THE TRK-PAM ACD856 IMPROVES MITOCHONDRIAL FUNCTION AND INCREASES BDNF LEVELS IN PRIMARY CORTICAL NEURONS

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Objectives

Although brain-derived neurotrophic factor (BDNF) [1] and nerve growth factor (NGF) [2] were originally characterized based upon their effects on neuronal cells, they are now also described to have non-neuronal effects. BDNF and NGF have been shown to play a role in conditions such as Alzheimer's disease [3], inflammatory disorders [4] [5] and depression[6], as well as controlling bioenergetics [7]. Interestingly, TrkB colocalizes with Complex IV of the respiratory chain [8], playing an important regulatory role on mitochondrial function.

ACD856 is a positive allosteric modulator (PAM) of the receptors for NGF and BDNF, i.e. TrkA and TrkB, respectively. Binding of ACD856 has been shown to lead to increased phosphorylation of the Trk receptors, increased release of neurotransmitters, induction of long-term potentiation and improved memory [9]. ACD856 was recently demonstrated to be well tolerated and to have a favourable pharmacokinetic profile in a clinical phase 1 study.

The aim of these studies was to explore the effects of ACD856 on mitochondrial function, cell membrane integrity and regulation of endogenous BDNF levels in mouse cortical neurons.

Methods

Effects of BDNF or ACD856 on mitochondrial function was investigated in cortical neurons (100.000 cells/well) at DIV 4-5 with glutamine as the main energy source (i.e. no glucose or pyruvate present). ATP levels and cellular membrane integrity were used to measure effects on bioenergetics after 3hrs of treatment. Effects on BDNF levels were studied by incubating cortical neurons (100.000 cells/well) at DIV10-13 with ACD856 and analysing BDNF levels by ELISA.

Results

BDNF and ACD856 demonstrated a dose-dependent positive effect on mitochondrial function as measured by an increase in ATP levels (figures 1 and 2), which was associated with increased cell membrane integrity (figures 3 and 4). This finding suggests that modulation of BDNF/TrkB signalling contributes to a general beneficial effect on neuronal health, i.e. counteracting cell membrane fragility in neurons.

To analyse the effects of ACD856 on endogenous BDNF levels in cortical neurons, culture media was first replaced and the basal levels of BDNF were measured after 3, 6, 12 and 18 hours. The levels of BDNF increased up to 12 hours and plateaued between 12 and 18 hours (figure 5). This led us to continue with 6 hours for the further experiments. Interestingly, ACD856 could, in a dose-dependent manner, increase the levels of BDNF with significant effects from 100 nM (figure 6).

References

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Figure 1. Effects of BDNF on ATP levels

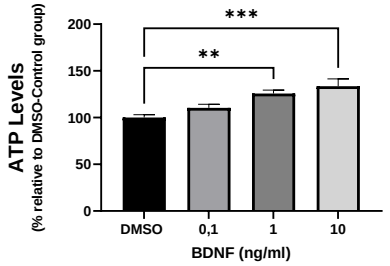


Figure 2. ACD856 increases ATP levels

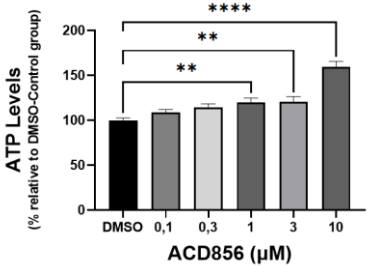


Figure 3. BDNF improves cell membrane integrity

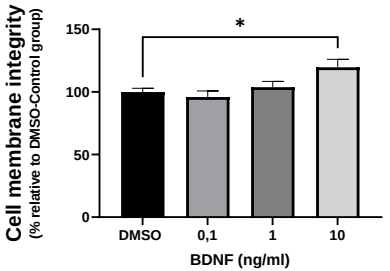


Figure 4. Positive effect of ACD856 on membrane integrity

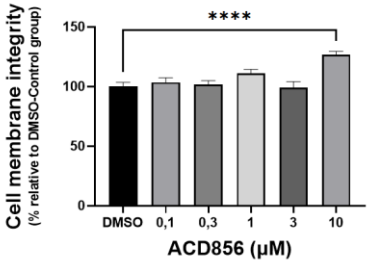


Figure 5. Time-dependent increase of BDNF in cortical neurons

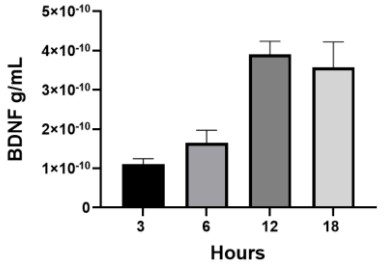
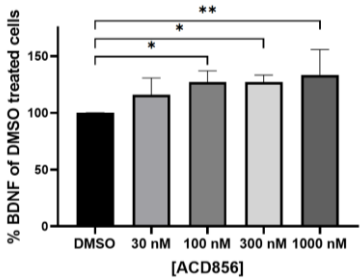


Figure 6. ACD856 increases BDNF levels in cortical neurons



*n ≥ 3 independent primary cultures from DIV6-7 (ATP) or 10-13 (BDNF). *p < 0.05 **p < 0.01 ***p < 0.001 ****p < 0.0001 vs vehicle-treated control values*

Conclusion

ACD856 is a positive modulator of Trk-receptors and phase 1 clinical trials was recently finalized demonstrating that ACD856 was well tolerated and displayed favourable pharmacokinetic properties. Herein, we demonstrate that ACD856 have beneficial effects on neuronal cells in a model of energy deprivation-induced neurotoxicity. Also, we observed increased levels of BDNF in cortical neurons, suggesting a feed-forward effect of the compound on BDNF-TrkB signaling. Our findings support that ACD856 may provide neuroprotective effects by improving mitochondrial function, increasing membrane integrity and by increasing levels of BDNF, suggesting that ACD856 could have disease-modifying effects, besides the pro-cognitive effects observed in different preclinical models.

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