Steroids not so depressing

By Tim Fulmer, Senior Writer

Mapreg S.A.S. researchers have shown for the first time *in vivo* that targeting microtubule-associated protein 2 with steroid derivatives can have an antidepressant effect in mouse models of depression.[1] Indeed, in some of those models, the company's MAP4343 had an onset of action that was faster than that for Prozac fluoxetine.

Mapreg founder, president and CEO Etienne Baulieu identified 3-methoxy-pregnenolone (MAP4343) in a screen for steroid derivatives that altered the function of microtubules in neurons. In 2006, Mapreg published data showing that the compound bound microtubule-associated protein 2 (MAP2) *in vitro* and improved recovery of locomotor function in rat models of spinal cord injury (SCI).[2,3]

Two years later, MAP4343 received EU Orphan Drug designation for SCI and started Phase I testing. Also in 2008, Baulieu came across a paper by researchers at **The University of Nottingham Medical School** that showed altered MAP2 levels in the hippocampus were accompanied by abnormal synaptic connections and depressive-like behavior.[4,5]

He hired corresponding author Massimiliano Bianchi as director of R&D psychopharmacology, and Mapreg has now confirmed the hypothesis that MAP4343 acts as an antidepressant by blocking MAP2 activity in the hippocampus and prevents depression-associated tissue pathology.

Indeed, in mice, a single subcutaneous dose of MAP4343 was able to cross the blood brain barrier, enter the hippocampus and induce changes in isoforms of tubulin-α, the endogenous substrate of MAP2.

Next, the company studied MAP4343 in the rat forced swim test, an assay used to screen for *in vivo* antidepressant activity. Animals receiving 4 mg and 10 mg doses of MAP4343 showed significantly decreased passive coping behavior compared with rats given vehicle ($p<0.05$ and $p<0.001$, respectively). High levels of passive coping behavior are a sign of depression.

The low dose had similar activity to a 10 mg dose of Prozac, which is marketed by **Eli Lilly and Co.** to treat major depressive disorder, obsessive-compulsive disorder (OCD), bulimia nervosa and panic disorder.

Bianchi declined to disclose how the dosing used in the depression models compared with the dosing used in the SCI trials.

Eli Lilly did not respond to requests for comment.

In a rat model of acute and chronic depression, MAP4343 given for 1–4 days significantly decreased short-term passive coping behavior compared with vehicle ($p<0.01$), whereas Prozac showed no effect. In the same rats, both MAP4343 and Prozac reduced coping behavior and anxiety at 7–10 days of treatment compared with vehicle ($p<0.001$ and $p<0.05$, respectively).

The findings were published in the *Proceedings of the National Academy of Sciences*.

Faster than Prozac

MAP4343's speed in the depression setting is intriguing, as first-line drugs such as Prozac and other selective serotonin reuptake inhibitors (SSRIs) can have a lag of 2–3 weeks between the start of treatment and clinical improvement.[6]

To better determine the time window of MAP4343's rapid antidepressant effects, Ronald Duman wanted to see MAP4343 tested in a rat model of depression that measures how acute and chronic stress induce anhedonia (the inability to experience pleasure) over time.[7]

Duman is professor of psychiatry, neurobiology and pharmacology and director of the Division of Molecular Psychiatry Abraham Ribicoff Research Facilities at **Yale University**.

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—Martin Beaulieu, Laval University

"To get a better idea of how rapidly MAP4343 works in depression, it would be useful to compare the short-term antidepressant effects of MAP4343 and ketamine in depression models," said Martin Beaulieu, assistant professor of psychiatry and neuroscience at **Laval University**.

In pilot trials, low doses of ketamine have shown antidepressant effects within two hours, with relief lasting for several days.[8] However, higher doses can trigger severe hallucinogenic and psychotic symptoms. Moreover, ketamine is a Schedule III controlled substance, which could complicate its use in depression.

Beaulieu cautioned that it will be "important to get a better idea of the specificity of this steroid derivative for MAP2 in the hippocampus, since various MAP isoforms occur throughout the CNS, where they help maintain microtubule stability. If MAP4343 were to hit some of those other isoforms too, there could be toxicity associated with impairing processes like axonal transport."

Bianchi said MAP4343 does not hit targets other than MAP2. "The compound was screened for *in vitro* affinity to 80 different neurotransmitter and steroid receptors and essentially negative results were obtained," he noted.

Moving forward, Mapreg "will continue to study MAP4343 for its possible use in other CNS alterations associated with aging and psychiatric disorders," said Baulieu, who was corresponding author on the paper. "Other derivatives of pregnenolone are also being studied."

Mapreg hopes to start a Phase II trial in SCI this year.

Baulieu and colleagues have applied for a U.S. patent covering the use of 3-methoxy-pregnenolone to treat depressive disorders and long-term neurological diseases. The IP is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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Laval University, Beauport, Quebec, Canada
Mapreg S.A.S., Le Kremlin-Bicetre, France
The University of Nottingham Medical School, Nottingham, U.K.
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