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).
> Inline 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 \([F(1,38) = 4.56, p = 0.039]\) compared to controls (Figure 2A,C).
> Female DVD-deficient rats only showed enhanced locomotor response to 0.1 mg/kg MK-801 at P140 \([Dose \times Age \times Diet \ F(1,38) = 4.56, p = 0.039]\) (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 ± 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 ± 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).

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 ± 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