Low (Therapeutic) Dose of Warfarin Is Not Associated with Cognitive and Exploratory Behavior Impairment in Rats: Mechanistic Studies (OR15-01-19)

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Objectives: In addition to its role in hemostasis, vitamin K (VK) is involved in brain function through various proteins and sphingolipid metabolism. Warfarin (W), a widely prescribed anticoagulant drug, exerts its beneficial effect in coagulation by partially blocking the recycling of the vitamin. In previous studies, we provided evidence that, when administered in large doses, W leads to cognitive and exploratory behavior impairment, and alteration in the VK dependent proteins Gas6 and protein S (PS) and their downstream pro-survival extracellular signal-regulated (ERK) and serine-threonine (Akt) kinases pathways. In light of its widespread use as oral anticoagulant, the present study aimed to investigate the impact of W on cognition and behavior, Gas6 and PS and their signaling pathways when administered in doses comparable to those used in the clinical setting.

Methods: Male Wistar rats (n = 14/gp) were fed an AIN-93 based diet containing 750 mcg phylloquinone/kg/d and were randomly allocated to treatment with 0.1 mg W/kg/d (in drinking water) (W group) or not (C group), for 9 wks. Spatial memory (Morris Water Maze) and exploratory behavior (Open Field) were assessed. Gas6, PS, pAkt, pERK, caspases −3 and −12 (apoptosis), brain-derived neurotrophic factor (BDNF), and microglial CD11b/c protein (a marker of inflammation), were assessed by immunoblotting in hippocampus (HPP), frontal cortex (FC), and striatum (STR), three regions involved in cognition. VK contents were determined in these 3 brain regions by HPLC. Group difference was tested by unpaired Student t-test.

Results: Low dose W had no impact on brain VK concentrations, spatial memory, and exploratory behavior (all P > 0.05). In contrast, W treatment was associated with numerous cell-signaling modulations, namely increased PS, ERK and Akt activity, and caspase −3 and −12 expression, in HPP; increased BDNF in FC and STR; increased expression of CD11bc in STR, (all P < 0.05).

Conclusions: This study provides evidence that low dose W is not associated with cognitive and behavioral impairment despite numerous cell-signaling modulations that have the potential to be beneficial or detrimental to the brain. Whether these events represent compensatory mechanisms to maintain homeostasis deserves further investigation.

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