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Research Report

# Opioid receptor agonists reduce brain edema in stroke

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ABSTRACT

Cerebral edema is a leading cause of mortality in stroke patients. The purpose of this study was to assess a non-selective opioid receptor agonist, biphalin, in decreasing reducing brain edema formation using both in vitro and in vivo models of stroke. For the in situ model of ischemia, hippocampal slices were exposed to oxygen glucose deprivation (OGD) conditions and we observed that hippocampal water content was increased, compared to normoxia. Treatment with the mu agonist, Tyr-D-Ala', N-CH, -Phe4, Glyol-Enkephalin (DAMGO), delta opioid agonists, D-pen$^2$, D-phe$^5$ enkephalin (DPDPE), and kappa agonist, U50 488, all significantly decreased brain slice water gain. Interestingly, the non-selective agonist, biphalin, exhibited a statistically significant ($P<0.01$) greater effect in decreasing water content in OGD-exposed hippocampal slices, compared with mu, delta, and kappa selective opioid agonists. Moreover, biphalin exhibited anti-edematous effects in a dose responsive manner. The non-selective opioid antagonist, naloxone, returned the water content nearly back to original OGD values for all opioid agonist treatments, supporting that these effects were mediated by an opioid receptor pathway. Furthermore, biphalin significantly decreased edema (53%) and infarct (48%) ratios, and neuronal recovery from stroke, compared with the vehicle-treated groups in a 12 h permanent middle cerebral artery occlusion (MCAO) model of focal ischemia. Biphalin also significantly decreased the cell volume increase in primary neuronal cells exposed to OGD condition. These data suggest that opioid receptor activation may provide neuroprotection during stroke and further investigations are needed in the development of novel opioid agonist as efficacious treatments for brain ischemia.



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*Abbreviations:* NKCC, Na, K, 2Cl cotransporter; BBB, blood-brain barrier; MCAO, middle cerebral artery occlusion; OGD, oxygen glucose deprivation; aCSF, artificial cerebral spinal fluid; TTC, 2,3,5-triphenyltetrazolium chloride; ANOVA, One-way Analysis of Variance; CCA, common carotid artery; ECA, external carotid artery; MCA, middle cerebral artery; DAMGO, Tyr-D-Ala', N-CH, -Phe4, Glyol-Enkephalin; DPDPE, D-pen$^2$, D-phe$^5$ enkephalin

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## 1. Introduction

Stroke is the third most common cause of death and leading cause of disability, following cancer and heart disease. Each year, about 795,000 people experience a new or recurrent stroke in the United States (Lloyd-Jones et al., 2010). On average, one person has a stroke every 40 s (Kahle et al., 2009).

Many drug candidates of differing pharmacological classes have been investigated in preclinical models of brain ischemia, but most studies have focused on reduction of infarction volume and neuronal cell death as a primary endpoint, rather than the formation of brain edema. Post-ischemic cerebral edema has been reported to be leading cause of death (Bounds et al., 1981) and also the predominant cause of neurologic deterioration in stroke patients (Bounds et al., 1981). Since the

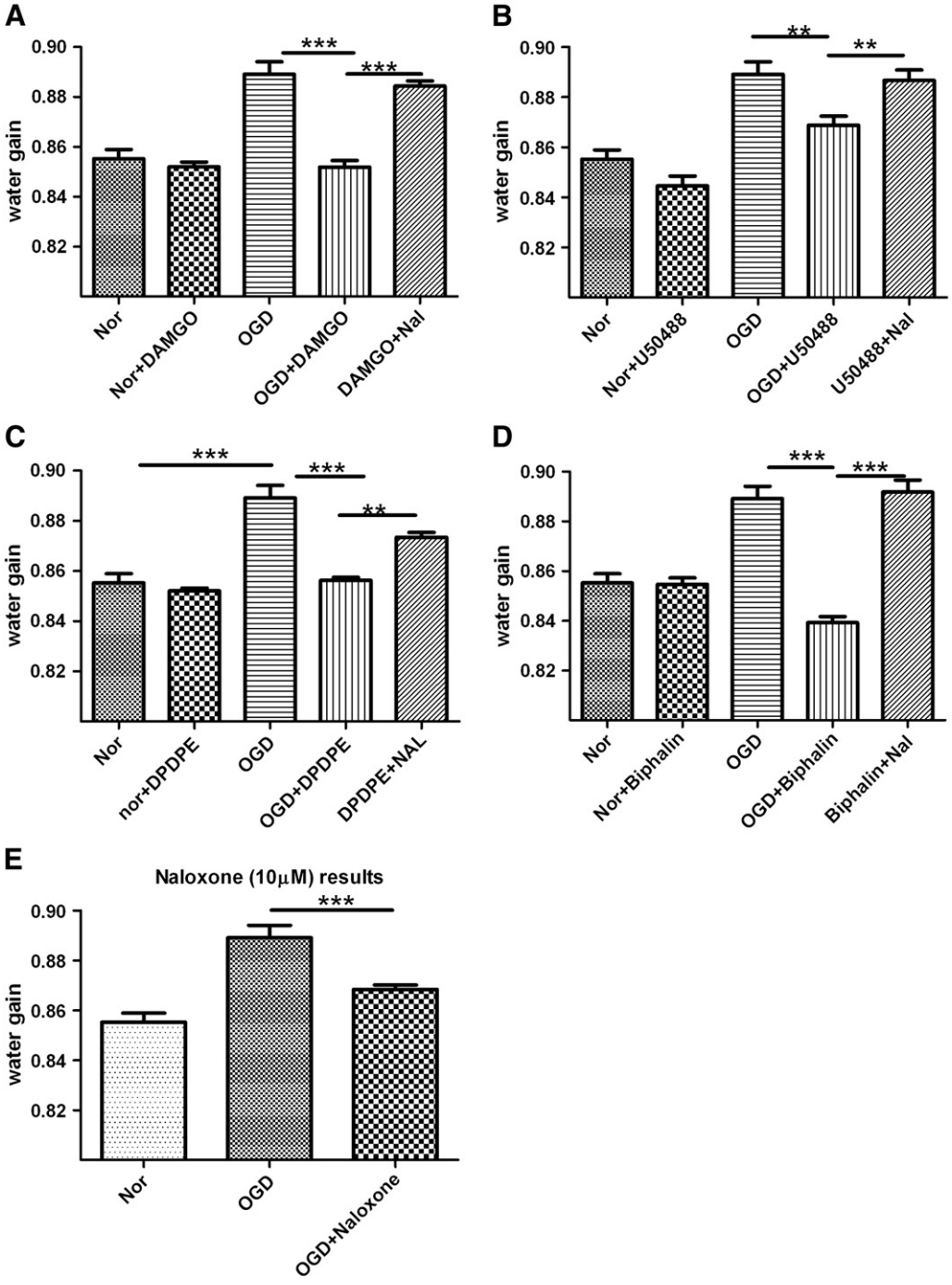


**Fig. 1 – Water content of hippocampal slices subjected to normoxia and OGD with or without the non-selective antagonist (naloxone), in the treatment of selective opioid receptor agonists A: Mu selective opioid agonist DAMGO (10 μM). B: kappa selective opioid agonist U50 488 (10 μM). C. Delta selective opioid receptor agonist DPDPE (1 μM). D. Non-selective opioid receptor agonist, biphalin (10 μM). E. Non-selective opioid antagonist, naloxone (10 μM). Values are expressed as means ± S.E.M. using one-way ANOVA and Newman–Keuls test, **: $p<0.01$; ***: $P<0.001$; $n=10–15$ slices.**