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HOT TOPICS

Mapping causal generators of appetitive motivation-hedonic functions in frontal cortex

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Neuropsychopharmacology; https://doi.org/10.1038/s41386-021-01154-8

Pharmacological, optogenetic, and chemogenetic mapping studies of neurobehavioral causation are revealing an often-remarkable degree of cortical localization for appetitive-motivation and hedonic functions. Recent identification of spatially-localized functional nodes within frontal cortex have yielded network-level insights that were not entirely predictable a priori. These function-mapping approaches have also demonstrated heterogeneity of neurochemical effects within an anatomical locus. Hence, insights into cortical localization of specific functions have depended upon finding just the right pharmacological or neurobiologically-specific tool.

One example has been the use of pharmacological microinjections that stimulate μ-opioid receptors (μ-ORs). These μ-OR-stimulating microinjections have long been known to increase feeding when placed sub-cortically in regions of rat nucleus accumbens, neostriatum, or amygdala [1]. Recently, μ-opioid microinjections in specific rat frontal-cortical subregions were found to similarly elicit increases in feeding and related behaviors, appetitive effects obtained neither from other opioid-receptor subtypes, nor from cortical monoamines or amino-acid transmitters [2, 3].

A fascinating spatial heterogeneity of opioid-modulated motivation functions across the frontal cortex has been revealed. Microinjections of the μ-OR agonist, DAMGO, in anteromedial orbitofrontal cortex (OFC) reveal a corridor where DAMGO engenders motivated hyperactivity in anticipation of food and increases food intake [4]. Further, in a smaller 8 mm^3 'hedonic hotspot' within rat anteromedial OFC, DAMGO microinjections enhance taste-reactivity 'liking' reactions to sweetness [3]. In contrast, DAMGO at other sites in the medial prefrontal cortex (PFC) produces 'wanting' without 'liking': failing to enhance, or even instead suppressing, hedonic taste reactivity; yet increasing consummatory food intake, food-reinforced operant responding, and anticipatory hyperactivity and approach [3, 4].

Moving caudally/laterally, near primary gustatory insula, DAMGO microinjections increase consummatory food intake but not anticipatory hyperactivity. Further caudally in another 6 mm^3 hedonic hotspot in parietal insula, DAMGO microinjection amplifies hedonic taste reactions without changing intake ('liking' without 'wanting') [3, 4]. Finally, studies of inhibitory control over food-motivated behaviors have identified a circumscribed site of ventromedial PFC where DAMGO engenders impulsive-like food-seeking behavior [4] and chemogenetic stimulation suppresses food bingeing and motor impulsivity [5]. Together, these results could suggest a network model wherein OFC serves as an interface between sensory/palatability computations in the insular cortex and more purely 'seeking-like', action-selection functions of medial PFC (see Fig. 1).

As time goes on, this model will be further refined and extended with new manipulations. However, the findings discussed above underscore that μ-OR agonists have been powerful tools to reveal previously unappreciated localization of functions in cortex. The clinical relevance of this approach is

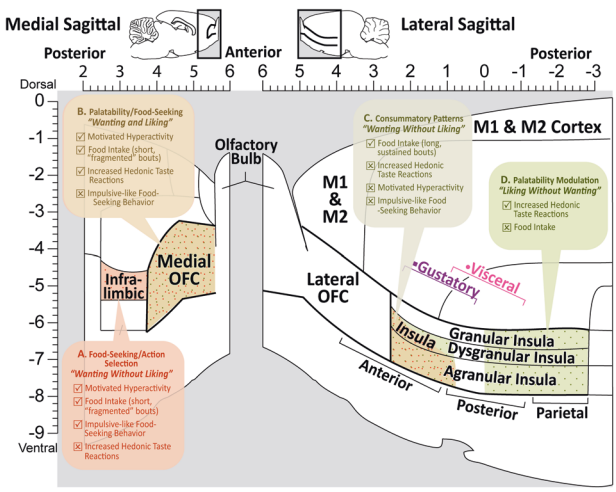

Fig. 1 Relative mapping of motivation/hedonic effects of localized μ-OR stimulations in frontal cortex of rat. Line drawings represent medial and lateral sagittal views of rat brain, highlighting effects in medial, orbitofrontal, and insular cortex. Numbered indices denote dorsal-ventral and anterior-posterior distances in mm. Sectors of insula reported by others to be associated with gustatory and visceral functions are indicated with brackets. Colored stippling represents enhancements of palatability/hedonic functions in green (e.g., increases in sucrose-elicited 'liking' reactions), and of motivation and related motor output modulation in red (e.g., increases in food intake, food seeking, motivated hyperactivity and instrumental action-selection). Transitional zones are shown in mingled green/red stippling. Within text boxes, checkmarks indicate that the stated function is present; 'Xs' indicate that the function is absent. Abbreviations: OFC = orbitofrontal cortex; M1, M2 = primary and secondary motor cortices. Modified from [3].

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Published online: 24 August 2021

bolstered by ligand-PET studies in humans showing μ-OR changes in homologous cortical regions related to obesity, eating disorders, and impulsivity (reviewed in [6]). Yet, μ-opioid peptides may be only one exemplar of a broad category of peptide modulators (including ones yet undiscovered) that profoundly impact cortical function. Indeed, already there is evidence that the peptide, orexin/hypocretin, produces many of the same motivation/hedonic effects in cortex as do opioids, including in hedonic hotspots [3]. Future work may identify novel players that can usher in a new era of peptide pharmaceuticals with which to manipulate cortical function.

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AUTHOR CONTRIBUTIONS

BAB wrote, and KCB helped co-write and edit, this article.

FUNDING

This work was supported by NIH grant MH074723 from the National Institute for Mental Health to BAB, and MH063649 & DA015188 to KCB.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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