

Developmental Vitamin D deficiency in the rat induces a sexually dimorphic delayed onset in sensitivity to MK-801

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PURPOSE

- Developmental vitamin D (DVD) deficiency has been proposed as a risk factor for schizophrenia.
- The psychosis presented in schizophrenia generally occurs in the post-adolescent period in humans with females generally showing a later age of onset than males.
- DVD-deficiency results in a heightened sensitivity to the psychomimetic, MK-801, induced locomotion in adult male rats and this can be blocked by Haloperidol (1).
- In line with other neurodevelopmental animal models it is important to understand the onset and progression of the sensitivity to MK-801 in DVD-deficient rats.
- The current investigation aimed to assess the effects of age and sex on the locomotor response of DVD-deficient rats to MK-801.

RESULTS

- There was no effect of DVD-deficiency on the response to MK-801 at P35 (Figure 1).
- Adult animals were assessed as a percentage of their own saline response to control for wave-to-wave variability and time of testing.
- Male DVD-deficient rats showed an enhanced response to 0.5 mg/kg MK-801 [F(1,38) 8.22, $p = 0.007$] at both P70 ($p = 0.042$) and P140 ($p = 0.015$) compared to controls (Figure 2A,C).
- Female DVD-deficient rats only showed enhanced locomotor response to 0.1 mg/kg MK-801 at P140 [Dose x Age x Diet [F(1,38) 4.56, $p = 0.039$] (Figure 2B,D).
- There were no significant effects of DVD-deficiency on the ataxia ratings at either P70 or P140 (Figure 3).

Figure 1.

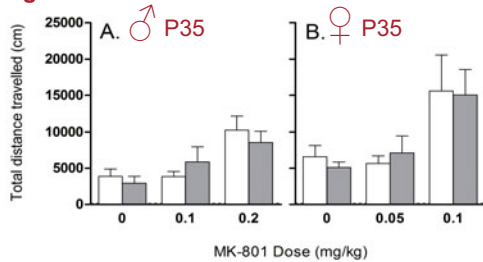


Fig 1. Locomotor response to MK-801 at P35. Male (A) and female (B) animals treated acutely with MK-801 at P35. Locomotor response (Mean \pm SEM) is expressed as the total distance travelled over 90 mins. DVD-deficient (grey) showed no differences compared to control (white) animals.

Figure 3.

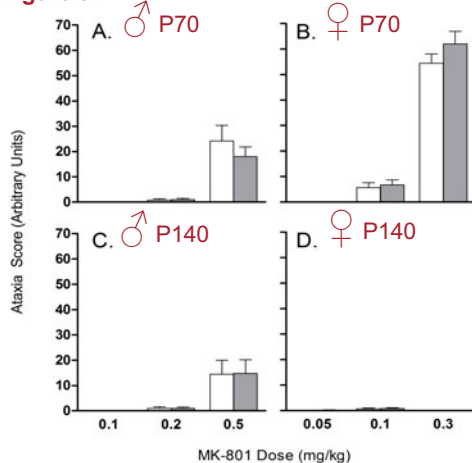


Fig 3. Ataxia response to MK-801 at P70 and P140. Male (A, C) and female (B, D) animals treated with MK-801 at P70 (A, B) and P140 (C, D). Ataxia scores (Mean \pm SEM) were no different between DVD-deficient (Grey) and control (White) animals at any dose. Note the high levels of ataxia generated by 0.3 mg/kg MK-801 in p70 females; due to this the same dose was not examined at p140 (D). Due to resolution issues of video footage P35 animals were not scored for ataxia levels.

METHODS

- Female Sprague Dawley dams were fed a vitamin D deficient diet for 6 weeks prior to conception and maintained on this diet until birth. Control dams were fed the same diet replenished with vitamin D. At birth all dams and offspring were provided with a diet containing vitamin D.
- The offspring of these dams were tested in an open field under a habituated protocol. Animals at postnatal day (P) 35 were tested acutely. The adult age groups (P70, P140) were assessed using a repeated injection paradigm over three weeks so that each animal received all doses and acted as its own control.
- The adult age groups were also scored for levels of ataxia by a scorer blind to treatment.

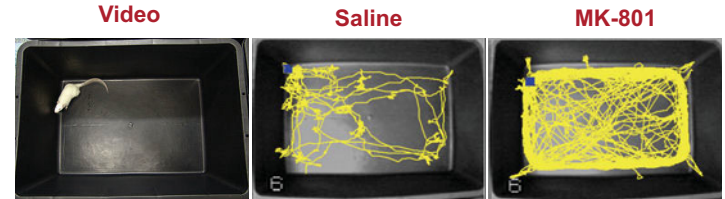


Figure 2.

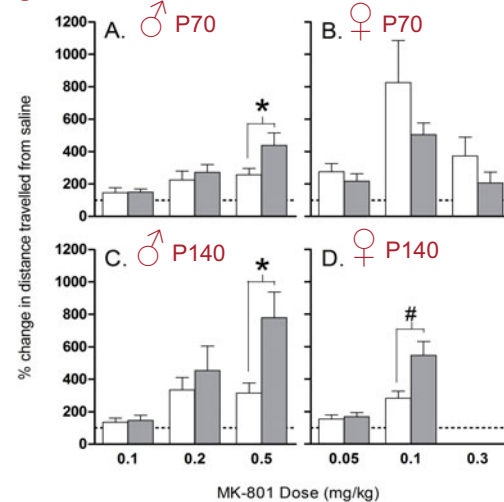


Fig 2. Locomotor response to MK-801 at P70 and P140. Male (A, C) and female (B, D) animals treated with MK-801 at P70 (A, B) and P140 (C, D). Locomotor response (Mean \pm SEM) is expressed as a percentage change from each animal's saline response (dotted line). DVD-deficient (grey) male animals showed a significantly elevated response to MK-801 compared to control (white) after 0.5 mg/kg at both P70 and P140. Female DVD-deficient animals showed a significantly increased response after 0.1 mg/kg at P140 only. * $p < 0.05$, # $p < 0.01$

CONCLUSIONS

- DVD-deficient rats showed a post-adolescent onset in sensitivity to MK-801 induced hyperlocomotion, and the time of onset of this sensitivity was earlier in males (P70) compared to females (P140).
- This parallels evidence seen in patients with schizophrenia; increased sensitivity to psychomimetic drugs compared to healthy individuals and a delayed onset of psychosis in females compared to males.
- This further highlights that Vitamin D is important in early brain development.
- We hypothesise dopamine/glutamate systems have been perturbed in early development due to DVD-deficiency, especially given the latter systems involvement in psychomimetic-induced locomotion.
- Further investigations into dopamine and glutamate release after MK-801 in the Nucleus accumbens using freely moving microdialysis are underway.

DISCLOSURE

The authors have no conflicts of interest to disclose.

REFERENCES

- (1) Kesby, J.P., Burne, T.H., McGrath, J.J., Eyles, D.W., 2006 Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: an animal model of schizophrenia. *Biol. Psychiatry* 60, 591–596.

