FE 201874, the first selective high-affinity rat $V_{1A}$ vasopressin receptor agonist

Rafik Marir$^1$, Anne Virsolvy$^2$, Kazimierz Wisniewski$^3$, Julie Mion$^4$, Michel G. Desarmenien$^4$ and Gilles Guillon$^4$

$^1$Ecole Nationale Supérieure de Biotechnologie, Constantine, Algeria
$^2$Laboratoire: Physiologie et Médecine Expérimentale du Cœur et des Muscles, INSERM U1046, Montpellier, France
$^3$Ferring Research Institute Inc, San Diego, CA, USA
$^4$CNRS, UMR-5203, Institut de Génomique Fonctionnelle, Montpellier, France

Distinct vasopressin receptors are involved in different physiological and behavioral functions. These functions are mediated by three distinct receptors known as $V_{1A}$, $V_{1B}$ and $V_{2}$, all belonging to the GPCR family. A recent review from M. Manning highlights the lack of a selective rat $V_{1A}$ receptor agonist which can specifically elucidate the functional roles of the $V_{1A}$ receptor in the rat (Manning et al., 2012). FE 201874 is a new derivative of the human selective $V_{1A}$ receptor agonist F180.

In our study, we performed a multi-approach pharmacological and functional characterization of FE 201874 in order to determine its pharmacological and physiological properties: several cell lines expressing vasopressin/oxytocin receptors (affinity and coupling to second messenger cascades), in an ex vivo model (aorta ring contraction) and in vivo in rats (proliferation of adrenal cortex glomerulosa cells and lactation).

FE 201874 exhibited nanomolar affinity for the rat $V_{1A}$ receptor; it was highly selective towards the rat $V_{1B}$ and $V_{2}$ vasopressin receptors and behaved as a full $V_{1A}$ agonist in all the pharmacological tests performed. FE 201874 bound to the oxytocin receptor, but with moderate affinity, and behaved as an oxytocin antagonist in vitro, but not in vivo (Marir et al. 2013).

These data demonstrate that FE 201874 would be particularly useful in pharmacological studies to better understand the central role of the V1A receptor in behavioral pathologies and diseases linked to stress.