AD/PD 2024
March 5-9

ACD856 is a biased positive allosteric modulator of Trk-receptors - enhances neurite outgrowth but do not affect pain signaling

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Background

The neurotrophins BDNF and NGF have been studied extensively and have important roles in neuronal survival, differentiation, neurogenesis, and synaptic plasticity, making these mechanisms of high interest for therapeutic development within Alzheimer's disease [1-3]. However, NGF and BDNF are also involved in other functions such as pain signaling. This broad range of effects is a result of a complex downstream signaling pathway diversifying their physiological effects.

Aim

The aim of these studies was to explore if ACD856, a novel positive allosteric modulator of Trk-receptors currently in clinical development for the treatment of Alzheimer's disease, showed any selectivity for different Trk-signaling pathways including, neurite outgrowth, cognition and pain signaling.

Methods

Primary mouse cortical neurons were treated with ACD856 and neurite outgrowth, as measured by neurite total length, was studied by immunocytochemistry. The effects of ACD856 on memory was investigated using scopolamine-induced memory impairment in the passive avoidance model. Effects of ACD856 on pain signaling was assessed using the Hargreave's plantar test measuring heat allodynia in male Sprague-Dawley rats.

Figure 1. ACD856 induce neurite outgrowth in cortical neurons

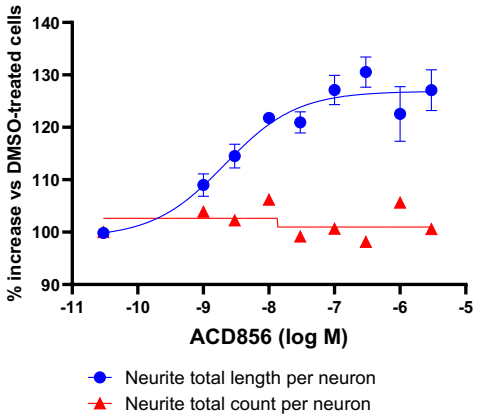


Figure 1. Primary mouse cortical neurons were treated with ACD856 for 4 days. Cells were fixed with PFA and neurites were stained with rabbit anti-mouse Tubulin III antibody. Identification and quantification of neurites were performed by automated fluorescence microscopy using a ArrayScan V from ThermoFisher. Results for neurite total length per neuron is the mean from six technical replicates (in each preparation) +/- range from two independent preparations of cortical neurons.

Figure 2. ACD856 reverses scopolamine-induced memory impairment

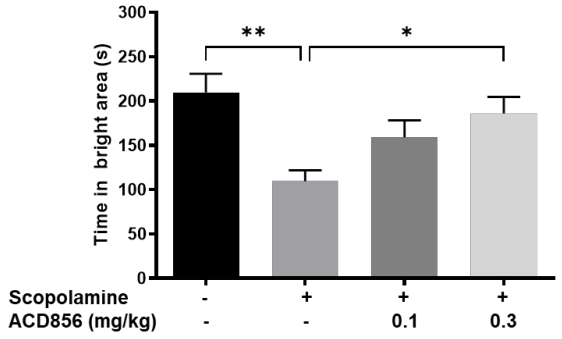
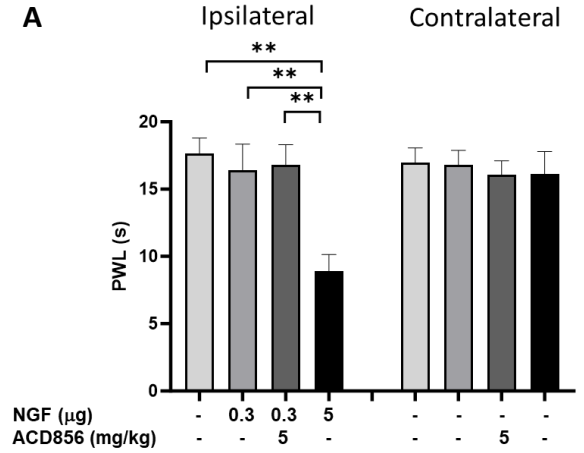


Figure 2. ACD856 was administered as a single s.c. dose at 0.1 or 0.3 60 min prior to the experiment, in combination with scopolamine (0.3 mg/kg, s.c.). ACD856 reversed scopolamine-induced memory impairment at the indicated doses. *p < 0.05 or ** p < 0.01 for scopolamine treated animals vs the control group or ACD856-treated animals.

Figure 3. ACD856 does not induce heat allodynia



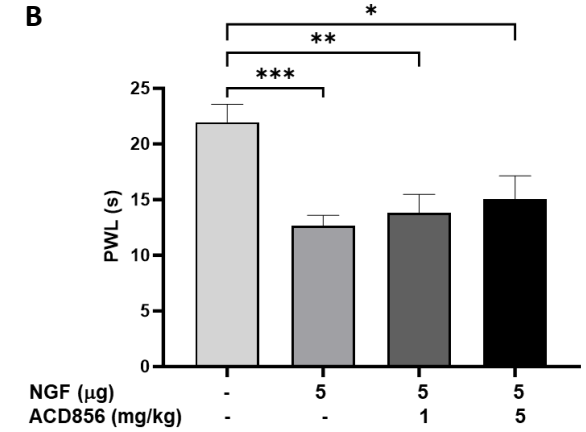


Figure 3. Animals were treated with ACD856 (1 and 5mg/kg) or vehicle repeatedly for 4 days by oral gavage. On the day of the Hargreave's test, animals were administered ACD856 orally 1h prior to the test. To induce thermal sensitivity, nerve growth factor (NGF) or vehicle (PBS), was given as an intra plantar injection into the animal's left hind paw (ipsilateral). A thermal stimulus (infrared beam) was applied to the plantar surface of both the left (ipsilateral) and right (contralateral) hind paw and the paw withdrawal latency (PWL) was assessed in both the ipsilateral (ILP) and contralateral (CLP) hind paw of each rat.

Results

ACD856 enhances neurite outgrowth in mouse primary cortical neurons (Fig. 1). Interestingly, ACD856 promoted extension of neurites rather than initiation of new processes using cortical neurons. In vivo experiments demonstrate that ACD856 significantly and almost fully revert scopolamine-induced memory impairments in mice in the passive avoidance (PA) model (Fig 2). Interestingly, results from Hargreave's plantar test in rats showed that ACD856 does not exacerbate heat allodynia induced by either a low (0.3µg) (Fig 3A) or high dose (5 µg) (Fig. 3B) of NGF nor does it induce heat allodynia by itself as judged by the effects on the contralateral paw (Fig. 3A).

Conclusion

The results demonstrate that while ACD856 can enhance neurite outgrowth and reverse cognitive impairment, it does not induce nor aggravate NGF-induced heat hyperalgesia. These findings indicate that the compound acts as a biased Trk-PAM with the advantages of neurotrophic support and cognitive enhancing effects, but without pain inducing effects.

This differential activation pattern of downstream signaling pathways provide for a significantly improved therapeutic and tolerability profile for this novel class of compounds.

References

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