

ผลกระทบระยะยาวของมอร์ฟีนไฮโดรคลอไรด์ ต่อฮอร์โมนอีส์ตราไดอล,  
โปรเจสเตอโรน, โปรแลกติน, คอร์ติซอล ในซีรัม และ พฤติกรรมทางเพศของ  
ลิงหางขาว (Macaca fascicularis) เพศเมียที่โตเต็มวัย



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LONG TERM INFLUENCE OF MORPHINE HYDROCHLORIDE UPON SERUM  
LEVELS OF E<sub>2</sub>, P, PRL, CORTISOL AND SEXUAL BEHAVIOURS IN  
ADULT FEMALE CYNOMOLGUS MONKEYS ( MACACA FASCICULARIS )



MISS WANNAPA SETTHEETHAM

ศูนย์วิทยทรัพยากร  
จุฬาลงกรณ์มหาวิทยาลัย

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การศึกษานี้มีวัตถุประสงค์เพื่อ 1) ศึกษาข้อมูลพื้นฐานของระดับอีสตราไดออล, โพรเจสเทอโรน,  
โพรแลกติน และคอร์ติซอล ในซีรัม พฤติกรรมทางเพศ และ metabolic turnover ของมอร์ฟีน  
ระหว่างรอบเดือนปกติ และ 2) ติดตามการเปลี่ยนแปลงระหว่างฉีดมอร์ฟีนไฮโดรคลอไรด์อย่างต่อเนื่อง  
และภายหลัง จากหยุดให้ยา ในลิงทางยาวเพศเมียที่โตเต็มวัย

ผลการฉีดมอร์ฟีนขนาด 0.1-3.2 มก.กก./วัน เข้าได้ผิวหนังลิงจำนวน 17 ตัว นาน 100-  
143 วัน พบว่า ค่า turnover rate ของกลุ่มลิงที่ได้รับมอร์ฟีนขนาด 0.1-0.8 มก./กก./วัน ไม่  
แตกต่างจากช่วงก่อนได้รับยา ลิงในกลุ่มที่ได้รับมอร์ฟีนขนาด 0.4 มก./กก./วัน หรือมากกว่าจะมีระดับ  
โพรแลกตินเพิ่มสูงขึ้นทันทีที่ได้รับยา ส่วนระดับคอร์ติซอลจะลดต่ำลงอย่างชัดเจน ในช่วงกลางและท้ายของ  
การให้มอร์ฟีน พฤติกรรมทางเพศลดต่ำลง รอบประจำเดือนยาวขึ้น ระดับอีสตราไดออลและโพรเจสเทอโรน  
ในซีรัมลดลง ค่า turnover rate ของมอร์ฟีนในลิงกลุ่มที่ได้รับมอร์ฟีนขนาด 1.6 และ 3.2 มก./กก./  
วัน จะลดลงอย่างชัดเจน และถึง steady state ในวันที่ 80 และ 45 ของการได้รับมอร์ฟีน ตาม  
ลำดับ กลุ่มลิงที่ได้รับมอร์ฟีนขนาด 3.2 มก./กก./วัน ทุกตัวจะขาดประจำเดือน อยู่ในภาวะ  
hyperprolactinemia และเกิด spontaneous galactorrhea

เมื่อหยุดให้มอร์ฟีนระดับโพรแลกตินในซีรัมจะลดลงสู่ปกติได้ภายใน 3 วัน ในขณะที่ค่า  
turnover rate ของมอร์ฟีนจะกลับสู่ระดับปกติภายใน 1 เดือน แต่ระดับคอร์ติซอลในลิงบางตัวยังไม่  
สามารถกลับสู่ระดับปกติได้ภายใน 3 เดือนที่ติดตามศึกษา

จากผลการศึกษาสรุปได้ว่า 1) มอร์ฟีนอาจมีผลกระทบต่อการสร้าง และ/หรือการหลั่งโพรแลกติน  
ได้โดยตรงที่ต่อมใต้สมอง 2) มอร์ฟีนอาจมีผลหลายระดับในการควบคุม hypothalamic-pituitary  
adrenocortical axis 3) ระดับอีสตราไดออล, โพรเจสเทอโรน และคอร์ติซอลในเลือดอาจเป็น  
ปัจจัยสำคัญในการควบคุมการเกิด spontaneous galactorrhea ขณะที่อยู่ในภาวะ  
hyperprolactinemia

ภาควิชา..... สหสาขาหลักสูตรคุณวุฒิปบัณฑิต  
สาขาวิชา..... วิทยาศาสตร์ชีวภาพ  
ปีการศึกษา..... 2534

ลายมือชื่อนิสิต.....  
ลายมือชื่ออาจารย์ที่ปรึกษา.....  
ลายมือชื่ออาจารย์ที่ปรึกษาพร้อม.....

## C025013 : MAJOR BIOLOGICAL SCIENCE

KEY WORD : MORPHINE/CORTISOL/E<sub>2</sub>/P/PRL/SEXUAL BEHAVIOURS/MACACA FASCICULARIS  
WANNAPA SETTHEETHAM : LONG TERM INFLUENCE OF MORPHINE HYDROCHLORIDE  
UPON SERUM LEVELS OF E<sub>2</sub>, P, PRL, CORTISOL AND SEXUAL BEHAVIOURS IN  
ADULT FEMALE CYNOMOLGUS MONKEYS (MACACA FASCICULARIS). THESIS  
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The objectives of this study are 1) to establish baseline hormonal profile levels of serum E<sub>2</sub>, P, PRL and cortisol levels as well as sexual behaviours and metabolic turnover of morphine during various phases of normal menstrual cycle and 2) to follow changes of these parameters during long term injection of morphine hydrochloride and after the drug withdrawal in sexually mature female cynomolgus monkeys.

Seventeen monkeys were injected subcutaneously with morphine at doses of 0.1-3.2 mg/kg/day for 100-143 days. The turnover rate of morphine was not altered significantly from pre-treatment values in 0.1-0.8 mg/kg/day morphine treated monkeys. Morphine at dose of 0.4 mg/kg/day and over promptly elevated serum PRL levels while cortisol levels were gradually suppressed and markedly declined in sexual behaviours. Postponement of menstrual cycle and Reduction of serum E<sub>2</sub> and P levels were also found in monkeys treated 0.8-1.6 mg/kg/day morphine. Significant decline in the turnover rate of morphine were found in monkeys treated with 1.6-3.2 mg/kg/day morphine, reaching steady state prior to D80 and D45 of the treatment respectively. Anovulation and complete absence of menstrual bleeding were found in all monkeys treated with 3.2 mg/kg/day morphine. Associated symptoms among these monkeys were hyperprolactinemia simultaneously with spontaneous galactorrhea particularly in monkeys who exhibited complete absence of menstrual bleeding during morphine treatment.

Morphine withdrawal induced prompt resumption of serum PRL levels to normal values within a few days whereas the return of normal turnover rate required not longer than 1 month. However, serum cortisol levels in some monkeys may remain lower than normal pre-treatment values as late as 3 months.

It is suggested that 1) morphine may exert direct stimulating influence on pituitary PRL synthesis and/or release, 2) morphine may have several sites of action on regulation of hypothalamic-adenohypophyseal-adrenocortical axis, and 3) E<sub>2</sub>, P and cortisol may play significant role on regulation of spontaneous galactorrhea in hyperprolactinemic state.

จุฬาลงกรณ์มหาวิทยาลัย



ภาควิชา ..... สหสาขาหลักสูตรดุริยางค์บัณฑิต  
สาขาวิชา ..... วิทยาศาสตร์ชีวภาพ  
ปีการศึกษา ..... 2534

ลายมือชื่อนิสิต .....  
ลายมือชื่ออาจารย์ที่ปรึกษา .....  
ลายมือชื่ออาจารย์ที่ปรึกษาร่วม .....



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## ABBREVIATION

Bo	=	Maximal binding count
B	=	Binding count
CPM	=	Count per minute
D	=	Day
E <sub>2</sub>	=	Estradiol-17 $\beta$
NSB	=	Non-Specific Binding
P	=	Progesterone
PRL	=	Prolactin
QC	=	Quality control
RCE	=	Recovery of extract
RCA	=	Recovery of assay
Tc	=	Total count
hr	=	Hour
t <sub>1/2</sub>	=	Half life
$\beta$	=	Turnover rate
$\mu$ Ci	=	Micro Curie
ft	=	Foot
g	=	Gram
$\mu$ g	=	Microgram
ng	=	Nanogram
pg	=	Picogram
fmole	=	Femtomole
pmole	=	Picomole
mIU	=	milli International Unit
min	=	Minute
ml	=	Millilitre