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PubMed Evidence on ACD856 and its Cognitive and Health-Promoting Effects

Introduction

ACD856 (also called ACD-856) is a small-molecule positive allosteric modulator of tropomyosin receptor kinase (Trk) receptors. Trk receptors are activated by neurotrophins such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF). These neurotrophins play key roles in neuron survival and plasticity, and their signaling is often impaired in Alzheimer's disease and other cognitive disorders. ACD856 was developed after the earlier compound ACD855 (ponazuril) was found to have a very long half-life in humans [1]. ACD856 has improved pharmacokinetics and potency and is being explored as a symptomatic and potentially disease-modifying therapy for Alzheimer's disease, depression and other conditions where cognition is impaired [2].

Mechanism of Action

- **Positive allosteric modulation of Trk receptors:** In vitro experiments demonstrated that ACD856 binds to TrkA and TrkB receptors and increases their catalytic efficiency without changing the affinity of NGF or BDNF for the receptor. In U2OS/TrkA cells, ACD856 potentiated NGF-induced signaling and even showed partial agonistic activity in the absence of ligand [3]. In SH-SY5Y cells overexpressing TrkB, treatment with BDNF plus ACD856 increased TrkB phosphorylation and downstream ERK1/2 activation, indicating enhanced signal transduction [4].
- **Neurotrophic and neuroprotective effects:** ACD856 enhanced neurite outgrowth in NGF-treated PC12 cells, increased SNAP25 (a presynaptic protein) and up-regulated BDNF in primary cortical neurons [5]. It provided neuroprotection against amyloid-β toxicity and energy deprivation by boosting neuronal metabolic adaptations and increasing ATP levels [6].
- **Selective modulation:** Compared with related receptor tyrosine kinases such as IGF1R and FGFR1, ACD856 showed higher efficacy at TrkA/TrkB/TrkC receptors and thus appears relatively selective for neurotrophin receptors [7].

These mechanistic findings suggest that ACD856 augments neurotrophin signaling, leading to improved synaptic plasticity, neuroprotection and increased BDNF production. Such effects underlie the compound's cognitive and mood-related benefits.

Preclinical Evidence for Cognitive and Nootropic Effects

Improved Memory and Cognitive Performance

- **Reversal of chemically-induced amnesia:** In passive avoidance tasks, scopolamine or MK-801 impaired memory in mice. A single subcutaneous dose of ACD856 (0.3 mg/kg) or repeated doses of the related ACD855 significantly reversed the scopolamine- and MK-801-induced memory deficits. The pro-cognitive effects were dose-dependent and were blocked by ANA-12, a TrkB antagonist,

indicating TrkB-dependent mechanisms [8]. Combined administration of low-dose ACD856 with the acetylcholinesterase inhibitor physostigmine showed additive reversal of scopolamine-induced impairment [9].

- **Restoration of age-related cognitive decline:** In 18-month-old mice with natural memory decline, a single treatment with ACD856 restored cognitive performance to levels comparable to 2-month-old mice [10]. This finding implies that the compound can enhance memory even in the absence of induced deficits.

- **Impact on different memory phases:** Experiments dosing ACD856 before training, after training or before testing showed that the compound significantly improved acquisition, consolidation and retrieval of memories in scopolamine-impaired mice [11]. These results indicate that ACD856 can support multiple stages of memory formation.

Antidepressant-Like Activity and Mood Regulation

- Repeated administration of ACD856 in rodents produced sustained antidepressant-like effects. After five daily doses, mice exhibited reduced immobility in the forced swim test even seven days after the last dose, indicating long-lasting mood-enhancing effects [12]. These effects lasted longer than those observed with ketamine.

- The antidepressant effect coincided with increased BDNF levels in the cortex and hippocampus of aged mice [13]. Elevated BDNF is known to promote synaptic plasticity and resilience and may explain the persistence of mood improvements.

Neuroprotection and Metabolic Adaptation

- ACD856 protected neurons against amyloid-β-induced synaptotoxicity and against energy deprivation. Treated neurons showed higher metabolic activity and shifted to glutamine-driven mitochondrial metabolism, which may reduce excitotoxic stress and support brain regions vulnerable to hypoglycemia [14].

- In aged mice, treatment with ACD856 increased BDNF levels in the brain [13]. Since BDNF declines with age and is associated with hippocampal atrophy and memory impairment, up-regulating BDNF may help maintain brain health and cognitive functions.

Enhancement of Cholinergic and Synaptic Function

- The earlier compound ACD855 increased hippocampal acetylcholine levels by ~40 % and facilitated long-term potentiation (LTP) in rat hippocampal slices. Both ACD855 and ACD856 acted as cognitive enhancers in TrkB-dependent behavioral models [15].

- These effects were synergistic with physostigmine (an acetylcholinesterase inhibitor), suggesting that positive modulation of neurotrophin signaling could augment cholinergic neurotransmission [9].

Neuroprotective and Disease-Modifying Properties

The preclinical results indicate that ACD856 is more than a symptomatic cognitive enhancer. Key findings include:

- **Increased neurotrophin production:** ACD856 increased BDNF levels both in vitro and in aged mice [16], implying a feed-forward mechanism whereby enhanced Trk signaling stimulates BDNF production and further supports neuroplasticity.

- **Neuronal resilience:** By boosting ATP production and supporting glutamine-driven metabolism, ACD856 helped neurons withstand energy deprivation [14].

- **Protection against Alzheimer's pathology:** The compound reduced amyloid-β–induced synaptotoxicity in primary neurons [14]. Such neuroprotective effects could slow synaptic loss and disease progression in Alzheimer's disease.

Together these observations suggest that ACD856 may exert disease-modifying effects by protecting neurons, promoting neuroplasticity and elevating endogenous neurotrophin levels.

Human Trials: Safety, Pharmacokinetics and Early Signals

Single Ascending Dose and Microdose Studies

A first-in-human program assessed ACD856 through an intravenous microdose study followed by an oral single ascending dose study in healthy subjects. Key findings were:

- **Pharmacokinetics:** In the microdose study, ACD856 exhibited a bi-exponential plasma decline with a terminal half-life of about 20 h, low plasma clearance and a low volume of distribution [17]. Oral administration showed rapid absorption, almost complete bioavailability and dose-proportional exposure [18]. Food slowed absorption and reduced peak concentration but had little effect on half-life or overall bioavailability [19].

- **Safety and tolerability:** No treatment-emergent or dose-related adverse events were observed in either study [20]. Liver enzyme elevations in one participant were attributed to intense weightlifting rather than the drug [21]. Overall, ACD856 was well tolerated at single oral doses up to 150 mg.

- **Comparison to ACD855:** The predecessor ACD855 had an elimination half-life in humans of ~68 days and was deemed unsuitable for development. ACD856 was selected because in vitro and animal pharmacokinetic data predicted a shorter half-life, which the microdose study confirmed [22].

Clinical Implications

The initial trials show that ACD856 is orally bioavailable, has a manageable half-life allowing once-daily dosing and appears safe in healthy subjects [23]. A follow-up multiple-ascending-dose study and quantitative electroencephalography assessment (not publicly available at full length) reportedly found no

safety issues and showed dose-dependent changes in EEG parameters consistent with central nervous system activity. These findings support further clinical evaluation in cognitive disorders.

Indications Beyond Alzheimer's Disease

While ACD856 is primarily being developed as a symptomatic and disease-modifying treatment for Alzheimer's disease, the drug's mechanism suggests broader utility:

- **Depression and mood disorders:** Sustained antidepressant-like effects and BDNF up-regulation in rodent models indicate potential efficacy in depressive disorders [12].

- **Cognitive impairment in other conditions:** The review article on positive allosteric modulators notes that ACD856 is being developed for depression, other psychiatric conditions, Parkinson's disease, traumatic brain injury and sleep disorders, all of which involve cognitive dysfunction [2]. Enhanced neurotrophin signaling could improve learning and memory across these conditions.

- **General nootropic and health-boosting properties:** By elevating BDNF, enhancing cholinergic function and promoting neuroplasticity, ACD856 may act as a general cognitive enhancer. Preclinical studies indicate improved energy metabolism and resilience to metabolic stress [14]. These properties suggest potential benefits for healthy individuals or those with age-related cognitive decline, though such use has not been formally tested in humans.

Limitations and Future Directions

- **Preclinical focus:** Most evidence for ACD856's cognitive enhancement and neuroprotective effects comes from in vitro or rodent studies. Translation to human cognitive benefit remains to be demonstrated in larger clinical trials.

- **Small early trials:** The Phase I studies involved small numbers of healthy subjects, limiting conclusions about safety and efficacy in patients with cognitive disorders [24]. Phase II trials will need to assess cognitive outcomes, mood and disease progression in patients.

- **Mechanistic complexity:** Trk receptor signaling is involved in many pathways. Positive modulation may have unforeseen effects, and long-term safety requires monitoring. Additionally, the chemical structure of ACD856 is undisclosed and off-target effects need evaluation.

Conclusion

ACD856 is a novel triazinetrione that acts as a positive allosteric modulator of TrkA/TrkB/TrkC receptors. Preclinical studies show that the compound enhances neurotrophin signaling, increases BDNF levels, promotes neurite outgrowth and provides neuroprotection against amyloid-β toxicity and metabolic stress [25]. These actions translate into improved memory, reversal of chemically induced amnesia, restoration of age-related cognitive deficits and sustained antidepressant-like effects in animal models [8] [12]. ACD856 also augments cholinergic neurotransmission and long-term potentiation, suggesting broad nootropic potential [15].

Early clinical trials indicate that ACD856 is safe, well tolerated and orally bioavailable with a manageable half-life [17]. The compound is positioned as both a symptomatic cognitive enhancer and a potential disease-modifying therapy for Alzheimer's disease and other cognitive disorders [26]. Its ability to enhance neuroplasticity and up-regulate BDNF may provide health-boosting benefits beyond Alzheimer's disease, including antidepressant effects and improved resilience to brain stressors. However, large randomized trials are needed to confirm efficacy, determine optimal dosing and assess long-term safety in humans.

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