**Epithelium-Derived Catecholamines as a Target in Age-Related Bladder Dysfunction** Mariana G. de Oliveira1, Gilberto De Nucci2

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**Introduction.** The bladder epithelium releases signaling molecules, including catecholamines, that regulate bladder function. A novel endogenous catecholamine, 6-nitrodopamine (6-ND), formed by epithelium-derived dopamine and neuronal nitric oxide (NO), was recently identified as a bladder relaxant, tenfold more potent than noradrenaline, and acts independently of the classic sGC/cGMP pathway¹. Aging impairs NO-mediated signaling and contributes to voiding dysfunction², but the role of nitro-catecholamines in this context remains unclear.

**Aims.** We investigated whether exogenous 6-ND could improve aging-related bladder dysfunction in mice.

Methods. Female young (3 mo) and middle-aged (14 mo) C57BL/6 mice received saline or 6-ND (60 nmol/day/ for 4 wk, s.c. by osmotic pump; n = 10/group). A void spot assay and electric field stimulation (EFS) of bladders, with or without mucosa, were performed. A sandwich bioassay tested middle-aged bladders incubated with mucosa from young C57BL/6 or triple NOS knockout (e/i/nNOS-/-) mice. Data were analyzed by one-way ANOVA (p<0.05). Institutional ethical approvals USF-0603/2024 and UNICAMP-6379-1/2024.

**Results.** Middle-aged mice showed increased void spots versus young (p=0.01), reduced by 6-ND treatment (p=0.01). Middle-aged bladders exhibited significant hypercontractility in response to EFS (~41% increase), which was further exacerbated by mucosa removal (p=0.04). Treatment with 6-ND significantly reduced this hypercontractility, restoring contractile responses to levels comparable to those of young bladders (p=0.02). Interestingly, incubation with mucosa from young mice also reversed the hypercontractility observed in middle-aged bladders during EFS (p=0.04), whereas mucosa from triple NOS knockout mice, lacking bladder 6-ND release2, had no significant effect.

**Discussion.** Decline in 6-ND signaling with age may drive bladder hypercontractility and dysfunction. Targeting epithelial catecholamines offers a potential therapeutic strategy.

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