Prolactin and Its Altered Action in Alzheimer's Disease and Parkinson's Disease

Hai Duc Nguyen^a Byung Pal Yu^b Ngoc Hong Minh Hoang^a Won Hee Jo^a
Hae Young Chung^c Min-Sun Kim^a

^aDepartment of Pharmacy, College of Pharmacy and Research Institute of Life and Pharmaceutical Sciences, Sunchon National University, Suncheon, Republic of Korea; ^bDepartment of Physiology, The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; ^cDepartment of Pharmacy, College of Pharmacy, Pusan National University, Busan, Republic of Korea

Keywords

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Abstract

Background: Prolactin (PRL) is one of the most diverse pituitary hormones and is known to modulate normal neuronal function and neurodegenerative conditions. Many studies have described the influence that PRL has on the central nervous system and addressed its contribution to neurodegeneration, but little is known about the mechanisms responsible for the effects of PRL on neurodegenerative disorders, especially on Alzheimer's disease (AD) and Parkinson's disease (PD). **Summary:** We review and summarize the existing literature and current understanding of the roles of PRL on various PRL aspects of AD and PD. **Key Messages:** In general, PRL is viewed as a promising molecule for the treatment of AD and PD. Modulation of PRL functions and targeting of immune mechanisms are needed to devise preventive or therapeutic strategies.

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Introduction

Neurodegenerative disorders (NDDs) affect millions of people, and Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common. An estimated 5.4 million (2016) and 930,000 (2020) Americans have AD and PD, respectively [1], but the specific causes of these diseases remain unknown [2–13].

Recent evidence shows that hormones influence the risks and developments of NDDs. For example, changes in the levels of thyroid hormones in the elderly may affect the development of NDD as thyroid dysfunction increases with age and is linked to oxidative stress by metabolic stimulation and antioxidant mechanisms [4, 12, 14–17]. In addition, thyrotropin-releasing hormone (TRH) exerts various effects on the central nervous system (CNS) that are independent of its hypothalamic-pituitary-thyroid axis function. TRH synthesis and expression decrease with advancing age, and TRH is implicated in aging-associated NDDs, including AD and PD. Interestingly, along with the production of thyroid hormones, TRH

also activates the secretion of prolactin (PRL), and these hormones are directly influenced by the presence of NDDs [8, 12, 18, 20]. PRL crosses the blood-brain barrier (BBB) and has strong modulatory effects on hypothalamic growth and many other brain regions [5, 21, 22]. PRL has been associated with immune system regulation as it has both inflammatory and anti-inflammatory effects in various NDDs [23–25]. Additionally, several reports indicate PRL has a role in the CNS and influences neurodegeneration [21, 26–32].

Recent data indicated that several genes (*Adora2a*, *Car3*, *Chat*, *Drd2*, *Egr2*, *Hif3a*, *Notch*, *Penk*, *Tac1*, *Ttr*, *Sema3A*, and *Penk*) induced by PRL are associated with the regulation of brain functions and processes associated with axons, synaptic transmission, and microglial regulation [33], and the expressions of these genes have been proven to be altered in neuroinflammatory diseases and NDDs [34–42]. Besides, PRL can enhance memory, cognition, and learning [43–46]. Therefore, PRL could be a potential molecule for the treatment of some NDDs such as AD and PD. Although, PRL levels in the CNS are often increased in AD and PD [47].

Nevertheless, the mechanisms responsible for the actions of PRL in a wide range of NDDs have not been determined, and the literature on these topics is often inconsistent [26]. In this review, we first describe general aspects of PRL in the contexts of biochemistry, metabolism, immune response, genes related to NDDs, memory, cognition, and learning. Finally, we summarize existing knowledge and the progress being made to understand the roles of PRL and its altered activities in AD and PD.

PRL Biochemistry and Metabolism

PRL levels start to increase in fetal circulation at gestation weeks 20–24 and then continue to increase from week 30 to term when they reach almost maternal levels [48–50]. Postpartum, serum PRL levels increase almost 10-fold but subsequently decrease steadily to reach normal levels at 3 months. PRL levels are lowest from 3 months to 9 years and then gradually rise during puberty to adult levels [51]. However, amounts secreted during each secretory blast and basal secretion are likely to be lower in the elderly, and PRL levels in older men are half those in younger men [52]. During the menstrual cycle, insignificant doses of gonadotrophin-releasing hormone influence PRL secretion, and in some women its levels are lower in the follicular phase than in the luteal phase and higher at midcycle. In normal pregnancies, PRL levels

ranged from 6 ng/mL in early pregnancy to 210 ng/mL near term [53]. Furthermore, basal PRL levels in lactating women remain elevated over the first 46 weeks postpartum [52, 54, 55].

When PRL release is assessed at the single-cell level, patterns of PRL secretion by individual lactotroph cells demonstrate sexual dimorphism [56]. Normal PRL levels in adult serum PRL differ in men and women (10–20 and 10–25 µg/L, respectively). PRL secretion is pulsatile and is greatest during rapid eye movement sleep and on average peaks at 4–6:00 a.m. [57]. PRL is excreted by liver and kidneys, has a circulatory half-life of 20–50 min [57, 58], and its production and metabolic clearance rates are 233–235 µg/day/m² and 40–46 mL/min/m², respectively [59]. However, among patients with chronic renal failure, the metabolic clearance rate tends to be reduced by one-third [60].

PRL in the CNS

PRLR-L and PRLR-S are expressed in the CNS, but the transport of PRL to brain is not dependent on PRLR but rather on an unidentified transport molecule. PRL can cross the BBB; however, a substantial amount of PRL and activation of the Janus kinase 2 (JAK2) and signal transducer and activator of transcription 5 (STAT5) pathways are needed to activate TIDA neurons at resting membrane potentials in mice [28, 61, 62]. Remarkably, in 1 study, it was found TIDA neurons exhibited irregular spontaneous action capacity, and their PRL-induced firing rates were not altered during lactation. The authors concluded that neuronal excitability and channel regulation often require a transient neuronal signaling pathway that involves the participation of PRLR-L and PRLR-S [28].

Several reports provide clues concerning the neural roles responsible for the effects of PRL. First, in the absence of hypothalamic stimulation, lactotropic cells were the only anterior pituitary cells that showed spontaneous electrical activity [63]. Ca²⁺ influx via voltage-gated Ca²⁺ channels activate PRL secretion, which accounts for basal PRL secretion [63]. Ca²⁺ plays a significant role in signaling pathways leading to protein activations, as exemplified by calcium-dependent protein kinase and the regulation of neurotransmitters by exocytosis-release [64], and neuron activation can generate action potentials that induce the neuron activation and/or the influx of Ca²⁺ into neurons, resulting in neurotransmitter or neuropeptide release [28]. Furthermore, PRL modulates Ca²⁺-de-

pendent K⁺ channels, and thus, might impact the release of neurotransmitters in various cerebral areas [28].

Second, PRL receptors exist in hypothalamic paraventricular and supraoptic neurons, and PRL activates neuronal activities from within these nuclei. Thus, PRL concentrations in the physiological range induce extracellular signal-regulated kinase 1/2 (ERK1/2) phosphorylation in neurons and the transcription of corticotropin-releasing hormone (CRH) [65–67]. Consequently, in hypothalamic cultured cells, PRL stimulation of CRH transcription is considered to inhibit regulation of the hypothalamic-pituitary-adrenal (HPA) axis indirectly [68]. In addition to activating the JAK/STAT pathway, PRL also activates the ERK/mitogen-activated protein kinase pathway in CRH neurons. This pathway can also be regulated by intracellular signals and in hypothalamus; it induces the expressions of vasopressin and oxytocin and promotes the expression of EGR-1 (early growth response protein 1) in magnocellular neurons [68–70].

Third, it was recently reported high PRL receptor expression in the subventricular zone is related to neurogenesis. PRL increases hippocampal precursor cell numbers in vitro and in vivo and impacts neuronal stem cell proliferation [46, 71, 72]. PRL also regulates cytoskeletal protein synthesis and contributes to neuronal differentiation because it activates ERK5 and increases the expression and protein levels of nestin and microtubule-associated protein 2 in neuroblastoma (SK-N-SH) cells [21, 31, 73].

Fourth, PRL interacts with BBB protected regions of the CNS because although vascular PRL does not cross the BBB, it can access the cerebrospinal fluid (CSF) readily and then enter PRL-responsive brain regions. PRL entered the CSF by a saturable transport mechanism through a receptor-mediated process. Additionally, the epithelial cells of the choroid plexus, which include the blood-CSF barrier, contain specific, high-affinity PRL receptors that may serve as sites of PRL transport from blood to CSF [74, 75]. Therefore, serum PRL is vital because PRL in the peripheral circulation can access the CNS through receptor-mediated mechanisms or circumventricular structures lacking a BBB [74, 76].

PRL is a normal component of CSF and its level in CSF is a function of its plasma level. In the presence of a pituitary tumor, regardless of the presence of suprasellar extension, CSF PRL levels may be barely detectable or elevated. In patients with a pituitary tumor (chromophobe adenoma) with suprasellar extension, PRL levels may be usually abnormally low [77], whereas in pregnant women and patients with a pituitary tumor, serum and CSF PRL concentrations are invariably elevated [78]. Fur-

thermore, at autopsy, CSF PRL levels were reported to be 3 times higher for hypoxia/ischemia than other causes of death. Furthermore, PRL levels were significantly elevated after culturing HIBCPP, SDR-P-1D5, or MSH-P3 cells (a human choroid plexus papilloma cell line, a rat PRL-secreting cell line derived from anterior pituitary lacking growth hormone, or a PRL-secreting cell line derived from miniature swine hypophysis, respectively) under hypoxic conditions for 10 min [79].

Relations between PRL Receptor and PRL and Immune Response

The long (PRLR-L), intermediate (PRLR-I), and short (PRLR-S) isoforms of PRLR have been most studied. PRLR belongs to the class-1 cytokine receptor superfamily, which also includes receptors for granulocyte and monocyte colony-stimulating factor, leptin, erythropoietin, interleukin-2 (IL-2), IL-6, and others [80, 81]. PRLR is displayed on all leukocytes of the immune system and in those of thymus and spleen [82]. In brain, PRL has been reported in hypothalamus, hippocampus, and cortex, and astrocytes and glial cells [83]. Types of PRLR isoforms expressed depend on tissue type and the molecular milieu, for example, on cytokine and hormone levels. Changes in isoform PRLR ratios control inflammatory response and autoimmunity [84]. Functions of PRL are mediated by its interaction with PRLR. PRL/PRLR binding can activate the JAK2 and STAT5 signaling pathways [84]. PRL also stimulates the syntheses of TNF- α , IFN- γ , IL-1 β , and IL-12p40 in macrophages by activating the JAK2-STAT1 pathway [85].

In man, PRLR-L is highly expressed in the pituitary gland and hippocampus. STAT1, STAT3, STAT5A, and STAT5B signal via PRLR-L and can interact with each other to form heterodimers or homodimers that translocate to the nucleus after phosphorylation. In granulocytes, the expressions of interferon regulatory factor 1 and iNOS require STAT1 [86]. In macrophages, STAT3 activation by PRL mediates anti-inflammatory effects and IL-10 secretion [87, 88], suggesting that PRL signaling through STAT3 has antiapoptotic and proliferative effects in STAT3 deficient mice [89]. In peripheral blood mononuclear cells, PRL induces iNOS expression through the activation of STAT5 [86]. In the CNS in a murine model, activation of STAT5 by PRL was associated with the progression of chronic mild stress-induced depression and neuron apoptosis in the CA3 hippocampal region [90], and in a mouse model of severe spinal muscular atrophy, PRL stimulated the functional expression of sur-

vival motor neuron by activating STAT5 and thus increasing motor function and survival [91].

PRLR is expressed in a wide range of cells in the immune system, including neutrophils, monocytes, macrophages, lymphocytes, natural killer cells, and microglia, and thus, PRL can mediate effects in all of these cells [92]. PRL also enhances T-cell activation via several mechanisms. (1) PRL regulates immune response sensitivity to dopamine agonists [93]. (2) PRL can phosphorylate and stimulate CD3 (a T-cell receptor component), ZAP70, and second messenger kinases Fyn [94–96]. (3) PRL activates CD25, which controls the proliferation and expansion of T-cell subsets [97]. (4) PRL stimulates CD69, which is necessary for the prolonged activation and proliferation of T-cells [97, 98]. (5) PRL can also enhance the expressions of CD40, CD80, and CD86 co-stimulatory molecules in antigen-presenting cells, [93]. (6) PRL induces cytokines that enhance T-cell responses, such as IL-1, IL-12, IL-16, and interferon- γ [93, 99].

T-box transcription factor TBX21 (T-bet) is an important regulator of function and effector differentiation in numerous different immune lineages such as natural killer T, CD4, CD8, and B cells [100]. Of note, T-bet was modulated in a CD4⁺ T cell line by PRL exposure. In T cells, PRL rapidly induces the expression of T-bet through JAK2, STAT5 [101]. The T-bet expression was induced by low-dose PRL after long-term PRL exposure, whereas high-dose PRL suppressed it. Specifically, low levels of PRL (10–30 ng/mL) may activate the JAK2/STAT5-mediated signaling pathway in CD4⁺ T cells. High levels of PRL (100 ng/mL) may activate the signaling pathway via SOCS1 and 3, resulting in suppression of T-bet activation [101, 102]. Furthermore, accumulating evidence indicates that PRL is functionally active in the CNS, mediates inflammatory processes, and has anti-inflammatory and protective functions [103] (Table 1).

Relations between PRL and Genes in the Context of Neurodegeneration

A study in the hippocampus of adult virgin female Wistar rat showed that several genes (*Adora2a*, *Car3*, *Chat*, *Drd2*, *Egr2*, *Hif3a*, *Notch*, *Penk*, *Tac1*, *Ttr*, *Sema3A*, and *Penk*) induced by PRL are related to the regulation of brain functions and processes associated with axons, synaptic transmission, and microglial regulation [104], and the expression of these genes had been previously shown to be altered in neuroinflammatory diseases and NDDs [35, 105–112]. Of note, *Adora2a* is related to synaptic im-

pairment in neurons, and high *Adora2a* expression is related to neurogenesis and hippocampal volume in AD [113, 114]. On the other hand, PRL also modulates genes of the extracellular matrix (*Colla1* *Colla2*, *Fmod*, *Ptgds*, and *Aldh1a2*), which are induced by physical activity and have been reported to suppress hippocampal aging in a premature aging animal model of AD [115]. Microglia are known to be related to either neurodegenerative or neuroprotective depending on their state of activation [107]. For example, microglia become reactive to inflammatory stimuli after brain damage, resulting in the secretion of inflammatory cytokines [116]. Microglia offer neuroprotection in NDDs by producing phagocytizing cellular debris, anti-inflammatory cytokines, and promoting neurogenesis via production of trypsinogen or insulin-like growth factor-1 [117].

Thus, PRL-induced genes associated with microglial functions might play important roles in hippocampal neuroimmunomodulation or prevent neuronal cell damage [118–121]. Remarkably, PRLR is also present in primary cell cultures of hippocampal neurons [122]. Thus, it has been suggested PRL could play a significant role in the prevention of hippocampus aging and in modulating microglial function process during hippocampal development and in the adult brain [122].

PRL Expression and Memory, Cognition, and Learning

PRL can enhance memory, cognition, and learning by several mechanisms. First, PRL regulates *Drd2* gene expression [104], which has been related to hippocampus-dependent plasticity, and thus, to hippocampal memory and learning [123]. Second, PRL might favor neuronal survival under conditions of kainic acid-induced excitotoxicity by increasing the expression of vesicular glutamate transporter 1, which is associated with Glu transport in neurons and contributes to the survival and plasticity of hippocampal neurons [124].

Increasing evidence indicates PRL positively influences memory, cognition, and learning [46, 125–127]. A previous study indicated that high and low levels of PRL are related to cognitive impairment in tasks involving processing speed and verbal recall in pregnant women [128], and in older men, higher PRL levels were related to poorer working memory and verbal ability [129]. A study on hippocampus-dependent memory in PRLR null mice reported learning and memory impairments in both sexes [46]. In a male rat hyperprolactinemia model, object recognition was impaired with no modification of spatial

Table 1. Effects of PRL in the CNS

No	Model	Methods	Cells	Effects	Ref
<i>Inflammation</i>					
1	1-day-old rat pups	Incubation of astrocytes with 1 nM PRL for 6 h	Astrocytes	Stimulates TNF- α and IL-1 α expression	[199]
2	A murine model with <i>Acanthamoeba castellanii</i> infection	Pretreatment of the microglia with recombinant PRL in combination with recombinant IFN- γ synergistically	Microglia	Release IL-1 α , IL-1 β , IL-6, and TNF- α	[200]
3	Rat and <i>Toxoplasma gondii</i> infection	Rat pretreated recombinant tumor necrosis factor alpha and PRL on <i>Toxoplasma gondii</i> infection	Microglia	Release IL-1 β , IL-3, and IL-6	[201]
4	Rat C6 glioma cells	A concentration dependent increase of NO release was observed in the C6 culture medium after 24 h of PRL (5–100 nM) stimulation	Glial	Release NO	[202]
5	In male Wistar rat	The intracerebroventricular injection of PRL (0.06–1 μ g, 2–20 min) or after inducing hyperprolactinemia by placing 2 anterior pituitary glands under the kidney capsule	Paraventricular and supraoptic hypothalamic nuclei	Activates iNOS, increases the production of NO	[203]
<i>Anti-inflammation</i>					
6	Adult male albino rats and male and female albino mice (3 months old)	Evaluated by measuring glial fibrillary acidic protein expression. Serum PRL was measured in rats by the Nb2 cell bioassay based on the proliferative response of the Nb2 lymphoma cells to PRL.	Retinal cells	Decrease retinal gliosis	[204]
7	Adult virgin female Wistar rats	Treatment with PRL for 24 h in ovariectomized rats, after that determine a decrease microglial activation in immunodetection of CD11b/c, and transcriptomic analysis by RNASeq revealed 162 differentially expressed genes	Glial and microglia	Decreased microglial activation in the hippocampus Produced morphological changes in glial cells and favors the expression of the genes involved in the maintenance of microglial functions (Ador2a, Car3, Chat, Drd2, Egr2, Hif3a, Notch, Penk, Tac1, and Ttr)	[104]
8	Male albino rats (7–9 weeks) and male and female albino mice (3-month old)	H ₂ O ₂ has been used as a direct oxidant to initiate and study cellular oxidative stress. Total ROS levels and antioxidant capacity were assessed. ARPE-19 human cells were assayed for apoptosis by measuring fragmented nucleosomal DNA.	Retinal pigment epithelium	Promotes the antioxidant capacity of ARPE-19 cells by reducing glutathione Reduces ROS production in retinal levels in retinal epithelial cells Protects against oxidative damage by promoting cell survival and reducing apoptosis in retinal epithelial cells	[205]
9	Pregnant female rats (Wistar)	Cell viability was determined by monitoring mitochondrial activity and using fluorescent markers for viable and dead cells. The intracellular calcium level was determined by a fluorometric assay and proteins involved in the apoptotic pathway were determined by immunoblot	Cultured rat hippocampal neurons	Protects against glutamate-induced apoptosis by preserving mitochondrial function and by increasing the production and activity of superoxide dismutases 1 and 2 (enzymes that participate in an antioxidant-type defense) Decreased lipid peroxidation in hippocampal neurons exposed to glutamate excitotoxicity	[206]
10	Adult virgin female Wistar rats (2-month old)	The levels of TNF α , iNOS, and IL6 as pro-inflammatory and IL-4 and IL-10 as anti-inflammatory markers were evaluated in rats treated daily with a single dose of 0.1 mg of PRL sacrificed 1 h after last PRL injection. Chronic treatment with PRL reduced the astro- and microgliosis in CA4, CA3, and CA1 hippocampal subfields induced by kainic acid	Hippocampus	Increase the secretion of IL-10 and IL-4 in the absence of excitotoxic damage Diminished the hippocampal astrogliosis and microgliosis induced by kainic acid Reduced hippocampal levels of pro-inflammatory cytokines and iNOS induced by kainic acid	[207]

PRL, prolactin; CNS, central nervous system; ARPE-19, adult retinal pigment epithelium-19; IL, interleukin.

learning [130], and in ovariectomized female rats, PRL prevented kainic acid-induced cognitive deficit in novel object recognition tests [131]. Furthermore, loss of PRL caused learning and memory deficits in PRL null mice, and these deficits were remedied by directly infusing recombinant PRL into hippocampus, which strongly suggested that PRL inadequacy in the adult mouse hippocampus is related to impaired learning and memory [46].

Effects of PRL in AD and PD

AD and PD are both associated with neuroinflammation. Based on a review of the literature, we listed immune targets that enable manipulation of the pathologies of AD

and PD in Tables 1 and 2. Furthermore, PRL levels in CNS are elevated in NDDs (Table 3).

Effects of PRL in AD

Although the presence of tau protein in several NDDs, especially in AD, has been widely reported, little is known about the relationship between PRL and tau protein [132]. Here, we describe the effects of PRL level in AD.

In Human Studies

In a multicohort study conducted on 344 AD patients and 325 cognitively normal controls, the PRL level was higher in patients with low A β 1–42 levels compared with controls, which suggested PRL might be related to the pathophysiology of AD [133]. Another study revealed

Table 2. The immune targets for manipulating AD pathology based on evidence in Table 1

Immune target	Main cell source	CNS functions	AD	PD
TNF- α	Leukocytes dendritic cells, fibroblasts	Being the prototypic pro-inflammatory cytokine, central to host defense, inflammatory responses, triggers cell death, and tissue degeneration [208]	Elevated TNF- α levels in AD can enhance A β production, decrease A β clearance, increase neuronal loss and cell death, and are implicated in cognitive decline in AD [209]	High TNF- α expression may contribute for faster dopaminergic neuron degeneration [210]
IL-1 (α , β)	Macrophages, epithelial cells	Acts as a neuromodulator in the healthy CNS, provide protection to the injured CNS, neuroinflammation, and of leukocyte recruitment to the CNS [211, 212]	Overexpression of IL-1 is related to β -amyloid plaque progression [213]	Elevated IL-1 can be increased disease progression [214]
IL-3	Th1 and Th2 cells, mast cells, and eosinophils	Activate the proliferation and activation of microglia, and enhance the differentiation of sensory and cholinergic neurons [215]	IL-3 neuro-protects neuronal cells against A β [216]	In an animal model of PD, IL-3 can suppress dopaminergic neurodegeneration in 6-hydroxydopamine-lesioned rats [217]
IL-4	Th2 cells, mast cells	IL-4 production in the CNS can regulate autoimmune inflammation by inducing an alternatively activated macrophages phenotype of the microglial cell [218]	Overproduction of IL-4 in AChEI-treated patients can cause an additional mechanism by which AChEI acts on AD progression [219]	Overexpression of IL-4 was associated with neuropathological processes for the degeneration of PD neurons [220]
IL-6	Macrophages, Th2 cells, B cells, and endothelial cells	Participate in neurogenesis (influencing neurons and glial cells), and in the response of mature neurons and glial cells in normal conditions and following a wide arrange of injury models, regulation in brain cells can be affected by cytokines and inflammatory factors as well as neurotransmitters and neuropeptides [221]	Part of the A β -driven inflammatory response [222, 223]	Elevated IL-6 can be a marker of increased mortality risk [224]
IL-10	Tregs, Bregs	Limit glial inflammatory responses and/or defend against insult to the CNS, recovery of autoimmune encephalomyelitis, controlling autoimmunity [225–227]	Elevated IL-10 can attenuate neuroinflammation, cognitive dysfunction, and neurodegeneration in AD [228]	Elevated IL-10 can be a neuroprotective factor in PD [229]
NO	Produce through the L-arginine to L-citrulline pathway mediated by NOS, NOS1 (neuronal NOS), NOS2 (inducible NOS), and NOS3 (endothelial NOS)	Regulation of the sleep-wake cycle, synaptic plasticity, and hormone secretion. NO as a Janus molecule in the survival mechanisms and cell death in brain cells [230]	Overproduction of nitric oxide can lead to neurodegeneration in AD [231]	Take part in the pathogenesis of PD by multiple mechanisms, especially neuroinflammation [232]
iNOS			iNOS knockout mice showed enhanced cognitive capacity and many pathologies in an animal model [233, 234] Excessive cytokines can activate the iNOS in microglia and astroglia cells and overproduce NO during the inflammation, which can cause neurodegeneration [235, 236]	Upregulation of iNOS is related to neuron destruction [237]

CNS, central nervous system; AD, Alzheimer's disease; PD, Parkinson's disease; AChEI, acetylcholinesterase inhibitors; IL, interleukin.

Table 3. Changes in PRL levels in AD and PD

Subjects	Age, years	PRL levels	Method	Conclusion	Ref
<i>AD</i>					
344 patients with AD 325 subjects with CN	AD: 73±8 CN: 72±8	–	Immunoassay based on Luminex xMAP technology	PRL was significantly correlated with CSF Aβ1–42 levels	[133]
494 patients with AD (204 patients assigned to olanzapine treatment, 196 to risperidone, and 94 to placebo)	Olanzapine: 77.9 Risperidone: 78.0 Placebo: 79.8	Risperidone: 2.2±2.1 µg/L; <i>n</i> = 169; Olanzapine: 0.3±0.6 µg/L; <i>n</i> = 155; Placebo: 0.1±0.2 µg/L; <i>n</i> = 84	Not applicable	Abnormally high PRL levels occurred in 78.0% of risperidone patients, compared with 16.7% for olanzapine and 5.0% for placebo	[238]
12 patients with probable AD 08 age-matched normal controls	AD: mean: 60.5; (range 42–72) Control: mean: 63.0; (range 43–74)	AD: 8.9 (2.2) ng/mL Control: 9.1 (1.5) ng/mL	Commercially supplied reagents	PRL did not change following naloxone and did not differ between groups	[135]
12 AD patients 10 elderly controls	66.9±2.6 for patients 66.1±1.8 for controls	AD: 5.68±1.47 µg/L Control: 5.82±2.28 µg/L	Double-antibody RIA kits purchased from Amersham	Increases in the plasma PRL level was found in both AD patients and controls following the administration of m-chlorophenylpiperazine versus placebo	[239]
7 patients with SDAT, 7 controls	SDAT: 82±4.2 Controls: 81.3±4.9	SDAT at: 0 min, 30 min, 60 min, 90 min: median: 220, 4,770, 3,480, 3,480, respectively (mU/L) Controls at 0 min 30 min 60 min 90 min: median: 160, 1,950, 2,050, 1,830, respectively (mU/L)	–	The response to metoclopramide was greater in the SDAT than in the controls	[136]
14 patients (6 women, 8 men) with MID 10 patients (5 women, 5 men) with SDAT	MID: median: 79 years (range: 66–88) SDAT: median: 79 years (range: 69–90)	MID at 0, 20, 40, 60 min: 9 (3–13), 36 (22–61), 30 (17–55), 26 (12–60) SDAT at 0, 20, 40, 60 min: 6 (3–9), 43 (12–96), 30 (9–65), 23 (2–40), respectively	Double-antibody radioimmunoassay	The results did not support the hypothesis that serum PRL responses to TRH stimulation are of diagnostic value in 1 differentiating between MID and SDAT	[137]
11 DAT patients included 6 men and 5 women 07 healthy age- and sex-matched normal volunteers	DAT: 60.4 (range 43–71 years) Controls: 61.6 (range 42–72)	DAT: 25.91 (SEM: 3.46) ng/mL Controls: 37.44 (7.23) ng/mL +Across the total subject population Women: 48.83 (5.78) ng/mL Men: 21.96 (2.17) ng/mL	Radioassay Systems Laboratories, Inc. (Carson, CA)	PRL blunting suggests that these findings are not necessarily reflective of affective symptomatology in this group	[240]
<i>PD</i>					
36 PD 69 controls	PD: 64 Controls: 66	PD: 292±32 mU/L Controls: 162±15 mU/L	Chemiluminescent reaction	Males with lower PRL levels reached lower scores in Beck depression inventory compared to those patients with normal or high levels of PRL. Low PRL levels were also positively correlated with lower, better scores in PDQ-39	[26]
44 PD patients (22 nondepressed PD, 10 minor depressed PD, 11 major depressed PD), 20 controls	Nondepressed PD: 56.4±6.3 Minor depressed PD: 57.7±6.6 Major depressed PD: 54.9±4.8 Controls: 56.9±6.2	Major depressed PD: 174.5±125.9 mU/L Nondepressed PD: 202.9±71.6 mU/L Controls: 222.2±50.1 mU/L	IRMA technique (PRLMAIA Clone; Sero diagnostics)	PRL responses to fenfluramine were significantly impaired in PD patients compared to controls, and the response was more blunted in major depressed PD in comparison with the nondepressed PD	[177]
21 PD patients 25 controls	PD: 64.6±2.0 Controls: matched age and sex	PD: 14.6±1.3 ng/mL Controls: 6.6±0.5 ng/mL	Micro-enzymatic	Serum PRL levels in PD patients were higher than that in controls, after 2 weeks treatment the serum PRL level had decreased	[186]
12 patients with YOPD 10 patients with OOPD 10 age-matched with OOPD (control A) 10 age-matched with YOPD (control B)	YOPD: 37.50±8.4 OOPD: 52.6±2.6 Control A: 51.4±7.2 Control B: 38.7±6.9	+Baseline: YOPD: 10.1±4.0 ng/mL OOPD: 9.8±2.4 ng/mL Control A: 10.9±3.7 ng/mL Control B: 8.6±4.1 ng/mL +Administration of 1.25 mg of bromocriptine induced suppression of PRL secretion	IRMA technique (PRL MAIA Clone; Sero Diagnostics)	The basal PRL levels were normal in both groups of patients. When given after bromocriptine, TRH-induced a lower PRL increase in OOPD than in control B	[164]

Table 3 (continued)

Subjects	Age, years	PRL levels	Method	Conclusion	Ref
15 patients with IPD (8 men and 7 postmenopausal women) 12 healthy controls (6 men and 6 postmenopausal women)	IPD: 63.3±6.4 Controls: 64.5±5.9	IPD: 221.2±45.6 ng/mL Controls: 207.4±42.6 ng/mL	Radioimmunoassay	The response of PRL to treatment with levodopa	[180]
Patients (<i>n</i> = 28, 8 males and 20 females) with known EP with seizures Patients with PD (<i>n</i> = 5, 2 males and 3 females) Patients (<i>n</i> = 12, 5 males and 7 females) with known EP Patients (<i>n</i> = 9, 4 males and 5 females) with other neurological diseases Healthy volunteers (<i>n</i> = 37)	EP with seizures: 29.6±3.7 (range 17–57) PD: 59.0±3.8 (range 42–69) EP: 30.7±3.9 (range 17–68) ND: 51.0±3.6 (range 43–67) Healthy volunteers: 36.9±3.2 (range 19–63)	ND: <i>n</i> = 9, 8.7±3.3 µg/L EP: <i>n</i> = 12, 8.2±2.8 µg/L Healthy volunteers: <i>n</i> = 37, 11.7±9.7 µg/L	Commercially available PRL and PRL antibody preparations	Chronic treatment with drugs affecting dopamine transmission had a profound result on PRL release, and a dose-dependent increase in PRL with neuroleptics was detected	[241]
13 with IPD (4 males and 9 females)	57.0±14.6	+Insulin hypoglycemia test (<i>n</i> = 11) Before treatment: basal 4.4±0.6; maximal 29.5±9.3 (ng/mL) During treatment: basal 3.1±0.5; maximal 31.7±9.1 (ng/mL) + TRH test Before treatment: basal 5.8±1.4; maximal 38.3±7.2 (ng/mL) During treatment: basal 5.8±1.7; maximal 28.7±6.0 (ng/mL) + L-dopa test Before treatment: basal 5.0±1.0; minimal 2.5±0.7 (ng/mL) During treatment: basal 4.8±1.4; maximal 2.4±0.5 (ng/mL)	Radioimmunoassay	A considerable proportion of low responses of PRL was detected	[168]
12 male PD	54–68	Group 1: average L-dopa: 0 min: 7.36 (SEM 1.57), 240 min: 3.25 (0.32) (ng/mL) Benserazide: 0 min: 8.17 (2.08), 240 min: 7.50 (1.78) (ng/mL) Madopar: 0 min: 5.80 (0.30), 240 min: 3.57 (0.75) (ng/mL) Group 2: average L-dopa: 0 min: 6.52 (1.00), 240 min: 3.10 (0.53) (ng/mL) Benserazide: 0 min: 5.73 (0.80), 240 min: 7.87 (1.76) (ng/mL) Madopar: 0 min: 7.85 (0.60), 240 min: 7.83 (1.71) (ng/mL)	Radioimmunoassay	PRL increase after benserazide compared with PRL response after carbidopa at the same dosage in untreated PD patients	[169]
Patients (16 women and 4 men) with IPD 8 controls (5 women and 3 men)	IPD: 56.4 (range: 30–76) Controls: 48.0 (range: 32–53)	Peak plasma PRL levels at 30 min: IDP with on Sinemet therapy: 60.8±6.9 ng/mL Control: 27.5±8.7 ng/mL IDP with Madopar therapy: 60.8±6.9 ng/mL Unmedicated subjects: 33.7±5.7 ng/mL Controls: 59.0±11.3 ng/mL	Double-antibody radioimmunoassay methods	Administration of TRH (200 µg iv) induced in unmedicated patients PRL responses significantly lower than those of sex and age-matched controls	[171]
08 PD	52–71	PD under L-dopa-carbidopa therapy: basal: 8.3 (SE 1.3) ng/mL Two weeks of cessation of treatment: 6.8 (0.8) ng/mL Both group after TRH administration: 32.8 (4.7) and 25.2 (5.3) ng/mL	Radioimmunoassay	Basal PRL levels and PRL response to TRH were within the normal range of 2 group patients' studies	[170]
39 IPD of 1–11 years duration (mean 6.2) (31 women and 8 men) 17 controls (13 women and 4 men)	IPD: 57.4 (range: 37–69) Controls: 47.0 (range: 35–71)	+Basal: Unmedicated patients: 4.9±1.0 ng/mL IPD on Madopar therapy: 5.1±1.0 ng/mL Controls: 5.4±0.6 ng/mL + After 90 min on Madopar therapy: controls: 111±5.0 ng/mL Unmedicated patients: 73±13.0 ng/mL IPD on Madopar therapy: 68.1±18.4 ng/mL +After 150 min on Madopar therapy: controls: 65±17.3 ng/mL Unmedicated patients: 32±5.3 ng/mL IPD on Madopar therapy: 29±6.1, ng/mL + PRL-releasing effect of Madopar was reduced (peak PRL levels 22.2±2 ng/mL at 60 min) + Withdrawal of Sinemet (peak PRL levels 63.7±25.8 ng/mL at 90 min)	Double-antibody radioimmunoassay	No difference was present in the PRL-lowering effect of lisuride in the different experimental groups	[157]
50 Age- and sex-matched PD patients	+Not receiving levodopa: group 1, 2: 58–75 Group 3: 54–76 +Receiving levodopa: group 4: 54–76 + Tested before and after combination levodopa therapy: group 5: 59–76	+Group 1: 0 min 181.66±23.10; 20 min 884.66±104.55; 60 min 639.33±68.54 (mU/L) + Group 2: 0 min 275.71±75.01; 20 min 2,028.57±465.32; 60 min 1,195.71±254.80 (mU/L) + Group 3: 0 min 277.77±47.54, 20 min 934.44±166.02, 60 min 605.55±104.21 (mU/L) +Group 4: 0 min 163.63±30.39, 20 min 1,168.18±196.44, 60 min 609.09±110.22 (mU/L) +Group 5: 0 min 220.00±38.79; 20 min 1,935.71±499.84; 60 min 1,230.00±242.20 (mU/L) +Group 6: 0 min 616.42±208.18; 20 min 1,590.00±383.95; 60 min 1,074.28±312.94 (mU/L)	Radioimmunoassay	PD who received levodopa regimen at levels that provided good clinical results did not record impaired thyroid function. The response of PRL to protirelin stimulation was similar to that found in both treated and untreated men	[175]

Table 3 (continued)

Subjects	Age, years	PRL levels	Method	Conclusion	Ref
7 patients with IDP (none of them had been treated with dopaminergic or anticholinergic drugs) 7 controls	IDP: 55.7 (range 37–68) Controls: 49.4 (range 32–72)	+IDP: received TRH 200 µg intravenously: 18.3±10.0 ng/mL Sinemet + TRH 13.2±7.2 ng/mL +Controls: TRH: 23.7±10.1 ng/mL Sinemet + TRH: 7.9±5.4 ng/mL	Radioimmunoassay	Levodopa with carbidopa-suppressed PRL secretion induced by TRH less effectively in IDP patients than in normal subjects	[181]
6 patients with PD, in which 2 patients who were studied before therapy defined as controls	55.33±11.48	Controls: 13.8±8.9 ng/mL; L-dopa-carbidopa: 12.8±4.9 ng/mL Dopamine agonist + L-dopa-carbidopa: 5.3±1.9 ng/mL	Radioimmunoassay	A dichotomy between PRL and GH responses to combined L-dopa-carbidopa and dopamine agonist therapy. Conservation of normal PRL regulation in 2 untreated PD patients indicates that dopaminergic neurons are not generally affected by this disorder	[172]
8 patients with PD, 7 control A 6 patients with HC and 6 control B	PD: mean 62.87 (range 56–69) Control A: mean 67.5 (range 63–78) HC: mean 50.5 (range 37–58) Control B: mean 67.5 (range 63–78)	PD: 8.2±1.1 ng/mL Control A: 15.9±3.1 ng/mL HC: 10.7±3.1 ng/mL (range 3.1–24.3 ng/mL) Control B: 15.7±1.5 ng/mL (range 9.0–19.2)	Radioimmunoassay double antibody	Changes of nocturnal PRL profile in PD and HC patients in respect to age-matched controls were observed	[178]

PRL, prolactin; AD, Alzheimer's disease; PD, Parkinson's disease; TRH, thyrotropin-releasing hormone; CSF, cerebrospinal fluid; MID, multi-infarct dementia; IDP, idiopathic PD; CN, cognitively normal; SDAT, senile dementia of Alzheimer type; DAT, dementia of the Alzheimer type; YOPD, young-onset PD; OOPD, old-onset PD; EP, epilepsy; HC, Huntington's chorea.

PRL serum levels were higher in AD patients than in normal controls but were only significantly higher levels in patients with severe dementia, which indicated dementia is associated with dysfunction of the tuberoinfundibular pathway that regulates PRL secretion [134].

In a double-blind, placebo-controlled study, PRL levels did not change after naloxone treatment and were no different in AD patients and controls, though cortisol levels increased in both groups after naloxone treatment. These findings suggest endogenous opioid systems do not significantly modulate human basal PRL secretion and that the activity of the HPA axis is increased in AD [135]. PRL secretion is subject to tonic dopaminergic inhibition through the tuberoinfundibular pathway. A case-control study examined the impact of a dopamine-blocking agent (metoclopramide) on serum PRL levels in patients with Alzheimer's senile dementia (SDA) and in nondemented elderly controls. Response to metoclopramide was greater in patients with SDA than in controls, and the authors pointed out that dementia is related to dysfunction in the tuberoinfundibular pathway, which regulates PRL release [136]. In another study conducted on patients with multi-infarct dementia or SDA, serum PRL levels were similar in the 2 groups, and PRL levels and degrees of dementia were not correlated, which indicated serum PRL does not respond to TRH stimulation and is of little diagnostic value in terms of differentiating these 2 conditions [137]. However, this study did not include normal subjects, and a sample size that is quite small reduced the power of the study to conclude whether both patients with multi-infarct dementia and SDA are essentially normal in PRL responses to TRH stimulation [137].

In Animal Studies

In an APPswe/PS1dE9 double transgenic murine model of AD, the expression of the PRL gene was downregulated during the early stages of amyloidogenesis [138, 139]. In addition, the expressions of PRLR and PRL were downregulated in the hippocampi of 3-month APPswe/PS1dE9 mice as compared with wild-type controls. The authors attributed these early perturbations to metabolic risk factors of AD, cognitive dysfunction, and Aβ deposition [140].

Glycogen synthase kinase-3 (GSK3) has been associated with the development of AD. PRL may activate Akt, which leads to the deactivation of GSK3 and the inhibition of tau phosphorylation, which suggests that the deactivation of GSK3 may explain why the absence of PRL contributes to the risk of AD development [30, 141–143]. On the other hand, PRL is involved in milk secretion and

is produced mainly during lactation in the anterior pituitary [144]. During lactation, increased PRL levels might reduce GSK3 activity and preserve PRLR, and explain low baseline GSK3 levels in lactating rats [145]. Furthermore, high levels of PRL can affect kinase-related signaling pathways that regulate p-tau expression, and thus, increase p-tau levels in several rat brain areas throughout pregnancy up to day 2 of lactation [146]. These findings indicate that by inhibiting the HPA axis, PRL acts as a regulator of tau phosphorylation [147]. Attenuated responsiveness of the HPA axis has been recognized in lactation. It could be explained that PRL, either taken up by choroid plexus cells into the brain and released from the pituitary into the blood or released within the brain itself from neuronal structures, may be a factor considerably involved in the blunted HPA response observed during lactation [147].

Torner et al. reported that intravenous administration of ovine PRL 20 min before plus-maze exposure reduces anxiety [147]. Furthermore, PRL also helps avoid stress-induced decreases in neurogenesis and suppresses excitotoxic cell damage in hippocampus [69, 148, 149]. A recent study reported that in the hippocampus of lactating rats sacrificed 20 min after stress, exposure to 1 episode of restraint stress reduced p-tau levels as compared with virgin rats or rats after weaning exposed to exposure to restraint stress [145]. Other studies have also reported stress-induced dephosphorylation of tau in the hippocampus of lactating rats, and not in virgin or rats 1-month post-weaning, and significant increases in hippocampal p-tau following acute or restraint stress in male mice [145, 150, 151]. Remarkably, stress also seems to be the physiological cause of hyperprolactinemia [152]. These findings suggested a relationship between PRL and p-tau. However, further studies are required to clarify the roles of PRL in AD during stressful conditions.

Parkinson's Disease

In this section, we first discuss changes in PRL levels in PD induced by different stimuli and then describe the effects of PRL in PD.

Change of PRL Levels during Treatment

PRL secretion is directly controlled by dopaminergic hypothalamic and supra-hypothalamic mechanisms [153, 154]. Agnoli et al. [155] reported an association between acute plasma PRL level increases and improved symptoms in PD. However, the results of studies on PRL levels in PD are inconsistent. Several studies have reported higher PRL levels in PD than in controls [26, 156, 157],

while others have reported lower levels [158–161]. In addition, several studies have reported that plasma PRL is not elevated in PD because of a lack of dopamine autoreceptors, the effects of dopamine agonists, a slow reuptake process, or the protective effects of local neurotrophic factors [162, 163]. Here, we describe in detail changes in PRL levels in PD induced by different conditions.

Thyrotropin-Releasing Hormone

Bromocriptine is a dopamine agonist and an ergoline derivative that is used in the treatment of PD and hyperprolactinemia. Kostic et al. [164] showed that basal PRL levels are normal in young- and old-onset PD patients. However, after bromocriptine administration, TRH-induced a smaller PRL increase in old-onset PD patients than in normal controls, and an even smaller response for young-onset PD, which was significantly less than that observed in old-onset PD. Another study found resting levels of PRL were normal in untreated PD patients, and that TRH-induced PRL increases and bromocriptine pretreatment attenuated this response [156]. These observations suggest that bromocriptine/TRH testing might provide a means of assessing the sensitivity of D2 receptors on lactotroph cells in PD patients, which is relevant because pharmacological responses of lactotroph cells may reflect dopaminergic disturbances in PD, especially in the D2 subtype mediates PRL suppression [164].

Levodopa, Benserazide, and Carbidopa

Levodopa, benserazide, and carbidopa are drugs given to PD patients. In the brain, levodopa works by being converted to dopamine. Benserazide is a peripheral decarboxylase inhibitor that increases the amount of levodopa crossing into the brain and its subsequent conversion to dopamine, whereas carbidopa inhibits peripheral metabolism of levodopa. Previous studies have shown the neuroendocrine effects of carbidopa and benserazide differ in PRL release. Although carbidopa had only a slight effect on baseline PRL levels, a single dose of benserazide was followed by a marked increase in plasma PRL [165–167]. In contrast, Vogel et al. [168] reported PRL levels were in the normal range before and during therapy with levodopa and benserazide.

Ruggieri et al. [169] investigated changes in plasma PRL levels following acute administration of levodopa, levodopa plus carbidopa, and levodopa plus benserazide in PD patients. PRL increases after benserazide treatment were compared with those after carbidopa treatment at the same dose in nontreated PD patients. The results obtained indicated benserazide can cross the BBB at the hy-

pothalamic level and block L-dopa metabolism at this level, and that hyperprolactinemia induced may not be modified by levodopa.

Rabey et al. [170] reported basal PRL levels and PRL response to TRH were within the normal range in 6 PD patients 2 weeks after treatment cessation and in 8 patients 2 years after L-dopa-carbidopa treatment. The authors pointed out that chronic use of L-dopa did not influence tonic PRL secretion or PRL response to TRH. Disconnection or response to TRH under the similar inhibition action of dopaminergic stimulation may indicate thyrotropic cells are more sensitive to the blocking effect of dopamine than PRL-secreting cells.

Madopar + Sinemet (L-Dopa-Carbidopa)

Madopar (L-dopa plus benserazide) is a common antiparkinsonian agent used in PD in order to increase dopamine levels in the brain. Martinez-Campos et al. [157] found Madopar increased plasma PRL levels in controls, unmedicated patients, and patients on Madopar therapy, but that in patients on Sinemet therapy the PRL-releasing effect of Madopar was significantly diminished. These findings suggested that Madopar administered chronically to PD patients could impair the PRL regulating effect of DA. The authors also noticed that chronic administration of Madopar induced changes in PRL responses possibly related to defective TIDA function, whereas the function of hypothalamic DA tended to be preserved after Sinemet treatment [171]. In a study on the regulation of PRL secretion, Bell et al. found that 2 nontreated PD patients had a normal 24-h mean PRL concentrations and exhibited normal increases during sleep, indicating dopamine deficiency in PD does not influence all dopaminergic neurons [172–174].

Lavin et al. reported dopamine receptors that mediate the inhibition of PRL release was less sensitive to dopamine in PD patients on long-term levodopa therapy than in normal subjects. The authors recommended further study to evaluate the long-term clinical efficacy of levodopa therapy [175].

Changes in PRL Levels in the Different Types of PD

Fenfluramine, is a serotonin releasing agent, has long been investigated as a possible serotonergic treatment option in PD [176]. In a case-control study, PRL responses to fenfluramine were significantly less in PD patients than in normal controls and were significantly more blunted in PD patients with major depression than in nondepressed patients [177]. Murri et al. [178, 179] assessed night-time plasma PRL levels in 8 PD patients, 6 Hun-

tington's chorea (HC) patients, and 6 age-matched normal controls. Plasma PRL levels in PD patients were significantly lower than in controls but PRL secretory patterns were similar in HC patients and controls. Reduced PRL secretion in PD might be due to serotonin deficiency in hypothalamus, which suggests serotonin induces PRL release by stimulating the secretion of PRL-releasing factors.

Bellomo et al. [180] noticed plasma PRL levels were higher in idiopathic PD (IDP) patients than in normal controls and that PRL nocturnal peak concentrations were markedly higher in IDP patients. However, the plasma levels of growth hormone, cortisol, and adrenocorticotrophic hormone were lower in patients than in controls. Lawton et al. [181] also showed that in IDP patients, levodopa with carbidopa-suppressed TRH-induced PRL release less effectively than in age-matched normal controls. These results suggest that the presence of hypothalamic disturbances in IDP patients can influence pituitary function, and extend the biochemical defects in IDP from basal ganglia to the hypothalamus.

PRL Levels in PD according to Human and Animal Studies

PD has been associated with genetic factors, virus infections, environmental toxins, oligomerization of α -synuclein, mitochondrial dysfunction, oxidative stress, inflammation, and aging [182, 183], but levels of hormones like PRL can also influence cognition, mood, and quality of life in PD patients. Below, we describe the role of PRL in PD.

In Human Studies

Evidence indicates that PRL levels are higher in PD patients than in normal controls, and it has been well-established PRL levels are negatively correlated with sex steroid levels, mood, and quality of life in PD. Furthermore, high PRL levels could antagonize the effects of sex hormones [184]. These findings suggest that high concentrations of PRL and its antigonadotropin activity in men with PD could lead to greater susceptibility to the disease [26, 185].

Selegiline, is a relatively selective and irreversible inhibitor of monoamine oxidase type B, has been used in the treatment of PD. In a previous study, serum IL-2 and PRL levels were higher in PD patients than in normal controls, but serum PRL levels decreased after treatment for 2 weeks with selegiline, amantadine, or Madopar. The authors suggested that a moderate increase in PRL secretion can increase IL-2 in PD patients [7, 186], and this

Fig. 1. Schematic diagram of the involvements of PRL in AD and PD. PRL, prolactin; AD, Alzheimer's disease; PD, Parkinson's disease; JAK2, Janus kinase 2; STAT, signal transducer and activator of transcription; GSK3, glycogen synthase kinase-3; IL, interleukin; T-bet, T-box transcription factor TBX21; TRH, thyrotropin-releasing hormone.

suggestion supports a report of increased IL-2 levels in patients with prolactinoma [20, 187]. Moreover, these findings support the immunomodulatory effect of PRL in PD.

In Animal Studies

In a mouse model of PD, plasma PRL levels were negatively correlated with bone mineral density. In addition, long-term levodopa therapy was found to be associated with bone loss, which suggested a link between dopaminergic neurons and bone metabolism via the modulation of PRL release [188]. Diethylstilbestrol is a synthetic form of the female hormone estrogen. In a long-term diethylstilbestrol-treated male Wistar rat model, Krawczyk et al. [189, 190] found the inhibitory activity of amantadine on pituitary PRL cell function appeared to be related to the modulation of D2 receptor function, the secretion of dopamine from hypothalamic dopaminergic neurons, and the downregulation of dopaminergic D2 binding sites. Sumanriole, is a highly selective D₂ receptor full agonist, has long been studied as a potential treatment option in PD and restless leg syndrome. McCall et al. found that

sumanirole dose-dependently reduced plasma PRL levels and dopamine neuron firing rates in substantia nigra pars compacta and suggested that sumanirole might provide a tool for studying D2 receptor subtype specificity in vitro and in vivo [191]. Atremorine is an enhancer of dopaminergic neurotransmission. In vivo studies in mice showed that Atremorine can improve neurodegeneration-associated motor dysfunction, inhibit dopaminergic neurodegeneration, and protect against microglia activation and neurotoxicity in substantia nigra induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [192–195].

Concluding Remarks and Future Directions

Serum PRL levels in patients with AD and PD vary depending on the different conditions (e.g., stage of disease and treatment). PRL levels, in particular, varied across the different types of PD. PRL has inflammatory and anti-inflammatory effects in the CNS. High levels of PRL may activate the signaling pathway via SOCS1 and 3, resulting in suppression of T-bet activation. STAT3 activation by PRL mediates anti-inflammatory effects and IL-10 secretion in macrophages, suggesting that PRL signaling

through STAT3 has antiapoptotic and proliferative effects. PRL may inactivate GSK3 and thus inhibit tau phosphorylation. Furthermore, PRL benefits memory, cognition, and learning and reduces stress and anxiety. Of note, several genes associated with microglial functions induced by PRL might play important roles in hippocampal neuroimmunomodulation or in the protection of neuronal cells (Fig. 1). However, more research is required to examine variations in basal neuroendocrine conditions and neuroendocrine changes associated with these diseases [6, 24, 196–198]. We suggest future research be conducted to clarify the roles of PRL and p-tau during stressful conditions and to evaluate the long-term clinical efficacies of combined therapies associated with inhibition of PRL release in PD [15]. In particular, research efforts targeting PRL functions and immune mechanisms are needed to aid the development of drugs for the prevention or treatment of AD and PD.

Statement of Ethics

Ethical approval for the literature search was not required.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception or design: H.D.N and M.S.K. Acquisition, analysis, or interpretation of data: H.D.N., N.M.H.N., J.R.H., H.Y.C., W.H.J., and M.S.K. Drafting the work or revising: H.D.N., B.P.Y., and M.S.K. Final approval of the manuscript: H.D.N., N.M.H.N., J.R.H., H.Y.C., W.H.J., and M.S.K.

Data Availability Statement

The data supporting this review was obtained from cited studies.

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