA in the mPFC



[a] Effects of CAR and DDCAR on extracellular levels of DA calculated as percentage of basal levels at 0 min (Mean ± SEM) in the mPFC of awake rats; two-way (mixed-effects model) ANOVA followed by Dunnett's multiple comparisons test; CAR: (♠) $P < .05$; (♣♠) $P < .01$; (**) $P < .01$; DDCAR: (*) $P < .05$; (**) $P < .01$.
[b] Extracellular levels (Mean ± SEM) of DA in the mPFC of awake rats; one-way ANOVA followed by Dunnett´s multiple comparisons test; (*) $P < .05$.
AUC, area under the curve; CAR, cariprazine; DA, dopamine; DDCAR, didesmethyl-CAR; mPFC, medial prefrontal cortex.

DDCAR but not CAR Significantly Increased the $AUC_{(0\text{-}240min)}$ Levels of DA Metabolites, DOPAC and HVA, in the mPFC



[a] Extracellular levels (Mean ± SEM) of DOPAC and HVA in the mPFC of awake rats; one-way ANOVA followed by Dunnett´s multiple comparisons test; (***) $P < .001$.
AUC, area under the curve; CAR, cariprazine; DA, dopamine; DDCAR, didesmethyl-CAR; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; mPFC, medial prefrontal cortex.

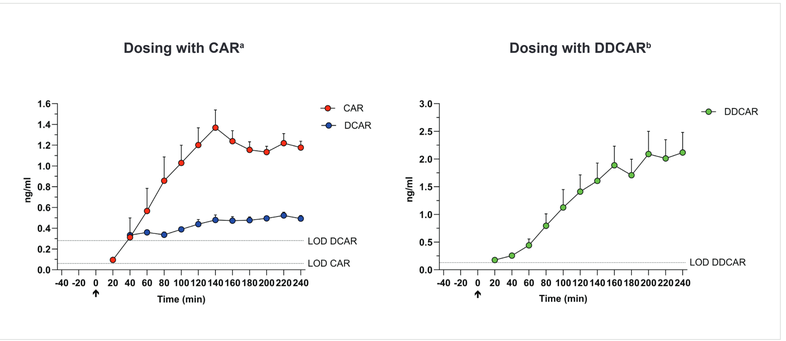
Summary[a] of CAR and DDCAR Effects in the mPFC

	CAR 0.1 mg/kg	CAR 1 mg/kg	DDCAR 0.3 mg/kg	DDCAR 3 mg/kg
DA	↓	-	-	↑
NE	↓	↓	-	-
5-HT	-	-	-	-
ACh	↓	↓	-	↓
HA	↓	↓	-	-
Glu	-	-	-	-
GABA	↓	-	-	-
Gly	-	-	-	-
D-Ser	-	-	-	-
MHPG	↓ ↓	↓	-	-
DOPAC	-	-	-	↑ ↑ ↑
HVA	-	-	-	↑ ↑ ↑
5-HIAA	↓	↓	-	-

[a] Effects of CAR and DDCAR on extracellular levels of neurotransmitters, monoamine metabolites and D-Ser in the mPFC of awake rats.The red (thick) arrows vs black (thin) arrows: the red arrows are statistically significant differences from the vehicle data for the relative $AUC_{(0\text{-}240\ min)}$, whereas the black arrows refer to significant differences for some specific time points of the time course as compared to the vehicle group, thus indicating trends.
5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; ACh, acetylcholine; AUC, area under the curve; CAR, cariprazine; DDCAR, didesmethyl-CAR; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; D-Ser, D-serine; GABA, gamma-aminobutyric acid; Glu, glutamate; Gly, glycine; HA, histamine; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol; mPFC, medial prefrontal cortex; NE, norepinephrine.

- Besides the observed effects on DA and its metabolites, the higher dose of CAR caused significant decreases in ACh, HA, MHPG, and 5-HIAA levels
- The levels of other analytes were only marginally decreased or not affected by any treatment

The Extracellular Levels of CAR and its Metabolite DCAR Gradually Increased in the mPFC and Remained Elevated Over the Entire 240-minute Sampling Period With DDCAR Being BLD



[a] Extracellular levels of CAR and DCAR in the mPFC of awake rats following treatment with CAR (1 mg/kg, peroral) at time 0 min. The levels of the second CAR metabolite, DDCAR, were not detectable when dosing with CAR.
[b] The levels of DDCAR were detectable in the mPFC following treatment with DDCAR (3 mg/kg, peroral) at time 0 min.
BLD, below the limit of detection; CAR, cariprazine; DCAR, desmethyl-cariprazine; DDCAR, didesmethyl-CAR; LOD, limit of detection; mPFC, medial prefrontal cortex.