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Leptin, Sonic Hedgehogs, and Neurogenesis— A Primary Cilium's Tale

Ubaldo Armato[1]*, Balu Chakravarthy[2], Anna Chiarini[1], Franco Chioffi[3], Ilaria Dal Prà[2] and James F. Whitfield[2]

[1]Histology & Embryology Section, Department of Life & Reproduction Sciences, University of Verona Medical School,Verona, Venetia, Italy
[2]Molecular Signaling Group, Institute for Biological Sciences, National Research Council of Canada, Ottawa, Ontario, Canada
[3]Neurosurgery Operative Unit, St. Chiara Hospital, Trento, Trentino, Italy

Abbreviations: DG: Dentate gyrus; GrC: Granule Cell; Gli-A: Gli-Activator; Gli-R: Gli-Repressor; Lep: Leptin; LepR: Lep Receptor; RG-NSCs: Radial Glial Neuronal Stem Cells; PM: Post-Mitotic; POMC: Proopiomelanocortin; Ptch: Patched; SGZ: Sub-Granular Zone; Shh: Sonic hedgehog; Smo: Smoothened; TAN: Transit Amplifying Neuroblast.

This story begins in the brain but not with neurogenesis. It starts with the 16-kDa Leptin (Lep) cytokine-hormone's first known role as a controller of body energy reserves stored as white fat [1-5]. Lep is produced by white-fat adipocytes and then carried into the brain across the bloodbrain barrier by endothelial short isoform Lep-a receptors (LepR-a's) or via the cerebrospinal fluid [1-5]. When it arrives in the hypothalamus, Lep induces arcuate nuclear anorexigenic proopiomelanocortin (POMC)-expressing neurons and orexigenic neuropepetide Y/Agouti-related peptide (NPY/AgRP)-expressing neurons to suppress appetite and prevent hyperphagic obesity by respectively stimulating and silencing these two types of neurons [1-5]. It does this via JAK2/STAT3 signaling from the long isoform LepR-b's (also known as ObR-b's) on these neurons [1-5]. But where do the arcuate neurons put their LepR-b's? Would they not just put them into their cytoplasmic membranes? Then the Lep story took an unexpectedly exciting turn when novel experimental results strongly suggested that the primary cilia protruding from the arcuate neurons carried the hyperphagia- and obesity-preventing LepR-b's. Reportedly, these tiny antennae, neurons throughout the brain are endowed with, probe their extracellular environments for relevant chemical agents and trigger proper responses to these and maybe to any cilia-bending mechanical stresses [6,7]. What were these game-changing results? Knocking out POMC neurons' cilia by disabling intraflagellar transport [8] or knocking out cilial adenylyl cyclase III in the hypothalamic neurons made adult mice unresponsive to Lep, hyperphagic, obese, and consequently hyper-leptinemic due to the build-up of Lep-producing adipocytes [9-15]. Then there was the Lep-resistant hyperphagia and extreme obesity of persons with the Bardet-Biedl syndrome caused by the failure of multi-protein complexes (one of which, BBS1, binds LepR-b) that transport components for cilial maintenance and functions from the Golgi apparatus to the ciliary basal body and from there into the cilium [14,16]. There were even more indications of cilial LepR-b. In fact, Lep was reported (i) to stimulate the proliferation of transit amplifying neuroblasts (TAN's), the granule cell (GrC) progenitors, in the hippocampal dentate gyrus (DG)—and, hence, the adult neurogenesis that is instead reduced in neurodegenerative conditions—and (ii) to improve memory in Alzheimer's disease (AD)-model transgenic mice [17-19]. Because of the known role of cilia in driving adult neurogenesis [20,21], these findings suggested that LepR-b's are concentrated in the cilia of the TANs in the sub-granular zone (SGZ) of the adult DG, one of the principal conditions—and al regions of adult neurogenesis in rodents and humans [22]. But despite these exciting and very convincing indications of LepR-b cilial localization, no one seems to have found these receptors in the cilia of hypothalamic arcuate neurons or DG GrC's [23]. Up to now, only Stratigopoulos and co-workers [24] have reported that exposing cultured murine arcuate neurons to Lep caused Lep•LepR-b complexes to cluster around the cilial basal bodies, the closest points anyone has seen LepR-b's come to cilia, but without actually entering the cilia. However, strong signals from Lep•LepR-b complexes clustering around the cilial basal barrier, a selective gateway to the cilial inner sanctum [25], might drive Lep intracellular signaling mediators into the cilium. The mystery engendered by the lack of convincing indications that LepR-b's operate from the primary cilia in hypothalamic arcuate neurons and hippocampal DG GrC's in the absence of the otherwise expected flurry of reports from LepR-b-loaded cilia, could be solved if Lep functions first by binding to LepR-b's located in the cell membrane. Then, the activated extra-cilial LepR-b's would stimulate a cilium-based mechanism that can drive different processes, including adult neurogenesis. So, what could this downstream cilium-based mechanism be and how could extra-cilial Lep•LepR-b complexes stimulate it? A very likely possibility is the Sonic hedgehog (Shh) signaling mechanism, known to be housed in the primary cilium, which Goetz and co-workers have vividly labeled a "hedgehog signal-transduction machine" [26] (Figure 1I). Indeed, it has very recently been shown that Lep triggers a phosphoinositide-3 kinase (PI3K)/Akt-mediated stimulation of Shh expression in rat hepatic stellate cells [27]. But to find out how Lep and the Shh's it generates might stimulate neurogenesis, we must first look into the SGZ of the DG before the appearance of Lep and the Shh's. Here we see a few slowly cycling self-renewing radial glial neuronal stem cells (RG-NSC's) generating rapidly cycling Shh-responsive TAN's, which, unlike their ancestral RG-NSC's, need their primary cilia and the primary cilium Shh mechanism to drive their proliferation [20,21]. In the mouse, by about four weeks after the generation of their ancestral progenitors from RG-NSC's in their SGZ niche, TAN's' surviving post-mitotic progeny start ripening. By about four weeks later, they have acquired fully mature dendritic spines and mossy fiber boutons and have moved up into the GrC layer. There they finally join the veteran GrC's encoding the data converging on them from various regions of the neocortex [26,27]. When Lep appears, the Shh's produced by the extracilial Lep•LepR-b-signaling from the cell membrane binds to Ptch (Patched) and pulls it out of the cilial membrane [26]. This releases Smo (Smoothened) from its cytoplasmic cage, from which it climbs up to the tip of the cilium (Figure 1I). There, Smo stops a processing machinery producing Gli-R (Gli-repressor) from Gli, but promotes the synthesis of the Gli-A (Gli-activator) transcription factor. Incidentally, Gli is carried

***Corresponding author:** Prof. Dr. Ubaldo Armato, MD, Histology & Embryology Section, Department of Life & Reproduction Sciences, 8 Strada Le Grazie, I-37134 Verona, Venetia, Italy, Tel: 0039-045-8027159; Fax: 0039-045-8027159; E-mail: uarmato@gmail.com

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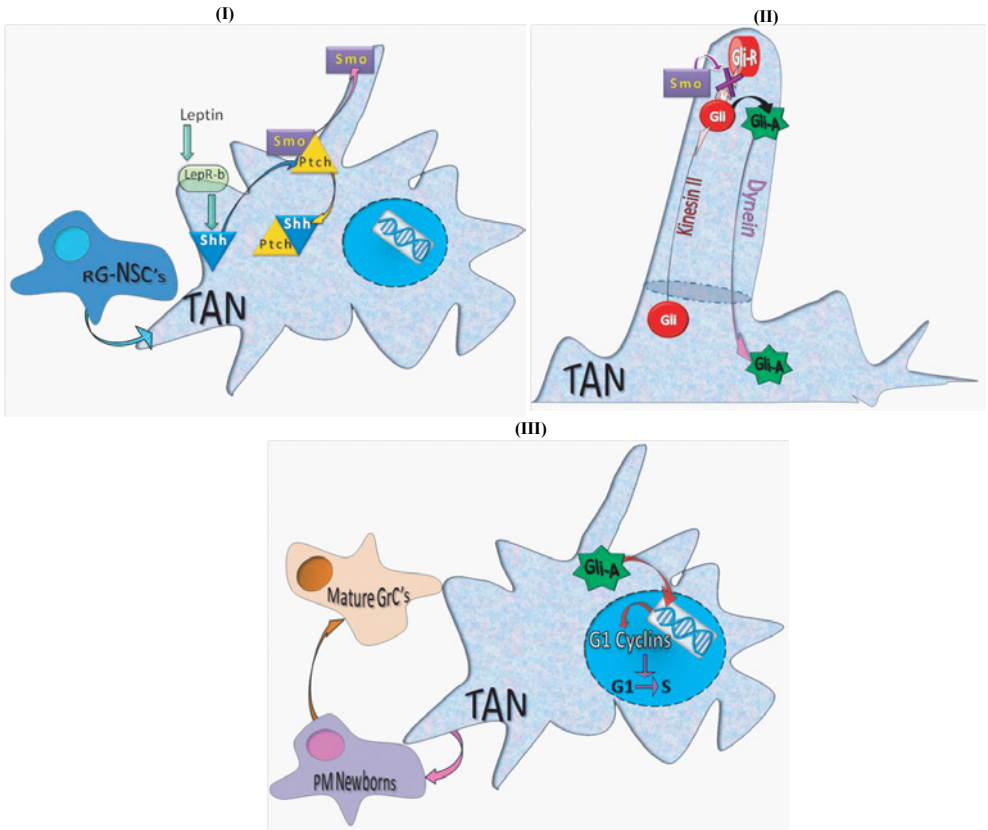

Figure 1: How Lep-induced signals from LepR-b's stationed in the cell membrane could stimulate the primary cilium-dependent proliferation of TAN's [20] generated by RG-NSC's in the DG of the adult hippocampal system.
(I) Signals from Lep•LepR-b complexes stimulate the production of Sonic hedgehog (Shh), which in turn causes Ptch (Patched) to leave the cilium. The key player in this mechanism is Gli, which is carried to the cilium tip and its processing machinery along the cilial microtubule trackway (the axoneme) by the kinesin-II carrier.
(II) In the presence of Ptch and the absence of Shh, Gli is processed by the tip machinery into Gli-R, its transcription repressor form [26]. But the Shh-driven exit of Ptch releases Smo's (Smoothened), which move up to the cilium's tip and enable the formation of Gli-A, the gene-activating form of Gli that is then transported down the trackway by the dynein carrier, and passes through the cilium's basal barrier.
(III) Gli-A then moves to the nucleus, where it stimulates the expression of the cyclins D and E for the cyclin-dependent protein kinase engines that drive the key stages of the pre-replicative build-up to DNA replication. Upon reaching the end of the transit amplifying part of the neuronal maturation program, the accumulated TAN's shut down their proliferative cycling machinery and become post-mitotic (PM) Newborns, which progressively mature and, if lucky enough to survive, become fully Mature GrC's that enter the GrC layer of the SVZ and join the veteran GrC's that process the data converging on the DG from the various regions of the neocortex.

by the kinesin-II transporter along the cilium's microtubular axonemal trackway to the cilial tip (Figure 1II). Now, the Lep-triggered Gli-A is carried by the dynein transporter down to the cilial basal body gateway through which it is released and reaches the nucleus to activate many target genes, among which are those for the G1 cyclins (cyclins D1, D2, E) that drive the build-up to the initiation of DNA replication and TAN's proliferation [19,26,30] (Figure 1III). Therefore, it seems that the neurogenesis-stimulating Lep might be a potential daily administrable arrestor of the development of Alzheimer's disease if it be given early enough, perhaps in the mild cognitive impairment (MCI) stage of the ailment. Incidentally, it also appears, from Lep's ability to strongly stimulate peri-lesional neurogenesis and angiogenesis in the poststroke cerebral cortices of mice, that Lep might also be used to attenuate the extent of stroke damage in humans [31]. Indeed, Lep can be safely given to human patients. Thus, a daily subcutaneous injection of recombinant methionyl human Lep has been safely given for a decade as the replacement therapy to four genetically obese humans to replace their missing Lep and with it to reduce their obesity and improve their cognitive abilities [32]. Of course, in the case of Alzheimer's disease, Lep would have to be part of a cocktail also containing an agent that can arrest the de novo production of the toxic, synapse-disrupting amyloid-β1-42 oligomers. However, only time and much more work will be needed to test this idea.

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