REVIEW ARTICLE

Novel Pharmacotherapies in Parkinson's Disease

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Abstract

Parkinson's disease (PD), an age-related progressive neurodegenerative condition, is associated with loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which results in motor deficits characterized by the following: akinesia, rigidity, resting tremor, and postural instability, as well as nonmotor symptoms such as emotional changes, particularly depression, cognitive impairment, gastrointestinal, and autonomic dysfunction. The most common treatment for PD is focused on dopamine (DA) replacement (e.g., levodopa = L-Dopa), which unfortunately losses its efficacy over months or years and can induce severe dyskinesia. Hence, more efficacious interventions without such adverse effects are urgently needed. In this review, following a general description of PD, potential novel therapeutic interventions for this devastating disease are examined. Specifically, the focus is on nicotine and nicotinic cholinergic system, as well as butyrate, a short chain fatty acid (SCFA), and fatty acid receptors.

Keywords Parkinsonism · Nicotine · Butyrate · Short-chain fatty acids · Depression · Comorbidity · Combination therapy

Introduction

Parkinson's disease (PD), the second most common progressive neurodegenerative disorder, is associated with loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) that leads to striatal dopamine (DA) deficiency (Blesa and Przedborski 2014; Hustad and Aasly 2020; Liu 2020; Simon et al. 2020). This loss of dopaminergic neurons results in motor deficits characterized by the following: akinesia, rigidity, resting tremor, and postural instability, as well as nonmotor symptoms that might also involve other neurotransmitter systems including the cholinergic system (Perez 2015; Mirelman et al. 2019; Quik et al. 2019; Stoker and Barker 2020). The nonmotor symptoms may include the following: emotional changes (e.g., depression, apathy and anxiety), cognitive deficits (e.g., mild to severe memory impairment), sleep perturbations (e.g., insomnia/hypersomnia), autonomic dysfunction (e.g., bladder disturbances, orthostatic hypotension, sweating), sensory symptoms

(e.g., pain, visual and olfactory deficits), gastrointestinal symptoms (e.g., constipation, nausea), as well as "social symptoms" (e.g., inability to produce facial expression or recognize other's verbal and nonverbal cues) (Perez 2015; Dinter et al. 2020; Prenger et al. 2020).

Neuronal degeneration in PD involves several cellular and molecular events including accumulation of misfolded proteins, failure of protein clearance, mitochondrial damage, oxidative stress, neuroinflammation, immune dysregulation, apoptosis, excitotoxicity, Ca^{++} dysregulation, as well as autophagy and dysbiosis (Hurley and Tizabi 2013; Maiti et al. 2017; Reglodi et al. 2017; Zeng et al. 2018; Genovese et al. 2020; Indrieri et al. 2020; Parra et al. 2020; Dorszewska et al. 2021; Giorgi et al. 2021; Harms et al. 2021; Rani and Mondal, 2021). In addition, mutations in a number of genes such as leucine-rich repeat kinase 2 (LRRK2), Parkin RBR E3 ubiquitin protein ligase (PARK2), Parkinson disease protein 7 (PARK7), PTEN-induced putative kinase 1 (PINK1), alpha- synuclein (SNCA), as well as polymorphism in DA receptor D2 gene (DRD2Taq1A) have been identified (Klein and Westenberger 2012; Song et al. 2019; Tran et al. 2020).

Although the etiology remains unsettled, it is believed that PD is a multifactorial disease, with both genetic and environmental factors playing a role. The biggest risk factor for PD is old age, where median age of onset is estimated to

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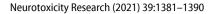
be around 60 years of age (Lees et al. 2009; Kouli et al. 2018). In addition, it is postulated that exposure to environmental toxicants such as pesticides, herbicides, and heavy metals may increase the risk of PD (Anderson et al. 2020; McKnight and Hack 2020). In the early 1980s, it was discovered that injection of underground laboratory preparations of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) could result in nigrostriatal degeneration and development of typical PD motor symptoms. MPTP is a potent analog of the opioid analgesic meperidine that gets metabolized into the neurotoxin MPP + (1-methyl-4-phenylpyridinium). MPP + is a mitochondrial complex-I inhibitor as well as substrate for DA transporter (DAT) and has been shown to selectively damage the dopaminergic cells in SNpc (Langston et al. 1983; Fujita et al. 2020). For this reason, MPTP models of PD are commonly used to investigate the mechanism of neurotoxicity and/or development of novel therapeutics (Schneider et al. 2021; Zheng et al. 2021). Similarly, rotenone, a pesticide which is also selective inhibitor of mitochondrial complex-I, is used in animal models of PD (Betarbet et al. 2000; Kouli et al. 2018). In addition, exposure to heavy metals such as manganese (Peres et al. 2016; Andrade et al. 2017; Ivleva et al. 2020) or iron (Ganz, 2018; Huang et al. 2019; Ndayisaba et al. 2019; Shi et al. 2019) have also been implicated in PD etiology. Interestingly, reduction of iron content via clioquinol was associated with a remarkable improvement of the motor and nonmotor deficits in an MPTP-induced monkey model of PD (Shi et al. 2020).

The most common treatment of PD is focused on DA replacement (e.g., levodopa = L-Dopa), which unfortunately losses its full efficacy in few years and can induce severe dyskinesia, or abnormal involuntary movements (Quik et al. 2019; Sy and Fernandez 2020; Bjørklund et al. 2020). For this reason, DA receptor agonists such as pramipexole and ropinirole may be used initially and inhibitors of DA metabolizing enzymes such as selegiline or rasagiline, both monoamine oxidase (MOA) inhibitors, or catechol-O-methyltransferase (COMT) inhibitors such as entacapone and tolcapone are often used in combination with L-Dopa

(Aradi and Hauser 2020; Zheng et al. 2021). Nonpharmacologic interventions including repetitive transcranial magnetic stimulation (rTMS), and in specific circumstances neurosurgery (i.e., deep brain stimulation) may also be applied (Li et al. 2020a; Sui et al. 2021). In addition, significant efforts are devoted to development of autologous, stem cell-derived grafts, as well as viral gene therapies (Stoker et al. 2018; Osborn et al. 2020; Stoker and Barker 2020; Tao et al. 2021). Nonetheless, more efficacious interventions targeting the neurodegenerative aspect of the disease are urgently needed. Here, we discuss potential use of nicotine or nicotinic cholinergic agonists/modulators alone or together with butyrate, a short-chain fatty acid and fatty acid 3 receptor (FA3R) agonists as alternative and/or additional interventions in PD treatment (Fig. 1).

nAChRs

The inverse relationship between PD incidence and any form of nicotine intake such as cigarette smoking (Hernán et al. 2002; Ritz et al. 2007; Li et al. 2015), smokeless tobacco (O'Reilly et al. 2005; Liu et al. 2017b; Yang et al. 2017), exposure to environmental tobacco smoke (Searles Nielsen et al. 2012; Han et al. 2020a; Liu et al. 2020), or even from a dietary source such as peppers (Ma et al. 2020) suggests a therapeutic potential for nicotine in PD. This contention is further supported by numerous preclinical studies indicating neuroprotective effects of nicotine, especially in dopaminergic cell models as well as in vivo models of PD (discussed below). Hereby, following a brief discussion of nicotinic cholinergic system, we will focus on its therapeutic utility in PD.

Nicotine's main targets are nicotinic receptors (nAChRs) that are widely distributed in the central nervous system (Clark and Pert 1985; Dani 2015; Wills and Kenny 2021). nAChRs belong to ionotropic class of receptors, which act by regulating directly the opening of a cation channel in

Fig. 1 Schematic diagram depicting current pharmacotherapies for PD which result in symptomatic relief of symptoms due increase in the striatal DA (left panel). Potential novel intervention that may target the neurodegenerative aspect of the disease and may also help with nonmotor symptoms (right panel)

Current Treatment: Symptom Abatement

- L-Dopa
- Dopamine Agonists
- COMT Inhibition
- MAO Inhibition

Mechanism:
↑ DA in Striatum

Potential Novel Intervention: Prevention of Neurodegeneration/ Help with Non-Motor Symptoms

- Nicotine
- Nicotinic Agonist or Modulator
- Butyrate or Other SCFA
- FA3R Agonist
- HDAC Inhibitor

Mechanism: Direct or Indirect Effect (e.g., through Gut Microbiome-Brain Axis) on Pathology

the neuronal membrane (Dani 2015; Changeux 2018; Papke and Lindstrom 2020). Various subtypes of these receptors with distinct anatomical, physiological, and pharmacological characteristics have been identified (Dani 2015). Although nAChRs are present at various sites and in various organs such as neuromuscular junction, autonomic ganglia, and the central nervous system, the subunit structures of these receptors are different from each other (Kalamida et al. 2007). Considerable information on interaction between neuronal nAChRs consisting mainly of alph4-beta2 or homomeric alpha7 subunits and other neurotransmitter systems is now available (Wittenberg et al. 2020; Wills and Kenny 2021). Moreover, specific responses of these receptors to nicotine and their involvement in cognitive functions have been investigated (Valentine and Sofuoglu 2018; Azimi et al. 2020). Indeed, a potential role of nAChRs in high-order cognitive processing has been suggested (Koukouli and Changeux 2020). Therapeutic potential for selective nAChR agonists in various neuropsychiatric and neurodegenerative disorders including PD (Quik et al. 2019; Tizabi et al. 2019; Liu 2020), depression (Gandelman et al. 2018; Tizabi et al. 2019; Conti et al. 2020), mild cognitive impairment or Alzheimer's disease (Vega et al. 2019; Azimi et al. 2020; Hahn et al. 2020; Koukouli and Changeux 2020), ischemia (Han et al. 2020b), schizophrenia (Terry and Callahan, 2020), pain (Bagdas et al. 2018), as well as energy balance (Seoane-Collazo et al. 2021) have been proposed. Given that there is a relatively high comorbid existence between depression and PD, a nicotinic intervention may have the added advantage of addressing both issues at the same time (Tizabi et al. 2019).

Role of the Nicotinic Cholinergic System in Parkinson's Disease

Multiple studies indicate that the normal function of the basal ganglia, intimately involved in movement regulation, is dependent on the equilibrium between the midbrain dopaminergic and striatal cholinergic systems (Aosaki et al. 2010; Scarduzio et al. 2017; Assous, 2021). Thus, acetylcholine can regulate striatal DA release via an interaction at various nAChRs (Quik et al. 2019; Liu 2020). Further importance of ACh in the basal ganglia is evident from the effect of cholinergic agents in patients suffering from various neurological disorders such as Tourette syndrome, dystonia, as well as PD (Assous, 2021). In various experimental animal models of PD (e.g., 6-OHDA lesioned rodents), the impairments in DA release appear to be exacerbated by loss of nAChRs activation, suggesting that nicotinic agonists may ameliorate the dopaminergic imbalance and may thus be useful therapeutic targets for PD (Shimohama and Kawamata, 2018; Quik et al. 2019). In this regard, a

number of in vitro and in vivo studies including primates and genetically modified mice have shown protective effects of nicotine against neuronal damage and/or neurotoxicity induced by 6-OHDA, MPTP, rotenone, methamphetamine, glutamate, and β-amyloid (reviewed in: Shimohama and Kawamata, 2018; Quik et al. 2019; Tizabi et al. 2019). These effects are mediated via selective nAChR subtypes containing β2 and α7 subunits (see Quik et al. 2019; Tizabi et al. 2019). We have also observed protective effects of nicotine against endogenous substances such as salsolinol (discussed later) and aminochrome that selectively damage dopaminergic cells (see Tizabi et al. 2019). More recently, protective effects of nicotine against toxicity induced by iron and manganese were also observed in cell culture (Getachew et al. 2019a). Additionally, Quik et al. (2019) have shown beneficial effects of nicotine against L-Dopa-induced dyskinesia in nonhuman primate models. Interestingly, nicotinic cholinergic system may also play a role in L-Dopa-induced dyskinesias (Bordia and Perez 2019). Hence, targeting nicotinic cholinergic receptors appears to offer a novel intervention in PD (Tizabi and Getachew, 2017, Quick, 2019; Tizabi et al. 2019, Liu 2020; Vetel et al., 2021). Nicotine's effects are likely to involve suppression of pro-inflammatory cytokines and stimulation of neurotrophic factors as well as suppression of oxidative stress (Barreto et al. 2015; Perez 2015; Tizabi 2019; Dong et al. 2020; Vetel et al. 2021).

Several human studies have assessed the effects of nicotine gum or patch in PD, most of which have not yielded positive results (Vieregge et al. 2001; Lemay et al. 2004; see also Tizabi and Getachew 2017). The negative finding in these trials is likely due to the mode of administration of nicotine (Tizabi and Getachew 2017). Thus, it is very important to consider the route of nicotine administration, where subdermal administration via patch may not achieve the desirable nicotinic receptor stimulation obtained via pulsatile nicotine (e.g., via inhalation) (Feathersone and Siegel 2015; Tizabi and Getachew 2017). The very complex dynamic interaction of nicotine with its receptors, where initial stimulation can be followed by rapid and differential desensitization of receptor subtypes, has to be critically considered in experimental paradigms so that maximal therapeutic outcome may be obtained (Dani 2015; Tizabi and Getachew 2017; Quik et al. 2019). Thus, it may be suggested that pulsatile stimulation of specific nAChRs in selective brain regions, particularly in the nigrostriatal pathway would be critical for its therapeutic effects in PD. This could be achieved by administering nicotine via inhalation, or nasal spray. It is of relevance to note that a recent clinical study using oral administration of nicotine, reported positive effects of nicotine on falls and freezing gait in PD (Lieberman et al. 2019). Furthermore, pulsatile nicotine preparations in forms of inhalers or nasal spray are available and approved by FDA for smoking cessation and could

be re-purposed for PD pending evaluation of their effectiveness in clinical trials. In addition, as alluded to earlier, potential usefulness of a pulsatile nicotine administration in improving nonmotor symptoms (e.g., depression or cognitive decline) that are commonly associated with PD (Quik et al. 2015; Tizabi and Getachew 2017; Tizabi et al. 2019), could be an added advantage of nicotinic therapy (Fig. 1).

Still, the addictive properties of nicotine (Stolerman and Jarvis, 1995; Willis and Kenny, 2021) might be of concern in its therapeutic application. In this regard, significant efforts are expanded in developing selective nicotinic receptor subtype agonists or nicotinic receptor modulators that would be of similar potency but without the addictive component (Ryan et al, 2001; Bordia et al., 2015). Nonetheless, taking into account the risk/benefit ratio of nicotine, it might still be a useful tool in PD until more suitable nonaddictive compounds are developed (Mitra et al. 2020).

It is of utmost importance, however, to emphasize that the suggested interventions are for pure nicotine available via pharmaceutical preparation and not smoking. The detrimental consequences of tobacco (chewed or smoked) or even e-cigarettes on various organs and lately in COVID-19 pandemic have been recognized (Li et al. 2020b; Ruszkiewicz et al. 2020; Tizabi et al. 2020), and hence, none of such modes should be attempted as self-medication by any PD patient. Moreover, controlled clinical trials of nicotinic preparations to establish the dose and efficacy and ultimate FDA approval are required for any nicotinic intervention in PD.

Butyrate

Butyrate is a short-chain fatty acid (SCFA) that is produced by gut microbiota and acts primarily as an energy source for colonic epithelial cells and has been shown to have anti-inflammatory, enteroendocrine and epigenetic effects that not only influences colonic and systemic health but can also affect the brain function (Cantu-Jungles et al., 2019). Recent advances in our understanding of the gut-brain axis has resulted in new insights and potential novel targets for therapeutic intervention in PD (Baizabal-Carvallo and Alonso-Juarez, 2020; Cirstea et al. 2020; Cryan et al. 2020). Indeed, it has been suggested that the initiation and progression of PD may be impeded through manipulation of the gut microbiota. Specifically, it has been suggested that misfolding of alpha-synuclein (α-Syn), a protein highly implicated in PD pathology, can be brought about via dysbiosis or altered colonic microbiota and subsequent neuroinflammation (Keshavarzian et al. 2015; Sampson et al. 2016; Meng et al. 2019; Koutzoumis et al. 2020). This contention is further supported by the observation that the composition of the gut microbiota and SCFAs might be altered in patients with

PD (Unger et al. 2016; Nuzum et al. 2020; Shin et al. 2020). Thus, there is a strong indication for therapeutic use of SCFAs, particularly butyrate, the most studied SCFA, for PD treatment. In this regard, a few studies have shown beneficial effects of sodium butyrate in various animal models of PD (St Laurent et al. 2013; Liu et al. 2017a; Funakohi-Tago et al. 2018; Russo et al. 2018; Srivastav et al. 2019; Hou et al. 2021), although at higher doses, this compound might aggravate the colonic inflammation in an MPTP mouse model (Qiao et al. 2020a). In vitro and in vivo studies have consistently found protective effects of sodium butyrate against dopaminergic cell damage brought about by alpha-synuclein (Paiva et al. 2017; Qiao et al. 2020b). This protection is against both transcriptional deregulation and DNA damage (Paiva et al. 2017). The postulated mechanism for in vivo effect of sodium butyrate in degradation of α-synuclein is via Atg5-dependent and PI3K/Akt/mTOR-related autophagy pathway (Qiao et al. 2020b). Beneficial effects of butyrate in PD are further evidenced by its attenuation of neurotoxic or motor impairments induced by 6-hydroxydopamine, rotenone, and MPTP (Funakohi-Tago et al. 2018; Srivastav et al. 2019; Hou et al. 2021).

We have also observed that butyrate as well as AR 420,626 (AR), chemical name: *N*-(2,5-dichlorophenyl)-4-(furan-2-yl)-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide), another agonist of the fatty acid-3 receptor (FA3R) can protect against salsolinol-induced toxicity in SH-SY5Y cells, which as discussed below has important implications for PD (Getachew et al. 2020). Salsolinol (SALS = 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline), which has structural similarity with MPTP, is an adduct formed as a condensation product of DA and aldehydes and is considered an endogenous DA modulator with selective toxicity to dopaminergic neurons in the substantia nigra (Storch et al. 2002; Maruyama et al. 2004; Naoi et al. 2004; Mravec 2006). Dysregulation of SALS, especially its (R) enantiomer in the brain, is thought to contribute to development of PD (Antkiewicz-Michaluk 2002; Xicoy et al. 2017). The observed higher level of SALS in the cerebrospinal fluid and urine of PD patients has led to the suggestion of its measurement as a potential marker for PD (Storch et al. 2002; Maruyama et al. 2004; Naoi et al. 2004; Sharma et al. 2013; Zheng et al. 2018; Voon et al. 2020), although elevated levels of systemic derivatives of norsalsolinol may also arise from the metabolism of levodopa (Scholz et al. 2004). That SALS may actually be produced by gut microbiota, further strengthens the gut-brain axis hypothesis of PD (Villageliú et al. 2018).

SH-SY5Y cells, human neuroblastoma-derived cell line, express high levels of dopaminergic activity and are used extensively to study possible mechanism(s) of toxicity and protection in nigral dopaminergic neurons (Copeland et al. 2007; Qualls et al. 2014; Xicoy et al. 2017; Getachew et al. 2019a). As alluded to above, we observed that both butyrate

and AR, a FA3 receptor agonist (Hudson et al. 2014; Bolognini et al. 2016; Kaji et al. 2018), fully blocked SALS-induced toxicity. However, the effect of butyrate was blocked partially, whereas the effect of AR was blocked totally by beta-hydroxy butyrate (BHB), a selective FA3R antagonist. This suggests that some of the effects of butyrate might be independent of FA3R activation (see below). However, since at least part of the butyrate effect is mediated through FA3R stimulation, it would not be unreasonable to suggest that agonists of this receptor might also be of therapeutic potential in PD treatment (Getachew et al. 2020) (Fig. 1).

Several mechanisms of action, including histone deacetylase (HDAC) inhibition, activation of Nrf2/HO-1 axis (activation of antioxidant defense and detoxifying genes), stimulation of glucagon like peptide-1, as well as binding to several specific G protein–coupled receptors (GPCRs) such as FA2R and FA3R (Liu et al 2017a; Funakohi-Tago et al. 2018; Cantu-Jungles et al. 2019) have been attributed to butyrate. That the effect of butyrate was partially blocked by a specific FA3R antagonist suggests that mechanism(s) other than activation of FA3R are also involved in its neuroprotective effects (Getachew et al. 2020). In this regard, protective effects of sodium butyrate against dopaminergic cell damage in vitro has been attributed mainly to HDAC inhibition (Paiva et al. 2017). Hence, targeting HDAC may also be a viable source for novel intervention in PD (Fig. 1).

It is noteworthy that butyrate not only may have neuroprotective effects but may also have beneficial application against several other diseases including graft rejection, inflammatory bowel disease, colorectal cancer, and diabetes, all of which carry an inflammatory component (Tikhonova, 2017; Alrafas et al. 2019; Baxter et al. 2019). More recently, butyrate was also advocated for treatment of obesity and sleep disorders (Baxter et al. 2019; Szentirmai et al. 2019). However, a possible drawback to butyrate's therapeutic use may be its poor pharmacological properties including short half-life and first-pass hepatic clearance (Witt et al. 2003; Sampathkumar et al. 2006; Yoo and Jones 2006; Ghosh et al. 2012). Therefore, if AR or any other selective FA3R agonist, with a better pharmacologic profile than butyrate, show similar effects as butyrate, then their use in the myriad of diseases mentioned above can be advocated. Moreover, since some of protective effects of butyrate may be due to HDAC inhibition, it would be of importance to determine whether such compounds would also have a similar effect on HDAC (Srivastav et al. 2019). Nonetheless, it is noteworthy that several selective FA3R agonists including AR were shown to be effective in blocking NSAID-induced enteropathy (intestinal pathology) in rats (Said et al. 2017).

Similar to what was observed for nicotine, butyrate also has shown antidepressant properties. Thus, it was observed that sodium butyrate functions as an antidepressant in several animal models of depression including maternal deprivation and chronic mild stress (Gundersen and Blendy 2009; Valvassori et al. 2014). More recently, it was reported that sodium butyrate also ameliorates depressive-like behavior in lipopolysaccharide-induced depression and that this effect is mediated via inhibition of neuroinflammation and oxido-nitrosative stress (Qiu et al. 2020). These effects are likely mediated through FA3R stimulation as it was shown that histone deacetylase inhibition was not a mechanism for butyrate's antidepressant effect (Gundersen and Blendy 2009).

As mentioned previously, there is relatively high comorbid existence between depression and PD. Hence, here also intervention by butyrate may have the added advantage of addressing both issues at the same time (Tizabi et al. 2019). In this regard, it is also noteworthy that drugs that have neuroprotective effects are likely to also show mood regulating and antidepressant properties (Tizabi 2016). On the other hand, antidepressants are also likely to show at least some neuroprotective effects (Tizabi 2016). This duality of neuroprotective/antidepressant effects are likely due to some overlap of circuitries as well as common neurobiological substrates involved in dysregulation of mood and neurodegenerative phenotypes, particularly in PD (Tizabi 2016; Tizabi et al. 2019). Moreover, recent advances also strongly connect gut microbiota not only with neurodegenerative diseases as discussed above but also with pain (Russo et al., 2018), neurodevelopmental disorders such as autism (Almeida et al. 2020; Lungba et al. 2020; O'Connor et al. 2021), neuropsychiatric disorders such as schizophrenia (Dinan and Cryan 2020; Kelly et al. 2020), and particularly depression (Caspani et al. 2019; Cruz-Pereira and Cryan, 2020). Several mechanisms including deficits in neurogenesis and synaptogenesis, reduced cortical and hippocampal expression of brain-derived neurotrophic factor (BDNF), exaggerated hypothalamic pituitary adrenal (HPA) axis response, and neuroinflammation have been implicated in dysbiosis and depressive-like characteristics (Caspani et al. 2019; Getachew et al. 2019b; Getachew and Tizabi 2019; Cruz-Pereira and Cryan 2020). Since as mentioned earlier, depression is a common manifestation with PD, agents such as butyrate or other compounds interacting with gut microbiota would be ideal candidates for further investigation in comorbid conditions.

Combination Therapy

An important consideration in disease modification is potential combination of drugs with various mechanism of action to affect the chain of events at various sites to prevent the pathology and/or the phenotype. Thus, it might prove prudent to combine the aforementioned drugs, namely nicotine and/or nicotinic agonists/

modulators with butyrate and/or an FA3R agonist for maximum efficacy. Moreover, such drugs may be added to current medications used in PD to improve therapeutic outcome, particularly for comorbid conditions. In this regard, some of the current medications might actually be targeting some of the same sites discussed above, albeit to a lesser degree. For example, it was recently demonstrated that COMT inhibitors that are commonly used in PD can also affect the gut microbiota implicated in PD (Grün et al. 2020). Interestingly, recent studies also provide evidence of nicotine interaction with gut microbiota (Chi et al. 2017; Pavia and Plummer 2020). Specifically, it was demonstrated that oxidative stress response as well as DNA repair genes were particularly enriched in gut microbiome of mice treated with nicotine (Chi et al. 2017). Thus, multi-level effects of nicotine and butyrate would render their potential additive or synergistic effects in PD and perhaps more specifically in PD-depression comorbidity a very viable outcome. In support of this contention, we have recently observed a synergistic interaction between nicotine and butyrate against SALS-induced toxicity in SH-SY5Y cells (under preparation).

In summary, nicotine or nicotinic agonists or modulators alone or together with butyrate and/or FA3R agonists hold significant promise as novel therapeutic interventions in PD.

Declarations

Conflict of Interest The authors declare no competing interests.

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