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Reaction of Dopamine with Malondialdehyde: A Possible Underlying Event in Parkinson's Disease

Marco d'Ischia, Claudio Costantini and Giuseppe Prota*

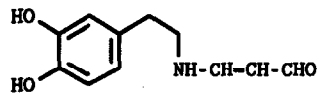
**Department of Organic and Biological Chemistry,
University of Naples
Via Mezzocannone 16, I-80134 Naples, Italy.**

Abstract. Under physiologically relevant conditions, malondialdehyde reacts with the neurotransmitter dopamine to give three major adducts that were identified as the enaminal **1**, the dihydropyridine **2** and the novel oxaazabicyclo[3.3.1]nonadiene **3**.

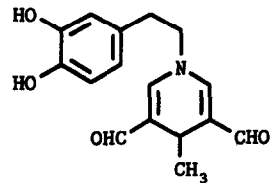
Malondialdehyde (propane-1,3-dial) is a highly toxic, carcinogenic and mutagenic metabolite which is commonly found in animal tissues as an end product of peroxidative degradation of polyunsaturated fatty acids[1,2]. Recently, an increase in the basal levels of malondialdehyde has been demonstrated in the brains of patients with Parkinson's disease[3,4], a debilitating neurodegenerative disorder of the elderly[5]. Notably, accumulation of malondialdehyde occurs selectively in the neurons of substantia nigra, which contain the specific neurotransmitter dopamine. We therefore hypothesised that, if a substantial flux of the dialdehyde gains access to dopamine-rich microenvironments, it may well react with the catecholamine pool, thereby interfering with its physiological functions possibly to form endogenous neurotoxins. Since no information was available in the literature to substantiate this hypothesis, we investigated the reactivity of malondialdehyde with dopamine under biologically relevant conditions.

Freshly prepared malondialdehyde[6,7] was allowed to react with dopamine at 1:1 molar ratio in 0.05 M acetate buffer, pH 5.5, at room temperature. The reaction, as monitored by HPLC and TLC, was found to proceed smoothly to give two major diphenolic products accounting for about 50 % of reacted dopamine. Straightforward spectral analysis[8,9] allowed us to formulate the compounds as the enaminal **1** (12 % yield) and

the 1,4-dihydropyridine-3,5-dicarbaldehyde **2** (38 % yield). Formation of **1** and **2** is in accord with the reported reactivity of malondialdehyde with primary aliphatic amines[10-13]. In analogy with the products obtained from reaction of malondialdehyde with aminoacids[10], compound **1** was present almost exclusively in the enaminal tautomeric form, and consisted of a mixture of the trans and cis isomers in the approximate ratio of 3 to 1.



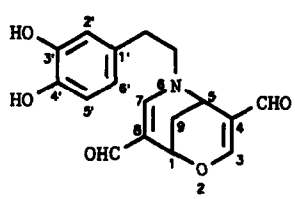
1



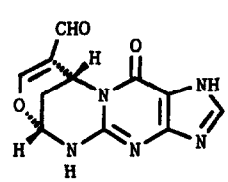
2

When malondialdehyde was reacted with dopamine at higher molar ratios, e.g. 5:1, an additional catechol product was formed, besides **1** and **2**. This was obtained in approximately 10 % yield as a colourless oil unstable to acids and alkali, which failed to crystallise[14]. Its absorption spectrum was characterised by a strong maximum at 250 nm and shoulders at 270 and 295 nm. Outstanding features of the ^{1}H-NMR spectrum[15] were, besides the signals for two α,β-disubstituted enal moieties, two characteristic spin systems for a >CH-CH$_2$-CH< and an ethylamine grouping, both experiencing an asymmetric structural environment.

Inspection of the ^{13}C-NMR spectrum[16], aided by DEPT multiplicity discrimination, revealed the presence of 17 carbons, consistent with a 3:1 adduct between malondialdehyde and dopamine. On these grounds, the compound was assigned structure **3**, which possesses the novel oxaazabicyclo[3.3.1]nonadiene ring system. Interestingly, a cyclic β-alkoxyacrolein moiety similar to that present in **3** is the key structural component of the adduct reported in the reaction of malondialdehyde with guanine[17] (**4**). Long-range heterocorrelated 2D NMR experiments confirmed the proposed arrangements between structural fragments.



3



4

Formation of the bicyclic system in **3** would expectedly involve sequential additions of malondialdehyde, in the form of the 3-hydroxypropenal tautomer[18], to the ethylamino chain of dopamine. Exposure of **1** to an excess of malondialdehyde, however, did not result in any significant formation of **3**. It is possible therefore that the dialdehyde undergoes dimerisation before reacting with the amino group of dopamine[19]. A third molecule of malondialdehyde would then add to yield eventually **3**. Direct proof for this mechanism is however lacking and other reaction paths may also be operative.

In conclusion, we believe that the observed reactivity of malondialdehyde with dopamine under physiologically relevant conditions provides a new chemical background to inquire into the mechanisms of degeneration of dopaminergic neurons in Parkinson's disease. Whether formation of adducts **1-3** occurs also in vivo and the possible neurobiological consequences are the focus of current investigations in our laboratory.

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REFERENCES AND NOTES

1. Bernheim, F.; Bernheim, M.L.C.; Wilbur, K.M. *J. Biol. Chem.*, **1948**, *174*, 257-264.
2. Esterbauer, H.; Lang, J.; Zadravec, S.; Slater, T. F. *Methods Enzymol.* **1984**, *105*, 319-328.
3. Dexter, D.T.; Carter, C.; Agid, F.; Agid, Y.; Lees, A.J.; Jenner, P.; Marsden, C.D. *Lancet II*, **1986**, 639-640
4. Dexter, D.T.; Carter, C.J.; Wells, F.R.; Javoy-Agid, F.; Agid, Y.; Lees, A.J.; Jenner, P.; Marsden, C.D. *J. Neurochem.*, **1989**, *52*, 381-389.
5. Langston, J.W. *Movement Disorders*, **1989**, *4* (suppl. 1), S15-S25.
6. Bertz, S.H. *J. Org. Chem.*, **1985**, *50*, 3585-3592.
7. Lacombe, A.; Kermasha, S.; Van de Voort, F.R.; Mills B.L. *J. Agric. Food Chem.*, **1990**, *38*, 418-423.
8. Selected spectral data of **1**. UV (H_2O) λ_{max}: 280 nm. EI-MS: m/z 207, 123, 84. ^{1}H-NMR (CD_3OD) (trans isomer) δ (ppm): 8.81 (1H, d, J=8.8 Hz), 7.36 (1H, d, J= 12.8 Hz), 6.70 (1H, d, J=8.0 Hz), 6.66 (1H, d, J=2.0 Hz), 6.53 (1H, dd, J=8.0, 2.0 Hz), 5.30 (1H, dd, J=12.8, 8.8 Hz), 3.42 (2H, t, J=6.8 Hz), 2.72 (2H, t, J=6.8 Hz).
9. Selected spectral data of **2**: UV (CH_3OH) λ_{max}: 230, 264, 386 nm. EI-MS: m/z 287, 272, 163. ^{1}H-NMR (CD_3OD) δ (ppm): 9.07 (2x1H, s), 6.90 (2x1H, s), 6.70 (1H, d, J=8.1 Hz), 6.66 (1H, d, J=2.2 Hz), 6.53 (1H, dd, J=8.1, 2.2 Hz), 3.73 (1H, q, J=6.5 Hz), 3.73 (2H, t,

J=6.5 Hz), 2.83 (2H, t, J=6.5 Hz), 0.96 (3H, d, J=6.5 Hz).

10. Nair, V.; Vietti, D.E.; Cooper, C.S. *J. Am. Chem. Soc.*, **1981**, *103*, 3030-3036.
11. Yoden, K.; Matsuzaki, R.; Iio, T.; Tabata, T. *Yakugaku Zasshi*, **1982**, *102*, 768-773. *Chem. Abs.*, **1982**, 98, 48093h;
12. Nair, V.; Offerman, R.J.; Turner, G.A.; Pryor, A.N.; Baenziger, N.C. *Tetrahedron*, **1988**, *44*, 2793-2803.
13. Kikugawa, K.; Ido, Y. *Lipids*, **1984**, *19*, 600-608.
14. Attempts to obtain a detectable molecular ion peak in the EI-MS spectrum (70 eV) were unsuccessful under a variety of experimental conditions. Usually, two major fragmentation peaks at 167 and 149 (base peak) m/z were observed.
15. ^{1}H-NMR (CD_3OD) of compound **3**: δ (ppm) 9.24 (1H, s, C4-CHO), 8.71 (1H, s, C8-CHO), 7.70 (1H, s, H-3), 7.29 (1H, s, H-7), 6.70 (1H, d, J=8.0 Hz, H-5'), 6.68 (1H, d, J=2.0 Hz, H-2'), 6.55 (1H, dd, J=8.0, 2.0 Hz, H-6'), 5.54 (1H, ddd, J=2.0, 2.0, 1.2 Hz, H-1), 4.50 (1H, ddd, J=2.0, 2.0, 1.2 Hz, H-5), 3.97 and 3.60 (1H, dt, J=13.0, 7.7 Hz and 1H, dt, J=13.0, 7.7 Hz, $CH_2N<$), 2.84 (2H, t, J=7.7 Hz, $C\underline{H}_2$-$CH_2N<$), 1.86 (1H, ddd, J=13.0, 2.0, 2.0 Hz, H-9a), 1.62 (1H, ddd, J=13.0, 1.2, 1.2 Hz, H-9b).
16. ^{13}C-NMR (CD_3OD) of compound **3**: δ (ppm) 191.63 (d, C4-$\underline{C}$HO), 187.76 (d, C8-$\underline{C}$HO), 169.01 (d, C-3), 158.43 (d, C-7), 146.77 (s, C-3' or C-4'), 145.44 (s, C-3' or C-4') 131.03 (s, C-1'), 122.24 (s, C-4), 121.69 (d, C-5'), 117.44 (d, C-2'), 116.83 (d, C-6'), 113.52 (s, C-8), 66.87 (d, C-1), 58.32 (t, $CH_2N<$), 45.49 (d, C-5), 36.33 (t, $\underline{C}H_2$-$CH_2N<$), 26.04 (t, C-9).
17. Marnett, L.J.; Basu, A.K.; O'Hara, S.M.; Weller, P.E.; Maqsudur Rahman, A.F.M.; Oliver, J.P. *J. Am. Chem. Soc.*, **1986**, *108*, 1348-1350.
18. Kwon, T.-W.; Van der Veen, J. *J. Agric. Food Chem.*, **1968**, *16*, 639-642.
19. Golding, B.T.; Patel, N.; Watson, W.P. *J. Chem. Soc., Perkin I*, **1989**, 668-669.

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