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REVIEW

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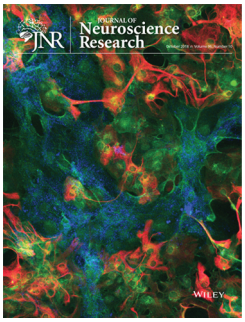

Hormetic approaches to the treatment of Parkinson's disease: Perspectives and possibilities

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Abstract

Age-related changes in the brain reflect a dynamic interaction of genetic, epigenetic, phenotypic, and environmental factors that can be temporally restricted or more longitudinally present throughout the lifespan. Fundamental to these mechanisms is the capacity for physiological adaptation through modulation of diverse molecular and biochemical signaling occurring from the intracellular to the network-systemic level throughout the brain. A number of agents that affect the onset and progression of Parkinson's disease (PD)-like effects in experimental models exhibit temporal features, and mechanisms of hormetic dose responses. These findings have particular significance since the hormetic dose response describes the amplitude and range of potential therapeutic effects, thereby affecting the design and conduct of studies of interventions against PD (and other neurodegenerative diseases), and may also be important to a broader consideration of hormetic processes in resilient adaptive responses that might afford protection against the onset and/or progression of PD and related disorders.

KEYWORDS

adaptation, aging, hormesis, neuroprotection, preconditioning, Parkinson's disease

1 | INTRODUCTION: ADDRESSING THE PREVALENCE OF AGE-RELATED NEURODEGENERATIVE DISORDERS

A major complication of normal healthy aging is an incremental risk of age-related conditions that can increase morbidity and adversely affect the quality of life. Indeed, with a lengthening life span of the global population, there is concomitant rise in the prevalence of neurodegenerative disorders such as Parkinson's (PD) and Alzheimer's (AD) disease (Kim, Beak, Charidimou, & Song, 2016; Li & Le, 2013). Thus, persistent—and important—questions, and ongoing research focus both upon those factors that may contribute to the development and

Significance

This paper provides the first integrative assessment concerning how the concept of hormesis may play a significant role in preventing the onset and severity of Parkinson's disease (PD) symptoms and disease processes. This paper identified and assessed 50 different potential chemotherapeutic agents that act via hormetic mechanisms and within the context of the quantitative features of the hormetic response to prevent PD-related effects. The use of hormetic strategies should become a central component in the prevention of chronic neurodegenerative diseases such as Parkinson's.

progression of these disorders, and if, how and to what extent these patho-etiologic variables might be mitigated and/or prevented.

Age-related changes in the brain reflect a dynamic interaction of genetic, epigenetic, phenotypic, and environmental factors that can be temporally restricted or more longitudinally present throughout the lifespan. Fundamental to these mechanisms is the capacity for physiological adaptation through modulation of diverse molecular and biochemical signaling occurring from the intracellular to the network-systemic level throughout the brain. In this context, hormesis defines thresholds of adaptive responses that have been shown to evoke and sustain adaptive plasticity to a range of stimuli and conditions (Calabrese, Cornelius, Stella, & Calabrese, 2010; Calabrese, Dhawan, Kapoor, Iavicoli, & Calabrese, 2015).

2 | HORMESIS: BACKGROUND AND PERSPECTIVES

A number of stressor agents can induce adaptive responses at low doses, but are less effective, and in some cases are even toxic at increasingly higher doses. This biphasic dose response pattern (i.e., low dose stimulation and high dose inhibition) is called hormesis, from the Greek, meaning "to excite" (Calabrese & Baldwin, 2002; Mattson, 2008). The concept of hormesis was first reported by Schulz (1887, 1888) who noted that low doses of many disinfecting agents enhanced yeast metabolism and survival at low doses, but became toxic at increasing doses. Other investigators extended these initial observations to reveal that biphasic dose responses are a highly generalized occurrence in and across all phyla and in numerous cell types. Calabrese & Baldwin (2000a, 2000b) have summarized the historical development of the concept of hormesis and its properties and putative mechanisms in response to a variety of chemical and ionizing radiation stimuli (Calabrese & Baldwin, 2000a, 2000b, 2000c, 2000d, 2000e). Yet, despite substantial documentation of hormetic dose responses in the scientific literature (Calabrese & Blain 2005, 2011), fields such as toxicology have long employed high doses to characterize biological responses, with extrapolation to low doses via linear and/threshold dose-response models. However, over the past several decades, there have been expanded investigations of biological responses to low doses of chemicals and radiation that have often revealed hormetic dose–response relationships, and more recently demonstrated the mechanistic bases of their effect(s) (Calabrese, 2013a).

These studies have shown hormetic dose responses to typically elicit a modest stimulatory effect, which is usually in the maximum range of 30–60% greater than control. Such stimulatory responses reflect either a direct stimulation or an overcompensatory effect, and occur independently of biological model, cell type, inducing agent, and mechanism (Calabrese, 2011, 2013a). Hormetic effects are currently being ever more considered for biomedically therapeutic applications (Calabrese, 2008a) in that these responses appear to be involved in a number of developmental, maturational, and aging processes (Calabrese et al., 2015; Segev-Amzaleg, Trudler, & Frenkel, 2013), and may subserve a spectrum of activities in neural systems, including protection against and/or recovery from certain neurodegenerative diseases, and/or injury (Calabrese, 2008b,2013b). The iterative recognition of hormesis has occurred in large part because traditional dose–response constructs, such as the threshold model, have not been able to satisfactorily and/or fully account for nonrandom biological activity below well-established thresholds of response.

3 | HORMESIS AND PARKINSON'S DISEASE

Consideration of employing hormetic models and approaches for therapeutics against neurodegenerative disorders is relatively recent, and has emerged only over the past 15 years (Calabrese, 2008c, 2008d, 2008e; Calabrese, Calabrese, & Giordano, 2017). For example, research linking hormetic mechanisms to PD has focused upon the ways that potential therapeutic agents may act within an experimental preconditioning framework to modify adaptive mechanisms that prevent or diminish effects induced by 6-hydroxydopamine (6-OHDA) and/or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

Interest in expanding this research to clinical translational applications is based upon concerns that long-term treatment of PD with levodopa often leads to end-of-dose and/or tachyphylactic exacerbation of signs and symptoms, and can evoke significant side effects, such as dyskinesia (Shulman, Taback, Bean, & Weiner, 2001). These deleterious effects have prompted the search for agents that might be useful in the prevention and treatment of PD, inclusive of other pharmacological approaches (Carradori & Silvestri, 2015; Huleatt et al., 2015), the use of low dose radiation (El-Ghazaly, Sadik, Rashed, & Abd-El-Fattah, 2015; Kojima et al.,1999) and herbal extracts, many of which are constituents of traditional Asian pharmacopeia (Zhang et al., 2015). Several candidate agents have been screened using in vitro models (e.g., PC-12, SH-SY5Y, and MN9 cells) that mimic key features of PD when exposed to agents such as 6-OHDA, MPTP, rotenone, and paraquat. Agents eliciting positive effect(s) in these in vitro models may be selected for further evaluation using in vivo rodent models. But it is of particular interest that in vitro testing of possible therapeutic agents for PD often involves a broad range of concentrations, permitting an enhanced assessment of the dose/concentration–response relationship. Within this framework, a number of studies have identified possible therapeutic agents for PD. Many of the agents tested show

therapeutic potential to diminish PD-like effects. Yet, it is common for such studies to evaluate only a modest range of concentrations, and thus limit the opportunity to assess a broader dose–response pattern. It is also of note that most of the papers published only evaluated the potential for reducing PD-like effects using a preconditioning protocol, with little attempt to apply the potential therapeutic agent within post-conditioning protocols (that may have clinical relevance).

Despite such constraints and limitations, it is noteworthy that a significant number of studies have evaluated potential PD treatments within a broad dose response framework. As summarized in Table 1[1], this literature has identified approximately 50 agents that display capacity to prevent some PD-related effects in one or more experimental models. Of these agents, the majority are of plant origin, with the remaining being either endogenous (e.g. creatine, estrogen, orexin, oleoylethanolamide [OEA]) or synthetic substances (lactacystin, apomorphine, and glucose oxidase). One agent (OEA) was both of plant origin and endogenous in mammalian systems. Several of the herbal agents were complex mixtures, such as Hepad, which is comprised of six different herbal substances. Another therapeutic treatment, Yi-Gan San (YGS), a treatment used in traditional Chinese medicine, is a mixture of nine different herbal extracts. These studies were published from 1996 to 2017, with the majority since 2007.

3.1 | Experimental models of Parkinson's disease: Inducing agents and dose-response features

A number of agents have been tested in at least one of 11 PD experimental testing systems, and involved the use of three in vitro cell lines (PC-12, Table 2; SH-SY5Y, Table 3 and MN9), or ex vivo mouse or rat substantia nigra and/or hippocampal cells. The agents most commonly employed to induce cellular effects were 6-OHDA, MPTP/MPP+, salsolinol, hydrogen peroxide (H_2O_2), L-dopa, and glutamate. Of particular significance to assessing possible hormetic effects was the selection/number of doses, and the dose range(s) in which the agents were evaluated. Typically, 3–10 treatment doses were used, and dose ranges varied between 3-fold (Xiao-Qing, Jun-Li, Yu, Jian-Qiang, & Pei-Xi, 2005) to 100,000-fold (Ba, Pang, Davidge, & Benishin, 2004), with the majority of experiments employing a dose range of $\leq$ 100-fold (see Tables 2 and 3). The timing of the chemoprotective treatments prior to the administration of the PD-inducing agent (e.g., 6-OHDA, MPTP) was also highly variable, ranging from a low of 15 min (i.e., apomorphine; Gassen, Gross, & Youdim, 1998a; polyphenols; Levites, Amit, Youdim, & Mandel, 2002) to a high of 14 days (i.e., nicotine; Ryan, Ross, Drago, & Loiacono, 2001; creatine; Matthews et al., 1999), with prior treatment exposures of 1 and 24 hr being most characteristically utilized.

Evaluation of the compounds/mixtures tested revealed substantial reduction in damages induced by (the subsequent) toxic agent(s). At the optimum dose, the reduction in pathogenic effects was approximately 30–60%, with some treatments approaching complete protection. The protective dose range varied according to the biological model, agent, endpoint, toxic threshold response concentration, and study design used (see Tables 2 and 3). The quantitative features of the hormetic dose response in these PD experiments are fully consistent with those described in the hormesis literature. The most striking similarity of the quantitative features of hormetic dose responses is the modest increase in amplitude, which occurs whether the response is a direct stimulation, as an overcompensation to a disruption in homeostasis, or within pre and postconditioning frameworks. Such quantitative consistency suggests that the amplitude of the hormetic dose-response provides a (quantitative) indication of the limits of biological plasticity (Calabrese, 2013c; Calabrese & Mattson, 2011). In contrast to the striking consistency in amplitude is the more variable width of the protective response. While there is considerable research describing mechanisms of the biphasic hormetic dose-response, these studies have not provided insight to factors that affect the magnitude or width of the stimulatory response. Thus, there is little understanding of how the amplitude of the hormetic response may be "regulated," or how it could be experimentally manipulated.

Assessment of other agents that evidenced protection against pathological effects in standard PD experimental models (but with typically more limited dose-range features) also showed a consistently similar maximum therapeutic effect in the 30–60% range (Levites et al., 2002; Nie, Cao, & Zhao, 2002; Soliman, Fathalla, & Moustafa, 2016). However, these experiments typically did not include a (broader) dose range that permitted more thorough evaluation of effects incurred at low(er) or high(er) doses (e.g., regressing toward the control group at lower doses, or becoming toxic and enhancing PD-like effects at higher concentrations) (Table 4).

The studies included in this report were chosen because they permitted assessment of an extended dose-response range (Table 5), and their dose-response features were fully consistent with those observed when using a priori evaluative criteria (Calabrese & Baldwin, 2001, 2003; Calabrese & Blain, 2005, 2011). Thus, the features seen in these PD studies conform to hormetic dose-response patterns. These observations have important clinical implications in that they suggest the potential benefit that such agents (theoretically) might afford. The induced protective responses seen in the PD models used are similar to those reported when preconditioning is employed in other biological systems, for other endpoints, and when using other inducing agents (Calabrese, 2016a, 2016b). Therefore, we posit that the quantitative dose-response features of these protective effects may be regarded as relatively generalizable.

An experimental approach to assess agents' capacity to prevent and/or slow the progression of PD-like effects involves the pretreatment of a model biological system (such as PC12 or SH-SY5Y cells) with the agents of interest. Pretreated cells are subsequently perfused with 6-OHDA, rotenone, paraquat, or other substances that induce a cellular stress and/or toxic response. In the majority of these experiments, by the end of the study, the control value (i.e., group treated only with the stressing agent) of cellular function decreased to about 40–60% of the original control (unexposed controls). The current literature does not provide information on the temporal changes in control values (i.e., after treatment with the stressing/toxic agent) until the end of the study. Hence, there is no information on the extent of recovery in the control group during the experimental period, nor is there information detailing the rate of injury/damage induced.

This experimental situation is complex, as the control group displays considerable induced damage that is presumed to be followed by

TABLE 1 Listing of hormetic Parkinson's disease treating agents

Agents	References
5,7-DHC	Kim et al. (2015)
6-OHDA	Lo et al. (2008)
9-me-BC	Hamann et al. (2008)
α-DHEC	Gille, Radad, Reichmann, and Rausch (2006)
Allicin	Zhou et al. (2014)
Antioxidants: GSH; NAC; DTT	Offen, Ziv, Sternin, Melamed, & Hochman (1996)
Apomorphine	Gassen et al. (1998a); Vaglini, Pardini, Viaggi, Caramelli, and Corsini (2008)
Berberine	Zhou et al. (2017)
Black tea	Levites et al. (2002)
BM	Singh, Murthy, and Ramassamy (2013)
Carnosic acid	Chen et al. (2012)
Citicoline	Radad, Gille, Xiaojing, Durany, and Rausch (2007)
CRE/Cyperia rhizome	Lee et al. (2010)
Creatine	Cunha et al. (2013)
Curcumin	Qualls, Brown, Ramlochansingh, Hurley, and Tizabi (2014)
Cyperi Rhizoma (CRE)	Lee et al. (2010)
Dopamine	Xiao-Qing et al. (2005)
Donepezil	Das and Tizabi (2009)
EGCG	Wang, Xu, Xu, and Chan (2009)
Estrogen	Ba et al. (2004)
Ginsenosides: Rb1; Rg3	Kim et al. (1998)
Ginsenoside Rb	Liu, Mao, Wang, Wang, and Xie (2015)
Glucose oxidase (GO)	He et al. (2011)
Green/black tea extracts	Levites et al. (2002)
H_2O_2	Xiao-Qing et al. (2005)
Hepad	Choi et al. (2015)
Isoborneol	Tian et al. (2007)
Isoquercitin	Magalingam, Radhakrishnan, and Haleagrahara (2014)
Lactacystin	Zhou, Xu, and Chen (2009)
L-Dopa	Zhong et al. (2014)
Lisuride	Gille et al. (2002a)
Lovastatin	Abdanipour, Tiraihi, Noori-Zadeh, Majdi, and Gosaili (2014)
Methamphetamine	El Ayadi and Zigmond (2011)
Mulberry juice	Kim et al. (2010)
Nicotine	Ryan and Loiacono (2001)
Oleoylethanolamide (OEA)	Galan-Rodriguez et al. (2009)
Orexin-A	Feng et al. (2014)
PCW	Park et al. (2009)
Pergolide	Gille et al. (2002b)
PRE/polygalae radix	Choi et al. (2011)

(Continues)

TABLE 1 (Continued)

Agents	References
PTS	Zhang et al. (2017a, 2017b)
Rapamycin	Radad, Moldzio, and Rausch (2015)
Rotenone	Yuyun et al. (2013)
Rotigotine	Radad, Scheller, Rausch, Reichmann, and Gille (2014)
Rutin	Magalingam, Radhakrishnan, and Haleagrahara (2013)
Salsolinol	Qualls et al. (2014)
SHXT	Lo, Shih, Tseng, and Hsu (2012)
Silymarin	Perez et al. (2014)
TBC	Lo et al. (2008)
Thymoquinone (TQ)	Radad, Moldzio, Taha, and Rausch (2009)
VIP	Offen et al. (2000)
Yi-Gan San	Doo et al. (2010a)
Zinc and manganese	Keller, Owens, Lai, and Devaud (2005)

recovery. However, cells pretreated with therapeutic agents may not be directly comparable to the control cells, as it is not possible to know whether reduction in damage is due to less insult induced, a greater capacity for repair/recovery, or some combination of both. This issue may be clinically relevant given that preventing damage would be an important consideration (and approach) for interventions in individuals who may be predisposed to PD. On the other hand, mitigating and/or prompting recovery from pathologic changes and effects would be important in the treatment of those who have already developed the disease.

Most published findings on hormetic responses for PD treatments employ time points, pairing of pretreatment and stressing agents, and delivery methods that render their protocols difficult for translational application (or perhaps even direct extrapolation) to clinical scenarios relevant to the prevention or therapeutics of PD (and other neurodegenerative disorders). Despite this, the fact that hormetic responses occur, and have been shown to exert neuroprotective and recuperative effects in in vitro, ex vivo, and in vivo models both compels the need for further and more detailed research, and maintains potential utility of hormetic approaches in therapeutic settings.

3.2 | Putative mechanisms

Any such research should also strive to elucidate and/or build upon prior studies of mechanism(s) of action and effect. Many of the studies

TABLE 2 Effect of therapeutic agents on Parkinson's disease model PC12: Width and amplitude of stimulation

References	PC12	Dose range (fold) stimulatory width	Amplitude (compared to control 100%)
Offen et al. (1996)	Antioxidants	≥ 10	160 (DTT); 275 (NAC), 275 (GSH)
Gassen et al. (1998a)	Apomorphine	715	60 (J)
Gassen, Pinchasi, and Youdim (1998b)	Apomorphine	14	200
Zhang et al. (2017a)	Berberine	80 NPC, PC	125, 125
Lee et al. (2010)	CRE	58	130
Levites et al. (2002)	Green/black tea	50 (GT); ~10 (BT)	155 (GT); 175 (BT)
Xiao-Qing et al. (2005)	H_2O_2	> 3	188
Magalingam et al. (2014)	Isoquercitin	≥ 10	250
Zhong et al. (2014)	L-dopa	~30	195
He et al. (2011)	Neuromelanin	< 20	118
Zhang et al. (2017a, 2017b)	PTS	~ 33, 66 PC	125, 233
Magalingam et al. (2013)	Rutin	> 10	210

TABLE 3 Effect of therapeutic agents on Parkinson's disease model SK-N-SH: Width and amplitude of stimulation

References	SK-N-SH Model	Dose range (fold) stimulatory width	Amplitude (compared to control 100%)
Chen et al. (2012)	Carnosic Acid	30	140
Cunha et al. (2013)	Creatine	50,000	155
Qualls et al. (2014)	Curcumin: Salsolinol	10	138
Qualls et al. (2014)	Curcumin: Rotenone	10	140
Das and Tizabi (2009)	Donapezil	$\geq$ 20	212
Ba et al., (2004); Wang et al. (2009)	EGCG	$\geq$ 10 (MTT); 100 (HtdR)	160 (MTT); 200 (HtdR)
Ba et al. (2004)	Estrogen	10^6	160
Tian et al. (2007)	Isoborneol	16	125
Zhou et al. (2009)	Lactacystin	10	135
Feng et al. (2014)	Orexin-A	> 4	135, 175, 175
Lo et al. (2008)	TBC	1000	29 (J), 172
Doo et al. (2010a, 2010b)	YGS	50	155

cited in the present paper demonstrating hormetic effects elucidate specific receptor- and/or organelle-based pathways. And while these papers reveal a broad range of mechanisms depending on the biological model and cell type, none defined mechanisms that may be operative in *both* stimulation and inhibition responses. For example, the same receptor may mediate a stimulatory *or* inhibitory effect; or may subserve stimulation *and* inhibition responses. As well, responses may involve activation of several intracellular (i.e., receptor-linked and nonreceptor-linked) pathways (Lo et al., 2008). Figure 1 principally represents hormetic dose responses in PD experimental models and primary tissue cultures mediating hormetic stimulatory responses for ~50 sample agents. Of particular interest is the similarity of quantitative features of the dose response, regardless of cell type or mechanism.

While it is understandable that investigators may tend to focus attention on the stimulatory/adaptive aspects of the dose-response in these neural models, an enhanced understanding of mechanisms

TABLE 4 Recovery dose response for studies with a limited dose response

References	Agent	Net increase protective response	Net (%)	Notes
Liu et al. (2015)	Allicin	45 -> 80	35	
Lo et al. (2012)	SHXT	21 -> 67	46	
Levites et al. (2002)	EGCG	40 -> 93	53	Protection drop off at higher dose
Sonsalla et al. (2012)	Caffeine	50 -> 95	45	Protection drop off at higher dose
Soliman et al. (2016)	Caffeine	60 -> 95	35	
Fu et al. (2014)	Acetylcorynoline	50 ->95	45	
Cunha et al. (2013)	Creatine	50 -> 80	30	
Tiong, Lu, and Bian (2010)	Hydrogen sulfide	48 -> 88	54	
Grunblatt, Mandel, Berkuzki, and Youdim (1999)	Apomorphine	32 (DA) -> 48; 43 (DOPAC) -> 58	16; 15	
Hara, Kamiya, and Adachi (2011)	Thapsigargin	50 -> 80	30	Protection drop off at higher dose
Singh et al. (2013)	BM	55 -> 80	25	
Guo, Li, Yu, and Chan (2013)	Luteolin	50 -> 90	40	
Park et al. (2009)	PCW	60 -> 85	25	
Nie et al. (2002)	GTPs; EGCG	60 (GTPs) -> 95; 60 (EGCG) -> 95	35; 35	

TABLE 5 Hormesis recovery dose response

References	Agent	% of original control value after stress (at conclusion of experiment) control group	% of original control value after treatment with protective and stress agents (at conclusion of experiment)	Relative increase (%) protective response as compared to control group (100%)
Ryan and Loiacono (2001)	Nicotine	41.6	81.5	196
Kim, Kim, Markelonis, and Oh (1998)	Rb1	~20% (estimate)	76.2	381
Kim et al. (1998)	Rb3	~20% (estimate)	67.3	336
Lo et al. (2008)	TBC	50	92	184
Qualls et al. (2014)	Curcumin	55 (Rotenone)	80	145
Qualls et al. (2014)	Curcumin	55 (Salsotinol)	78	142
El Ayadi and Zigmond (2011)	Meth	58	90 (ATP)	155
Zhang et al. (2017a, 2017b)	PTS	62	86	139
Ba et al. (2004)	Estrogen	48	78 (B)	162
Ba et al. (2004)	Estrogen	25	48 (C)	192
Ba et al. (2004)	Estrogen	10	30 (D)	300
Ba et al. (2004)	Estrogen	15	30 (E)	200
Chen et al. (2012)	Carnosic	46	78	169
Cunha et al. (2013)	Creatine	62	98	158
Doo et al. (2010b)	YGS	50	80	160
Galan-Rodriguez et al. (2009)	OEA	40	80	200
Lee et al. (2010)	CRE	45	60	133
Levites et al. (2002)	EGCG	33	52	157
Perez et al. (2014)	Silymarin	5	22	462
Tian et al. (2007)	Isoborneol	38	92	242
Wang et al. (2009)	EGCG	50	76	152
Wang et al. (2009)	EGCG	52	95 (H)	182
Zhang et al. (2017a, 2017b)	Berberine	60	80	133
Zhou et al. (2009)	Lactacystin	50	80	160

mediating the stimulatory *as well as* inhibitory components of the hormetic dose-responses is equally—and in some cases, arguably more—important (Calabrese, 2013a), which reiteratively suggests and supports the need for continued, and more detailed research.

4 | DISCUSSION

4.1 | Assessment of possible Parkinson's disease therapeutic agents via hormesis

A number of agents can significantly reduce damage in PD models when administered prior or concomitant to the stressing agent. As well, studies have shown some prevention or mitigation of PD-like effects when the potentially protective treatment was administered after the stressor agent (i.e., a type of postconditioning; Kim et al., 1998). However, there is insufficient experimental research to offer general conclusions on this latter effect. A diversity of agents is capable of affording neuroprotective effects, inclusive of both specific single compounds and complex mixtures. Regardless of the treatment or mechanisms (e.g., GSH increase, ATP stabilization/increase), the maximum extent of protection, and the patterns of response exhibited were similar to qualitative and quantitative features of the hormetic biphasic dose-response.

There was one study in which vasoactive intestinal peptide (VIP) was employed as chemoprotective pretreatment to prevent damage from two stressor compounds (i.e., salsolinol and rotenone) that were simultaneously administered (Qualls et al., 2014). In this study, pretreatment prevented damage induced by both agents in a pattern consistent with the hormetic dose-response. However, another paper revealed that salsolinol protected against rotenone but not 6-OHDA (Offen et al., 2000). Yet, in another study on the treatment of nicotine and donepezil an additive protective response was observed (Das & Tizabi,

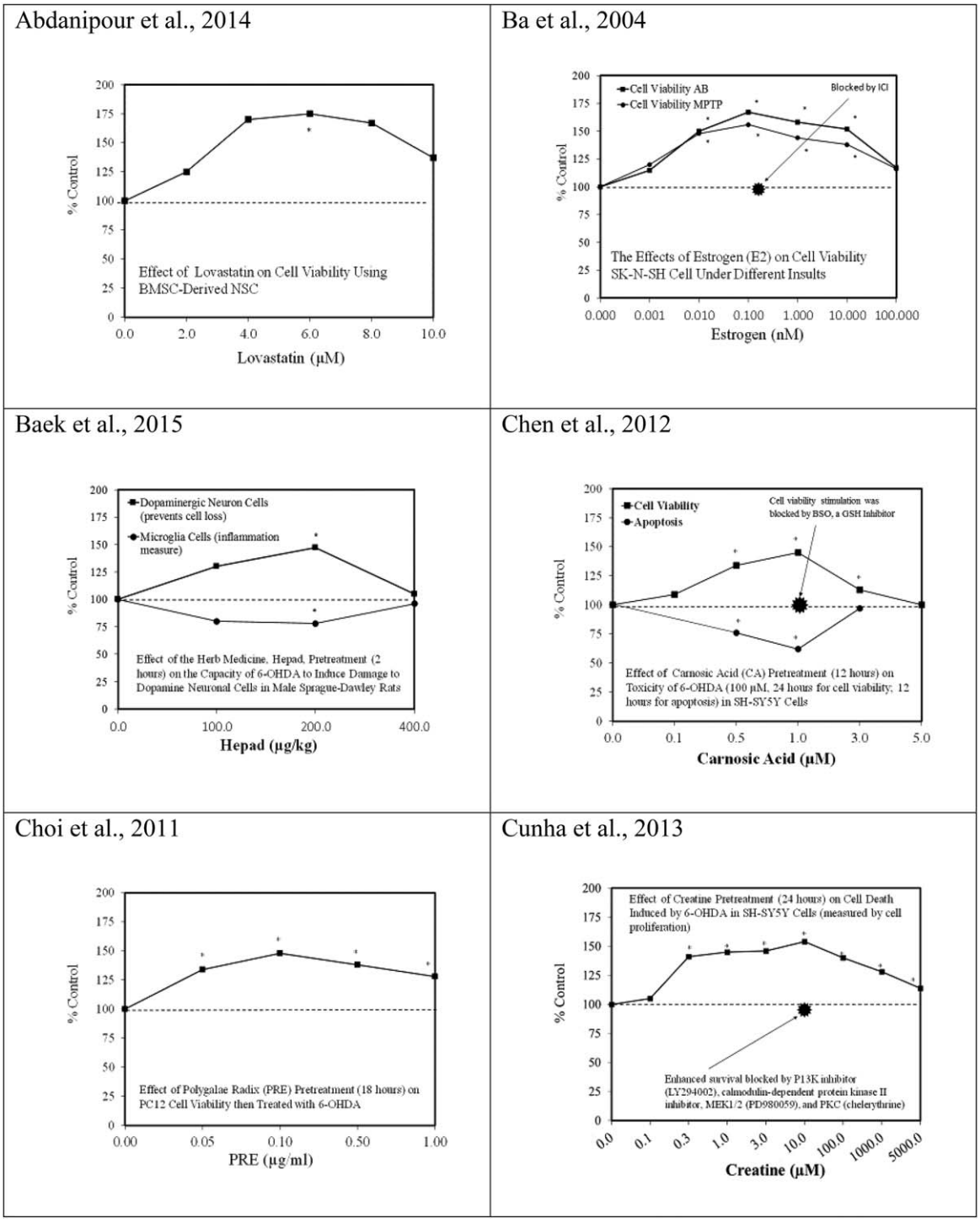


FIGURE 1 Hormetic dose responses in Parkinson's disease and related experimental models. ✸= mechanism

2009). It is interesting to note that many of the agents that offer protection against damage in multiple PD models have also been evaluated for their capacity to affect other neurodegenerative diseases (e.g., AD and Huntington's disease), often with comparable success—especially when the underlying mechanism appears to involve upregulation of antioxidant responses (e.g., increases in GSH and ATP). These findings suggest that by exerting hormetic responses, several agents may have potential to prevent or reduce PD-like effects. These agents produced stimulatory effects in the range of 30–60%, and produced inhibition at higher doses. The effective dose range was found to be highly variable. This variability is important, as the optimal dose may be relatively close to a (high) dose that is ineffective and/or toxic. Given the often considerable interindividual diversity in response to pharmacological agents, this variability in dose range would need to be considered and evaluated in any attempt to translate experimental findings to clinical applications.

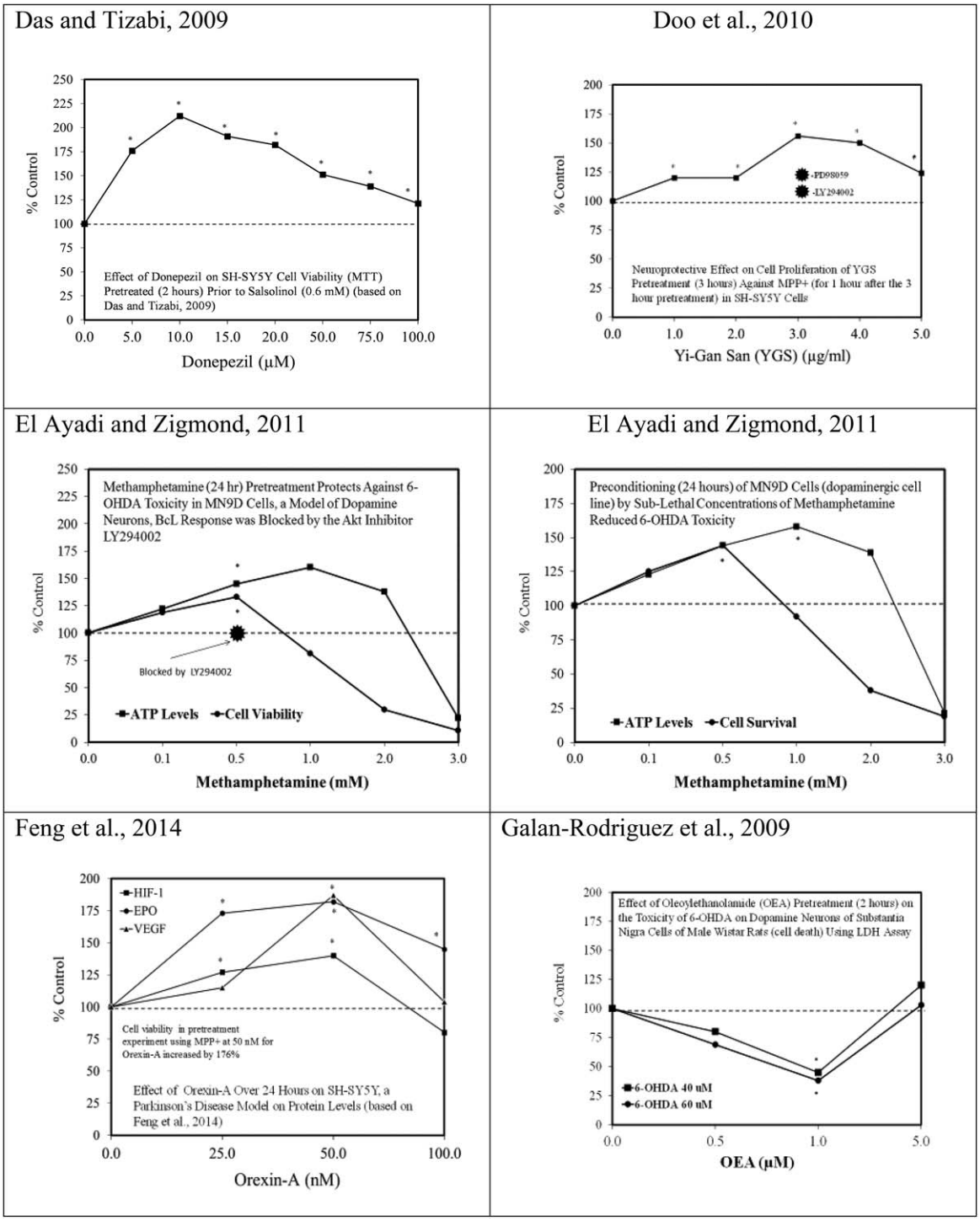
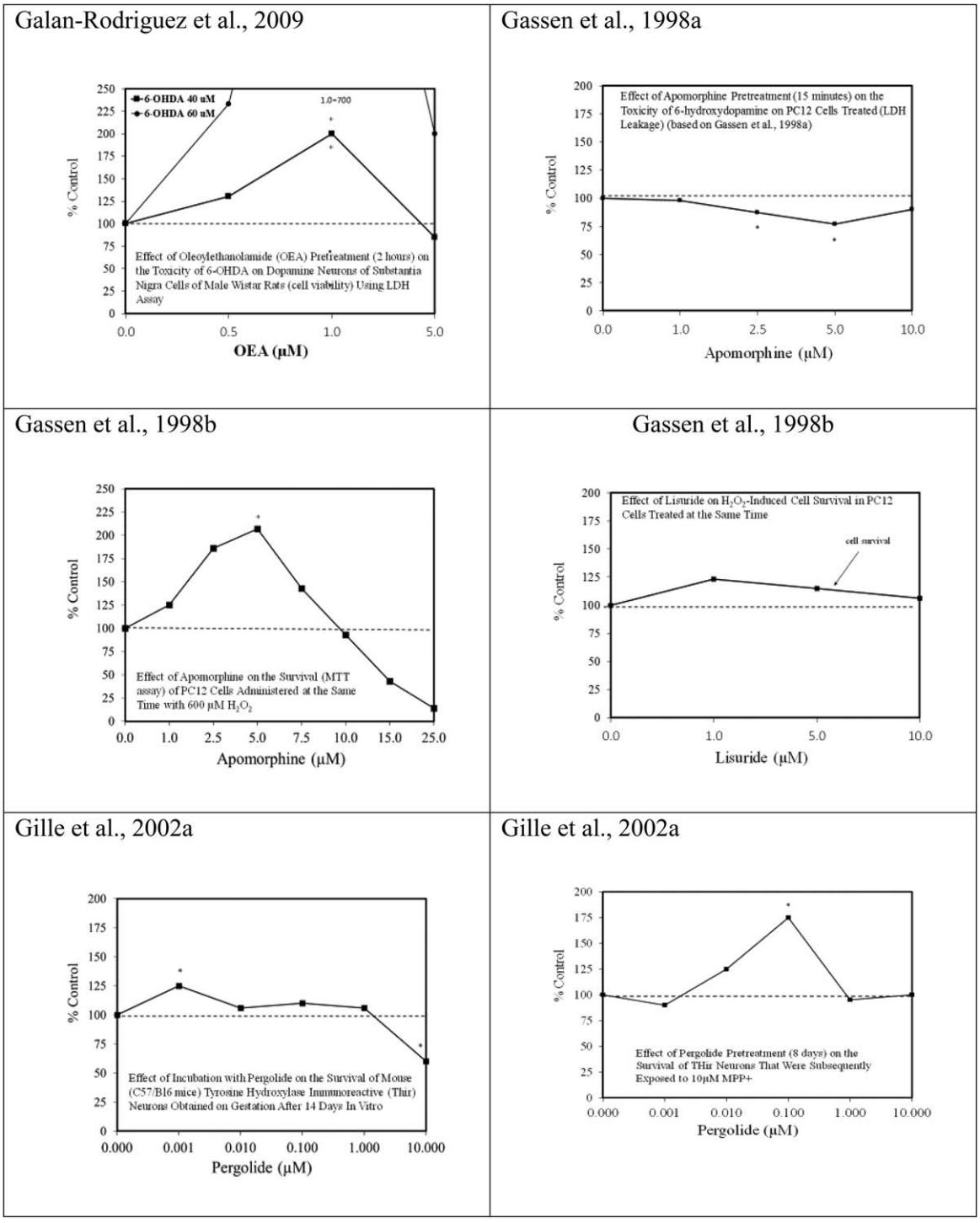


FIGURE 1 (Continued)

4.2 | Hormesis and resilience: Toward a broader perspective, goal, and role

We maintain that findings demonstrating the activity and mechanisms of hormetic dose-responses warrant further consideration. Hormetic mechanisms may be operative in, and therefore might be clinically accessed for induction of biological resilience. Resilience, the ability to adequately respond to allostatic loads and perturbations, is regarded as a fundamental component of positive adaptability in dynamic, nonlinear biological systems (Holland, 1992; Holling. 1973). Multiple factors, (e.g., genetics, environment, trauma) during prenatal and adolescent development have been shown to both affect and be affected by the capacity for resilience, and to influence health and susceptibility to disease and dysfunction (Gallopin, 2006; McEwen, 2003; Varadhan, Seplaki, Xue, Bandeen-Roche, & Fried, 2008). Thus, there is increasing



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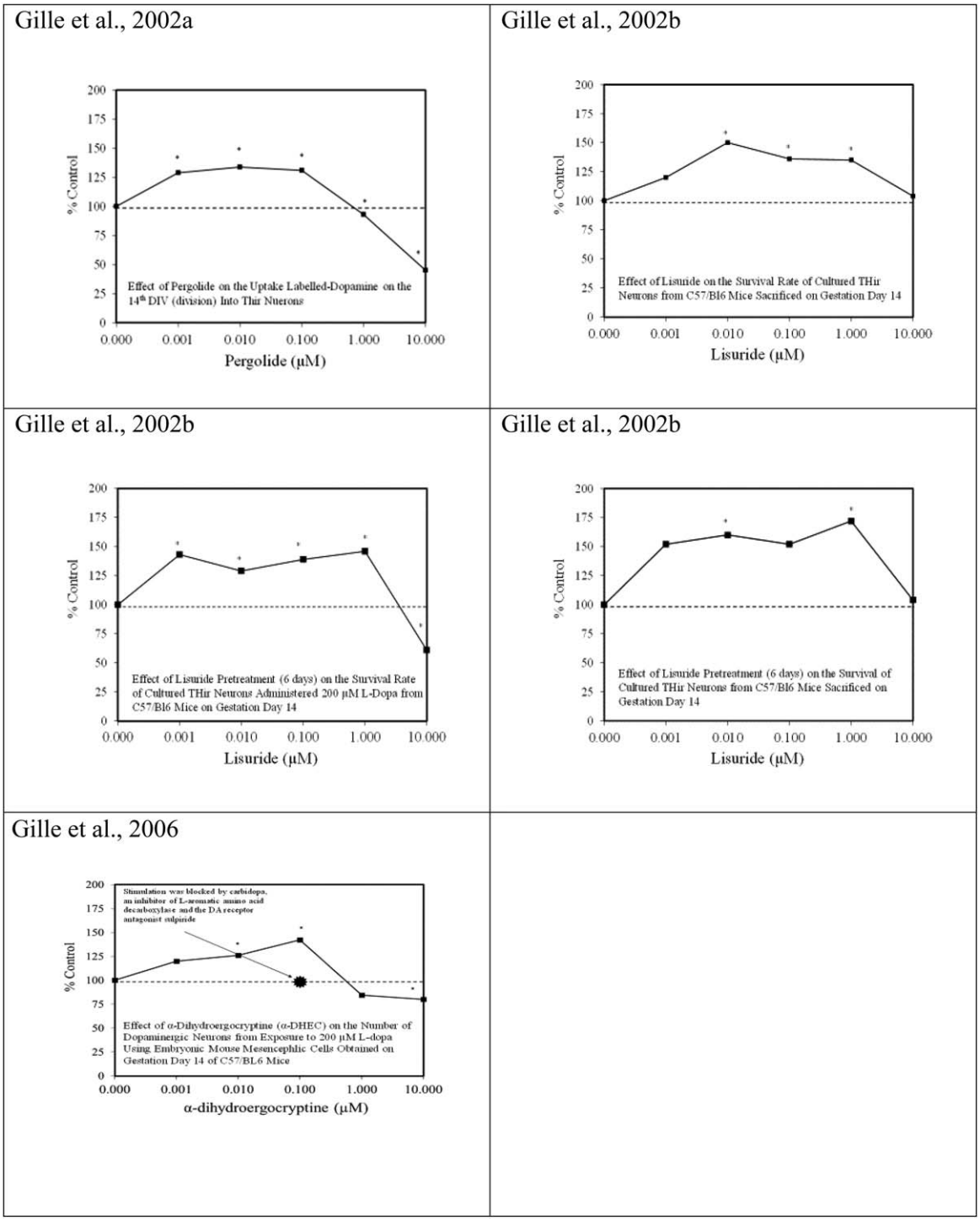
interest in gaining improved understanding of cellular mechanisms of resilience, and to translate this knowledge into approaches toward promoting health and resistance to insult and injury. Cellular resilience entails metabolic and signaling mechanisms that enable recovery and adaptive processes following stress.

Resilient phenotypes will typically conform to the quantitative and temporal features of the hormetic dose–time response relationship, often within a preconditioning context. While the amplitude of induced resilience is modest, such processes may incur relatively durable effects as a consequence of the type and extent of preconditioning (Gidday, 2015). We propose that such hormetic responses may be important to improving clinical approaches to neurodegenerative disorders. For example, given that the onset and progression of PD are age-dependent, engaging preconditioning methods "early and often" may



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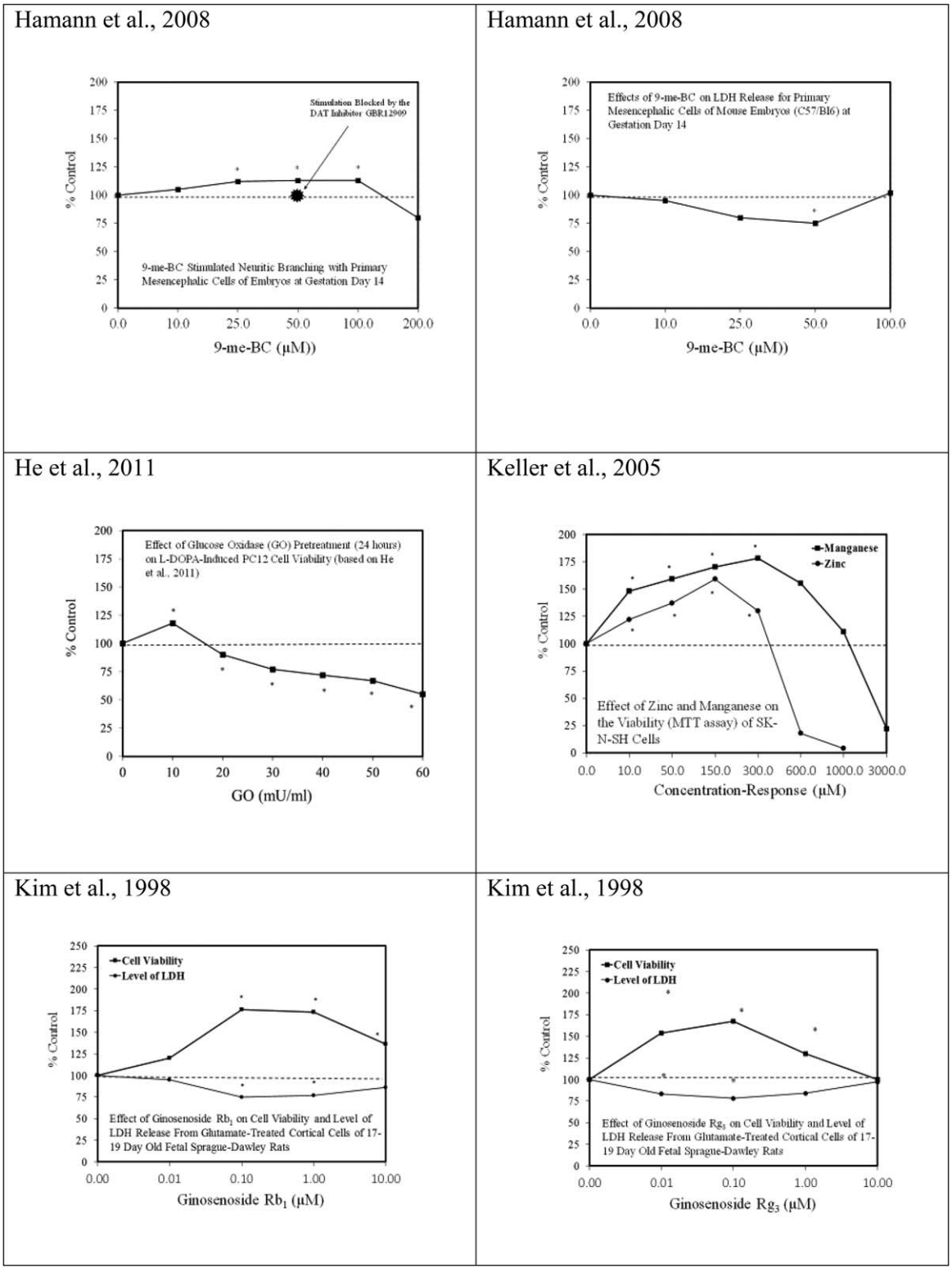
prove to be of value in individuals who have been identified with disease diatheses, and/or who are in prodromal or early phases of the disease process. This is of note given that preconditioning-induced hormetic resilience has been shown to decrease with age in a variety of animal models (although some success has been achieved in restoring these functions via exercise, dietary modification, and pharmacological interventions; Calabrese, 2016c; Calabrese et al., 2015).

The question remains as to whether, and to what extent preconditioning methods can and should be used in the treatment of PD and other neurodegenerative conditions. As well, it will be important to further explore and define those ways that hormetic responses can be engaged to optimize function and protection in neural systems, so as to maximize the effectiveness of existing and newly developing therapeutics (e.g., novel pharmacological agents; noninvasive and invasive brain



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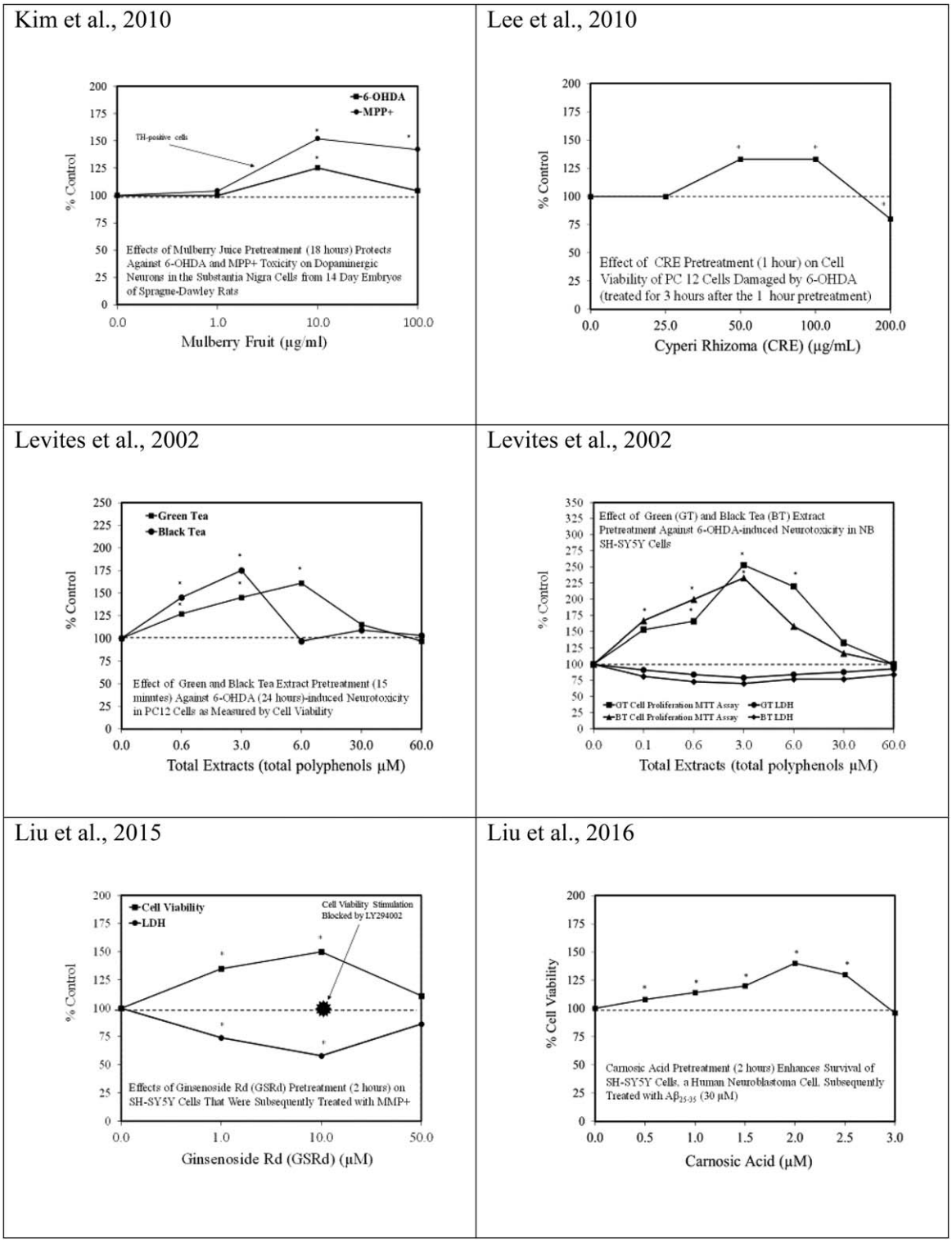
stimulation). To date, the pharmacological treatment of PD is still mostly reliant upon the use of levodopa, some 50 years after its introduction for the therapeutic management of Parkinsonian patients. Levodopa therapy is characterized by a strong symptomatic effect on motor symptoms and, at certain levels, could act following hormetic properties. For instance, the possibility to induce and maintain the so-called "long-duration response" (Quattrone et al., 1995; Zappia et al., 1999) that is a sustained clinical benefit appearing days or weeks after



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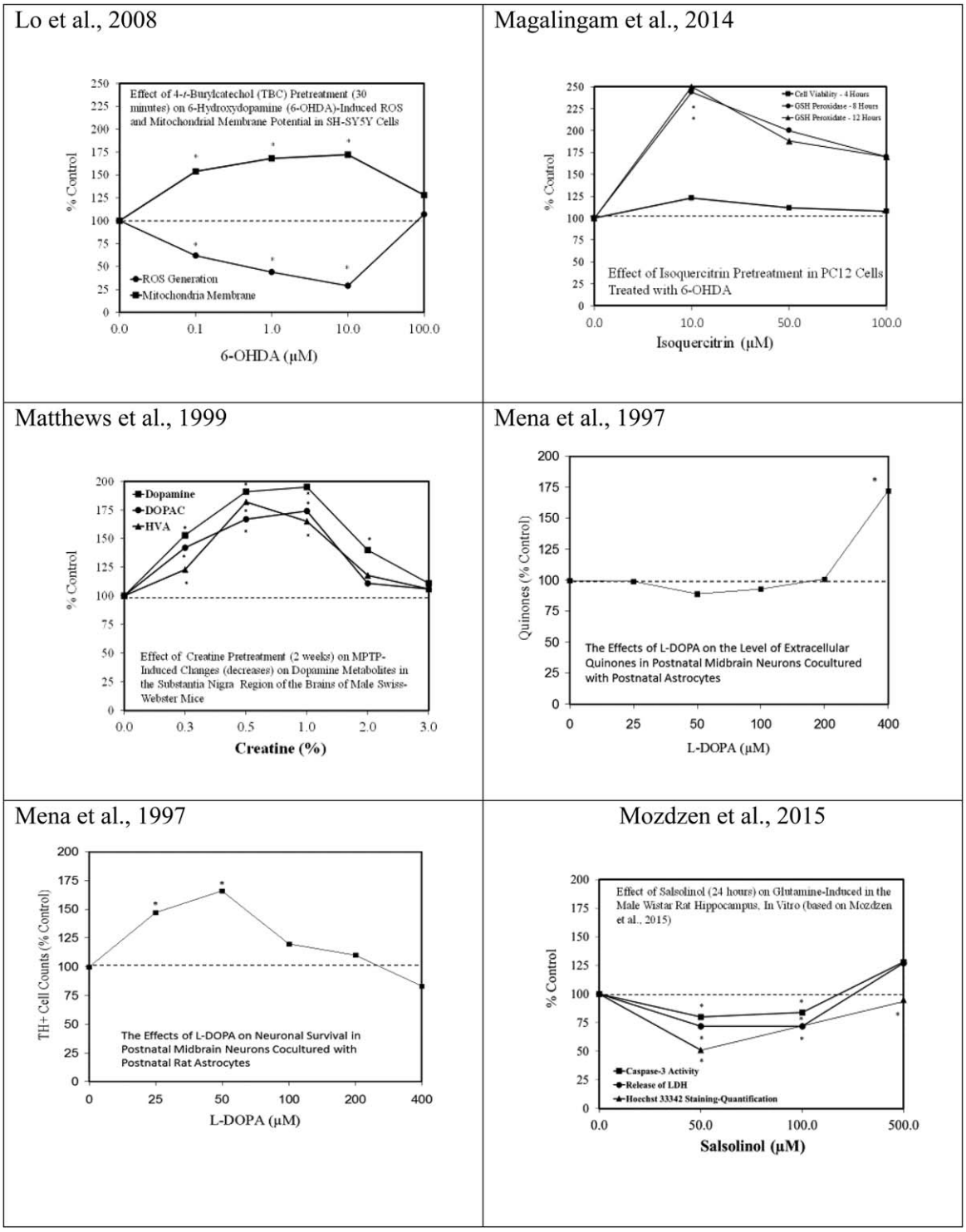
beginning the treatment, is mainly due to the administration of low cumulative doses of levodopa, whereas higher dosages may have detrimental effects (Zappia et al., 2000). Furthermore, it is well known that levodopa may influence complex cognitive functions, such as working memory and cognitive control that are mediated by mesocortical dopaminergic pathways (Miller & Cohen, 2001). Additionally, the effects of levodopa could be recognized as a hormetic-U-shaped dose-response, in light of the (low dose-induced) improvements as well as (high dose-induced) impairments observed (Cools & D'Esposito, 2011).



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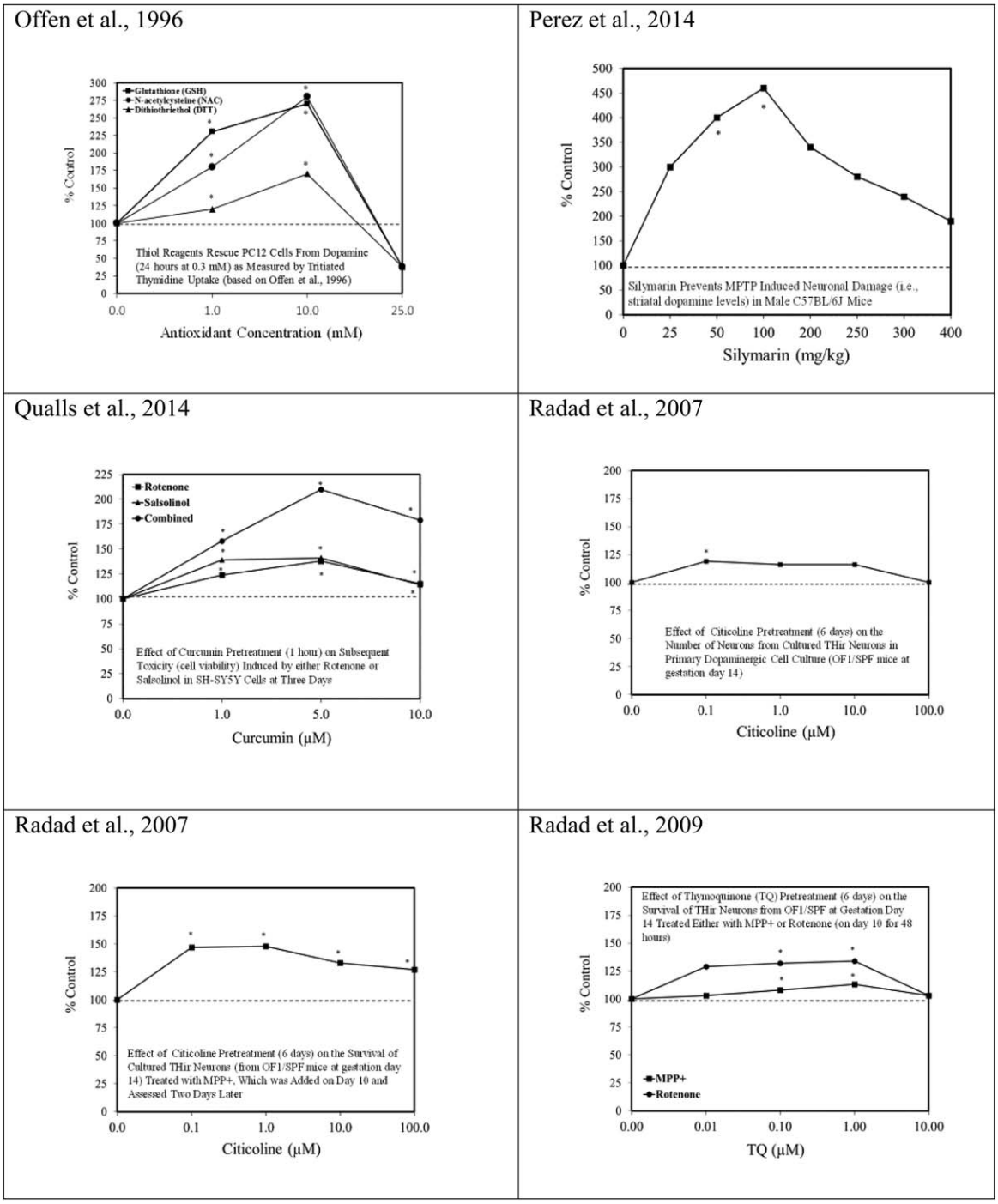
Recent research demonstrates that neuroinflammatory events play a critical role in the progression of PD. Such processes involve activated proinflammatory microglial M1 phenotype via cytokine production. Studies have shown that progression of PD can be mitigated and in some instances reversed via neuroprotective agents (e.g., donepezil; rosiglitazone) that exert hormetic dose-responses to induce microglia to express and sustain the anti-inflammatory M2 phenotype (Chen, Hou, Xu, & Wu, 2015; Pisanu et al., 2014). Moreover, hormetic biphasic dose-responses may be involved in the process of macrophage reprogramming and polarization that is produced by chemicals, as well



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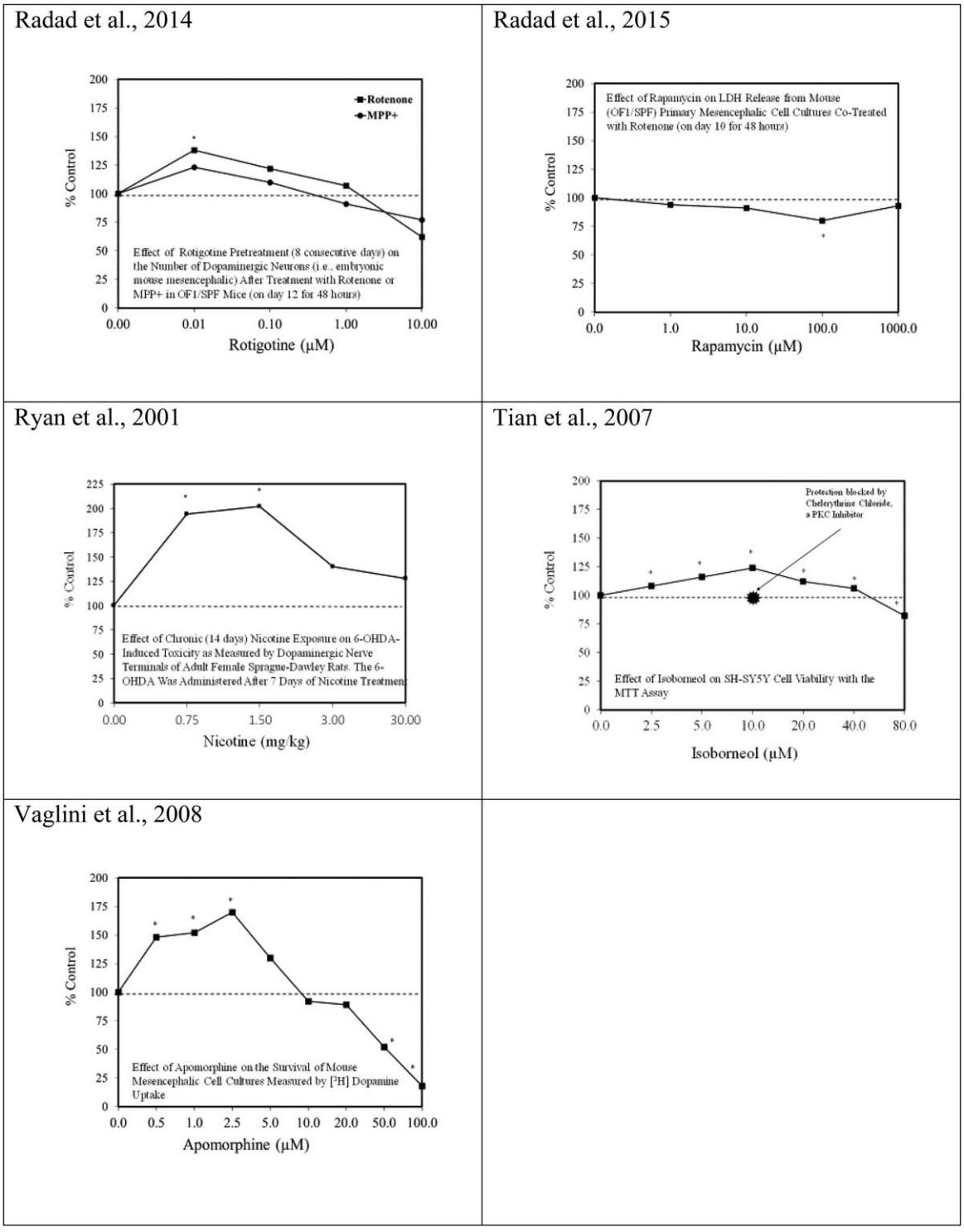
as ionizing radiation (Genard, Lucas & Michiels, 2017; Walton, 2017; Wu et al., 2017). Other studies have shown that preconditioning-induced protection responses are associated with increased M2 polarization across multiple organs/cell types (e.g., bone, Young et al., 2009; spinal cord, Hayakawa et al., 2014; mesenchymal stem cells, Lin et al., 2017, Mountziaris, Tzouanas, & Mikos, 2010; Kidney, Hato et al., 2015) reflecting the generality of the adaptive strategy. These findings suggest that hormetic mechanisms may play a role in mediating M1 or M2 macrophagic cell (e.g., microglial) phenotypes that respectively mediate pro and/or anti-inflammatory functions that are likely operative in pathologic and adaptive processes.

We propose that further studies of hormesis, preconditioning, and resilience will be vital to ongoing international efforts in translational neuroscience (e.g., the European Union Human Brain Project, U.S. Brain Research through Advancing Innovative Neurotechnology [BRAIN] initiative; China Brain Project; etc.) that are focused, to some extent, upon



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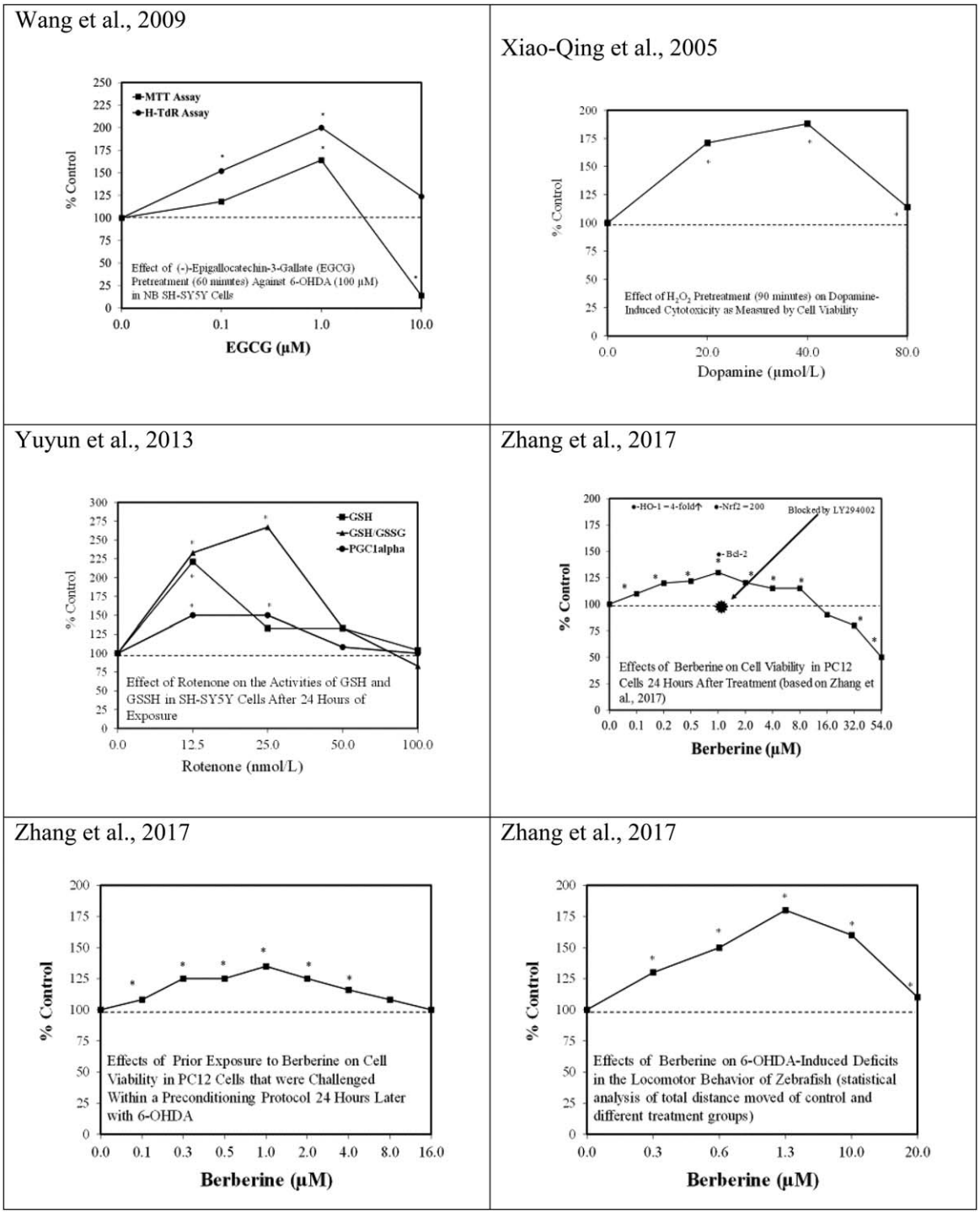

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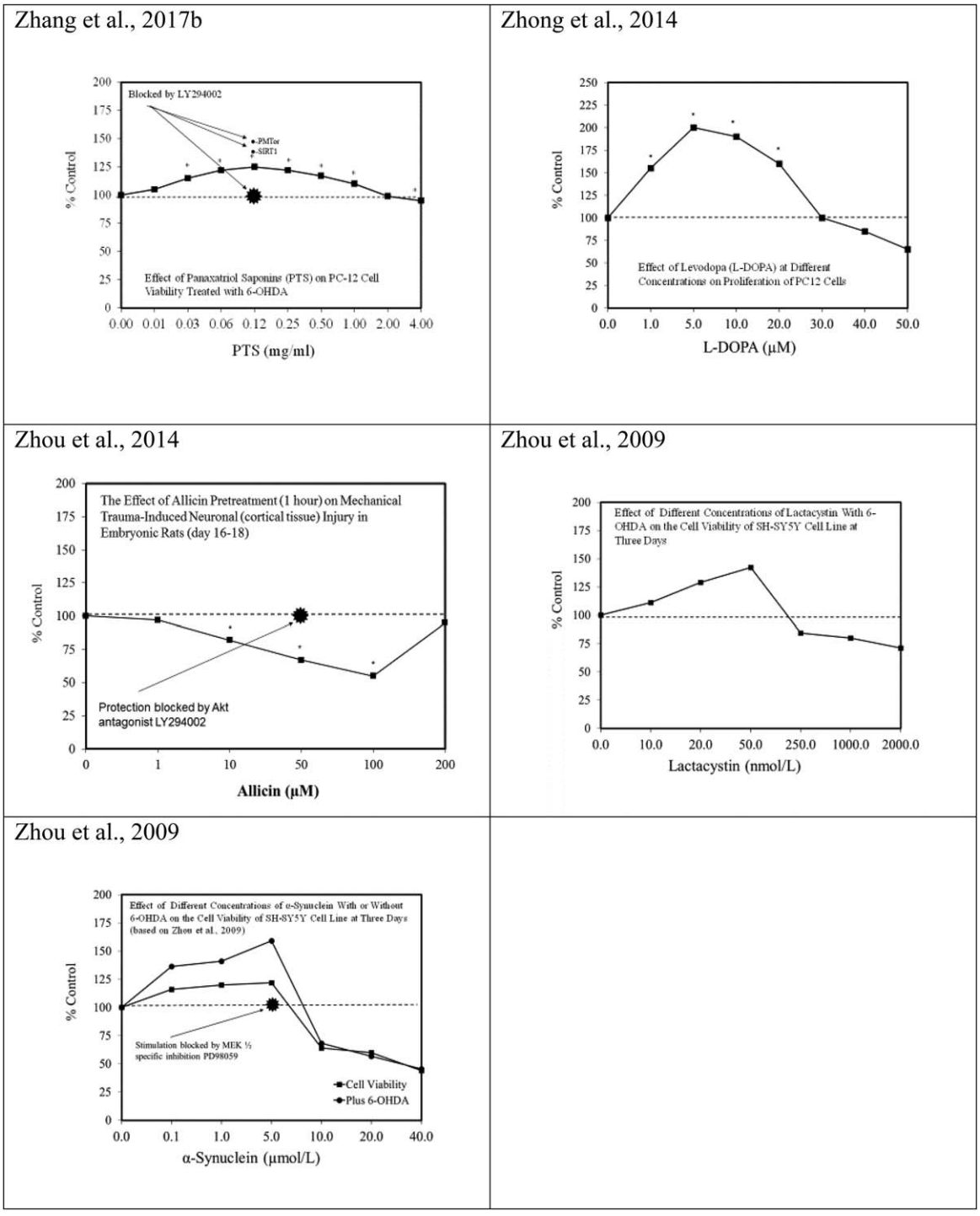

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improving diagnosis, treatment, and/or prevention of neuropsychiatric disease and injury. Indeed, a further understanding of hormesis may foster increased capability to harness subtle, yet potent mechanisms of physiological adaptation, which may enable a synergistic approach to clinical intervention(s) to allow more effective, efficient, and affordable care. The integration, optimization, and personalization of such treatments pose both a challenge and opportunity to the biomedical sciences and clinical medicine, to which our group remains dedicated.

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AUTHORS' CONTRIBUTIONS

All authors had full access to the study and take responsibility for the integrity and the accuracy of the study concept and design. *Drafting of the manuscript*: VC, AS, ATS, SM, MS, FA, DM, JG, MZ, CF, EJC. *Critical revision of the manuscript for important intellectual content*: VC, EJC and JG. *Study supervision*: VC and EJC. All authors read and approved the final manuscript.

NOTE

[1]The data used to construct the figures of hormetic dose responses were obtained via a search of the current (2018) hormesis database (Calabrese & Blain, 2005, 2011). These two references provide the reader with a detailed description of the methodology of the evaluative criteria (e.g., study design, statistical analysis, study replication criteria, and other criteria), and a description of the nearly 40 fields of information obtained from each of the dose response entries into the hormesis database (Calabrese & Blain, 2005, 2011). The hormesis database is continuously expanded on a weekly basis. The database has been complemented with several other hormesis databases designed to estimate the frequency of hormesis in the toxicological and pharmacological literature via the use of a priori and evaluative criteria (Calabrese & Baldwin 2003; Calabrese, Staudenmayer, Stanek, & Hoffmann, 2006; Calabrese, Stanek, Nascarella, & Hoffmann, 2008; Calabrese, Hoffmann, Stanek, & Nascarella, 2010).

CONFLICT OF INTEREST

There is no conflict of interest to declare.

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