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REVIEW [REVISIÓN]

PHEROMONAL MODULATION OF REPRODUCTIVE FUNCTION IN MAMMALS

[MODULACIÓN FEROMONAL DE LA FUNCIÓN REPRODUCTIVA DE LOS MAMÍFEROS]

Matthieu Keller[1,2,3*], Marie Bedos[4], Mélanie Jouhanneau[1,2,3], Mariangela Martini[1,2,3], Socorro Retana-Márquez[5] and José A. Delgadillo[4]

[1] INRA, UMR85 Physiologie de la Reproduction et des Comportements, F-37380 Nouzilly, France. UMR 6175 INRA/CNRS/Université de Tours, 37380 Nouzilly, France; Tel. + 33 247 427 275; Fax. + 33 247 427 743
[2] CNRS, UMR6175 Physiologie de la Reproduction et des Comportements, F-37380 Nouzilly, France
[3] Université François Rabelais de Tours, F-37041 Tours, France
[4] Centro de Investigación en Reproducción Caprina, Universidad Autónoma Agraria Antonio Narro, Torreón, Coahuila, Mexico
[5] Departamento de Biología de la Reproducción, Universidad Autónoma Metropolitana, Itzapalapa, Mexico
E-mail: mkeller@tours.inra.fr
** Corresponding author*

SUMMARY

Social olfactory signals, often known as pheromones, are powerful regulators of reproductive function. These chemosignals can be detected by two olfactory systems, namely the main or the accessory olfactory systems. While initially anatomically segregated, both systems converge functionally as they can detect and process overlapping sets of chemosignals. This convergence also takes place at the level of their central projections in the hypothalamus. It is probably at this level that future investigations will be needed. Indeed, if the physiology of both olfactory system and reproductive function are now quite well characterized, the interrelation between both systems is unclear. Among the many cell populations that can serve as targets or relays for the pheromonal information in the hypothalamus are GnRH cells or the recently discovered Kisspeptin population which have been showed to be activated after pheromonal activation. However, many works will be needed before having a definitive picture.

Keywords: pheromone; reproductive axis; GnRH; Kisspeptin; main and accessory olfactory systems.

RESUMEN

Las señales olfatorias sociales, llamadas generalmente feromonas, regulan la función reproductiva. Estas señales químicas pueden ser detectadas por dos sistemas olfatorios, llamados sistema olfatorio principal y sistema olfatorio accesorio. Aunque anatómicamente están separados, los dos sistemas convergen funcionalmente y pueden detectar y procesar un conjunto de señales químicas. Esta convergencia ocurre también a nivel de sus proyecciones centrales en el hipotálamo. Es probable que a este nivel deban desarrollarse las futuras investigaciones. En efecto, si bien la fisiología de los dos sistemas olfatorios y su función reproductiva han sido bien caracterizadas, la interrelación entre los dos sistemas es aún desconocida. Entre las poblaciones celulares que pueden servir como blancos o relevos para la información feromonal en el hipotálamo están las células de GnRH o la recientemente descubierta población de células Kisspeptina las cuales son estimuladas por la activación feromonal. Sin embargo, mucho trabajo será necesario antes de tener un conocimiento amplio de los mecanismos involucrados.

Palabras clave: Feromona; eje reproductivo; GnRH; Kisspeptina; sistema olfatorio principal y accesorio.

PHEROMONES AS CHEMOSIGNALS MEDIATING INTRASPECIFIC COMMUNICATION

In many mammalian species, olfactory signals resulting from social interactions have been shown to play a powerful role in the regulation of reproductive function. Especially, a special class of chemosignals, known as pheromones, has been shown to regulate many aspects of reproductive physiology and behavior.

For example, pheromonal chemosignals have been shown to be highly involved in the regulation of mate choice and sexual behavior, but also in other reproductive behavior which ensure a successful reproduction, including territorial and aggressive behavior as well as parental behavior (for a review, see Keller et al., 2009, 2010).

Even if there have been many controversies around the definition of pheromones, especially in mammals, in which olfactory dependent behaviors are under the control of more subtle regulations than those found in insects, we will refer to the term "pheromone" under its very broad definition, initially introduced by Karlson & Lüscher (1959) as "chemosignals that provide information to conspecifics about sex or endocrine status or which stimulate hard-wired species-specific social behaviors".

From the initial classification, pheromones were already known to trigger either powerful short-term behavioral changes ("releaser" pheromone) or long-term neuroendocrine changes ("primer" pheromone). A well known example of releaser pheromone is the nipple search behaviour that is induced by the mammary pheromone in rabbit pups (Schaal et al., 2003). Among classical primer pheromonal effects are the well known estrus synchronisation (Whitten, 1956, 1957), estrus suppression (Van der Lee & Boot, 1955), pregnancy block (Bruce effect; Bruce, 1959) and finally modulation of puberty onset (Vandenbergh, 1967, 1969) in mice.

The distinction between primer and releaser pheromones is however schematic as pheromonal compounds can have both primer and releaser effects. In mice, it has been shown that a single pheromonal compound present in urine of sexually mature male, such as brevicomin, is able both to stimulate female estrus but also to trigger male aggression towards intruders (Novotny et al., 1985). In addition, primer and releaser effects are also often closely interrelated: it is clear that when specific male chemosignals stimulate female's reproductive status, this change also impact the behavioural response of females towards males. For example, ram or buck odors have been shown to induce ovulation in ewes and goats during the anestrus period (the so called "male effect"; Delgadillo et al., 2009), but this reactivation of the reproductive axis also stimulates estrus behavior.

The dual olfactory system

In most mammalian species at least two olfactory systems are able to detect pheromonal chemosignals: the main and the accessory (or vomeronasal) olfactory systems. These systems differ both in the organization of their sensory receptors and their central projections.

In the main olfactory system, olfactory compounds are detected at the level of the main olfactory epithelium (MOE) which lies at the end of the nasal cavity. In this epithelium, sensory olfactory neurons express various types of olfactory receptors which have been now identified 20 years ago (Buck & Axel, 1991). The olfactory information is then processed at the level of the glomerular cell layer of the main olfactory bulb, before to be relayed more centrally in the amygdala and other cortical structures.

The main olfactory system is usually thought to detect volatile complex odorants present in the environment and is therefore thought to be involved in the processing of odors related to social attraction and complex social recognition, thus allowing animals to distinguish sex, social or reproductive status of conspecifics.

It is probably in mice that the effects of some volatile olfactory pheromones have been the most extensively studied. Mice urine consists of a large number of distinct chemical compounds that vary according to the sex, social or physiological status of the emitter (Andreolini et al., 1987). In male mice urine, the volatile urinary compound (methylthio) methanethiol (MTMT) has been shown to activate a subset of mitral cells in the main olfactory bulb (MOB) and to enhance urine attractiveness to female mice (Lin et al., 2005).

Beside the main olfactory system, the accessory olfactory system detects pheromones through the vomeronasal organ (VNO), a blind-ended tubing located at the basis of the vomer bone (Meredith and O'Connell, 1979; Keverne, 1999). The VNO contains a sensory epithelium not directly exposed to the airflow and therefore, pheromones need to enter the VNO duct through a pumping mechanism.

VNO neurons send projections to the accessory olfactory bulb (AOB) glomeruli. Luo et al. (2003) have demonstrated, using electrophysiological recordings in behaving animals, that AOB cells are only activated when mice make direct physical contact with the odorant source (for example the ano-genital region of a conspecific), thus giving access to non-volatile pheromones to the VNO.

From the AOB, the major projection of the accessory olfactory system is to the medial amygdala (Scalia & Winans, 1975). Among the targets of medial amygdaloid projections are the preoptic and mediobasal hypothalamic areas (MPOA and MBH).

According to the anatomical segregation between both systems and their extensive functional differences, it has been usually thought that the MOE detects volatile

odorants in the environment while the VNO detects non-volatile pheromones.

Convergence of both olfactory systems

Recent results show that the functional dichotomy between both olfactory systems is not so definitive because both the VNO and MOE have the ability to detect large overlapping sets of chemosensory cues. For example, by using both in vitro electrophysiological and imaging methods, it has been demonstrated that VNO neurons can express very specific responses to urinary volatile compounds, such as farnesenes or brevicomine (Leinders-Zufall et al., 2000; Del Punta et al., 2002).

Whether the accessory olfactory system can be directly stimulated by volatile pheromones in the airflow (i.e. without direct physical contact with the olfactory source) remains controversial but some experiments reported the activation of the AOB by volatile compounds delivered in the airstream (Xu et al., 2005).

It has been well established that volatile ligands can get access into the VNO by being bounded to transport proteins belonging to the lipocalin family. In this case, the association between volatile ligands and lipocalins enter into the VNO after direct contact with the pheromonal source. Among these proteins that act as carrier for volatile ligands, some, such as major urinary proteins have been now clearly characterized and might also serve by themselves as cues for individual recognition, especially because: 1/ they exhibit a high degree of polymorphism (MUPs; Hurst et al., 2001); 2/ they are able to stimulate immediate early gene expression in specific regions of the accessory olfactory bulb (Brennan et al., 1999) and 3/ they seem to be able to trigger complex social behaviour including aggression, urinary marking or social preference (Hurst et al., 2001; Chamero et al., 2007; Roberts et al., 2010).

It is also well known that some pheromones detected by the main olfactory system can trigger specific reproductive behavior. For example, the volatile steroid androstenone in boar saliva, which is detected and processed by the main olfactory system, induces lordosis in receptive sows (Dorries et al., 1995, 1997). In sheep, the male effect involves the main olfactory system (Cohen-Tannoudji et al., 1989; Gelez et al., 2004; Delgadillo et al., 2009). Indeed, lesioning the vomeronasal pathway does not affect the ewe's neuroendocrine luteinizing hormone (LH) response to the ram. In mice, MTMT in male mouse urine is also detected by the MOB and is a potent attractant for female mice (Lin et al., 2005). With regard to mother–young relationships, removal of the MOE abolished the nipple-searching behavior induced by the rabbit mammary pheromone (Hudson & Distel, 1986; Schaal et al., 2003). In sheep, the ewe learns the individual odor of its lamb during the very early hours following parturition. This learning which will lead to an individual acceptance of the newborn at suckling is mediated by the main olfactory system (Lévy et al., 1995; Keller et al., 2004). Finally, in humans, who do not have a functional VNO, it has been shown that women exposed to female axillary secretions showed changes in LH pulses (Shinohara et al., 2001), thus suggesting that axillary secretions contain one or more compounds that may act as a pheromone in humans.

Finally, some pheromonal signals seem to be processed in parallel by the two olfactory systems. Calcium imaging studies on in vitro preparation have shown that some sensory neurons respond to peptides derived from the major histocompatibility (which can act as chemosignals) in both the VNO and the MOE (Spehr et al., 2006). The thresholds of sensory neurons responses to MHC peptides differ in both VNO and MOE, and the transduction mechanisms underlying the detection of these same MHC chemosignals by sensory neurons in the VNO and MOE depends on distinct sets of transduction mechanisms. For example, local field potentials to MHC peptides are inhibited by the drug 2-aminoethoxydiphenylborate (or 2-APB) in the VNO, but not in the MOE (Leinders-Zufall et al., 2000; Spehr et al., 2006). Similar results have been obtained with the odorant 2-heptanone: its detection appears to be dependent on the Trp2 gene in the VNO, while in the MOE, detection of 2-heptanone depends on the CNGA2 (Lin et al., 2004). At the behavioral level, this processing of the same olfactory signals is not just a redundancy. Indeed, specific activation of each system can lead to distinct behavioral outcomes. Thus, in the vomeronasal system, MHC-class I peptides signals has been shown to sustain information about individuality in the context of the Bruce effect (Leinders-Zufall et al., 2004) while processing of MHCclass I peptides in the MOE support social preferences (Spehr et al., 2006). This demonstrates that MHC processing via the MOE does not replace VNO sensory inputs.

Pheromonal pathway to the hypothalamus

After anatomically distinct initial relays, the olfactory information from the main and the accessory olfactory systems then converge to the level of the amygdala before reaching several hypothalamic regions including the bed nucleus of the stria terminalis, the medial preoptic area and the ventromedial hypothalamus. For example, in mice, it has been shown that social olfactory information can be transmitted directly from the MOB to the 'vomeronasal' amygdala (Kang et al., 2009). From the amygdala, it is clearly established that opposite-sex

odors are able to stimulate the hypothalamus and trigger LH release in many species and situations.
At which levels pheromones act to activate the gonadotropic axis and the associated regulation is still unclear, but the GnRH cells in the anterior hypothalamus have been shown to be a target of pheromonal information (Figure 1). Indeed, GnRH neurons receive directly or indirectly stimulations from both the main and the accessory olfactory systems (Boehm et al., 2005; Yoon et al., 2005). These olfactory projections on GnRH cells could ultimately lead to chemosignal control over surge of LH which occurs during key reproductive events such as estrus or puberty.

For example, it has been clearly shown in ungulates that the exposure of female to the odor of the male induces activation of GnRH neurons both when measuring Fos protein expression and electrophysiological activation (Gelez & Fabre-Nys, 2006; Ichimaru et al., 2008). GnRH is also released naturally when male rodents (mice and hamsters) encounter female chemosignals, and intracerebrally injected GnRH restores mating behavior in sexually naive male hamsters after removal of the vomeronasal organ (Westberry & Meredith, 2003; Keller et al., 2006). In male hamster, chemosignals found in female vaginal fluid activate regions of the brain that receive input from the vomeronasal/accessory olfactory system and are important for mating behavior. Mating or exposure to female chemosignals produces increased Fos protein expression in the amygdala, bed nucleus of the stria terminalis, and MPOA which contain cell bodies and/or fibers GnRH neurons. Like in sheep, this activation can be measured directly at the cellular level (Yoon et al., 2005). This Fos activation of GnRH cells in the MPOA can be reproduced through electrical stimulation of the vomeronasal organ in male hamsters (Meredith & Fewell, 2001).

In addition to the GnRH level, Kisspeptin, a key upstream regulator of GnRH has been recently discovered and can also serve as a target for pheromones to modulate the reproductive axis. Kisspeptin is the peptide product of the *Kiss1* gene and the endogenous ligand of the G protein-coupled receptor 54 (GPR54). Kisspeptin immunoreactive neurons are present in the sexually dimorphic anteroventral periventricular (AvPv) hypothalamic nucleus and also in the periventricular (Pen) and in the arcuate hypothalamic nuclei of the mouse hypothalamus (Clarkson & Herbison, 2006; Desroziers et al., 2010). Central administration of Kisspeptin activates GPR54 to stimulate very efficiently gonadotropin secretion (Messager et al., 2005).

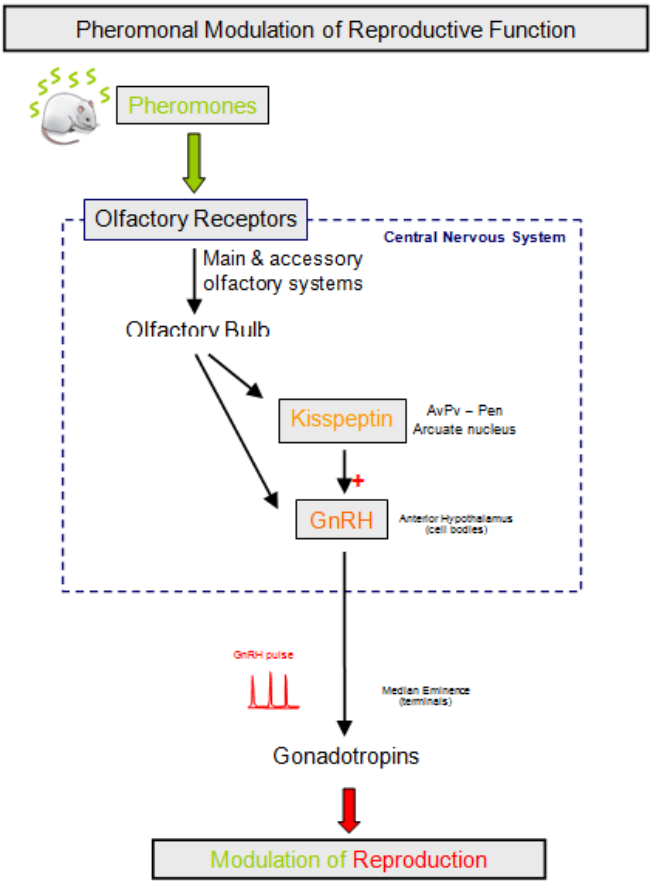

Figure 1: Interaction between the olfactory and the reproductive axis. Among the targets of the gonadotropic axis, both GnRH and Kisspeptin cell populations.

Different studies suggest that Kisspeptin and GPR54 are involved in both the regulation of puberty onset and preovulatory GnRH/LH hormone surge. Regarding puberty onset, of foremost importance is the absence of puberty in the GPR54 and Kiss1-KO mouse (Colledge, 2009). Developmental studies examining hypothalamic Kisspeptin levels have also found correlations with the onset of puberty in the rat (Navarro et al., 2005), mice (Clarkson & Herbison, 2006) and monkey (Shahab et al., 2005). Also, gain of function studies have reported that exogenous Kisspeptin administration can advance the onset of puberty in prepubertal female rats (Matsui et al., 2004; Navarro et al., 2004). Regarding the preovulatory GnRH/LH surge, it has been shown that Kisspeptin is able to restore reproductive function when the hypothalamic-pituitary axis is quiescent. For example, i.v. infusion of a low dose of peptide in anestrous ewes induces an immediate and sustained release of gonadotropin (Messager et al., 2005).

From these data, it is quite clear that Kisspeptin can represent a new level to study the impact of pheromones on the reproductive axis, because the reproductive events that are controlled by Kisspeptin are also under the modulation of pheromones.

Whether pheromones activate or modulate Kisspeptin neurons is at present poorly known. However, several sets of data suggest that pheromones may have this potential. For example, we have obtained preliminary data (Figure 2) showing that opposite-sex pheromonal stimulation induces Fos activation in Kisspeptin neurons in pubertal females, as previously observed by Bakker et al. (2010). Furthermore, Murata et al. (2011) have shown, using electrophysiological approaches that buck odors are able to stimulate the GnRH pulse generator in the arcuate nucleus of the hypothalamus.

While the available results are still fragmentary, future studies will probably bring new evidences showing that Kisspeptin can be a target of pheromones. Especially, many experimental situations, such as puberty acceleration or the effect of male odors on non breeding females in ungulates, seem to be well suited to explore these questions.

Potential applications of pheromones as regulators of reproductive physiology and behavior

Beside the exploration of the physiological and neuroendocrine events occurring during pheromonal modulation of reproductive function, we would like to emphasize that the use of pheromones may yield potential applications for the control of reproduction in various fields ranging from agronomy, ecology and even to clinical sciences. Some of these potential applications are briefly summarized thereafter.

First, at the agronomic level, pheromones have been shown to impact the reproductive function not only of laboratory rodents but also of farm animals. As already mentioned, ram or buck odors have been shown to induce ovulation in ewes and goats during the anestrus period (Delgadillo et al., 2009). In the context of sexual maturation, pheromonal acceleration of puberty in females by male's chemosignals has been suggested in several important domestic farm animals (Izard, 1983; Vandenbergh, 1989) including pigs (Brooks and Cole, 1970) or heifers (Izard & Vandenbergh, 1982). In these examples but also probably in many others, using pheromones to modulate farm animal reproductive function constitutes a promising alternative to the use of exogenous hormonal treatments in the context of sustainable development. Indeed, the treatments used in the current management procedures of farm animal reproduction often lead to the release of large amounts of chemical and/or hormonal compounds potentially acting as endocrine disruptors in the environment.

At the level of ecological applications, pheromonal effects have been shown to have some ecological validity. For example, modulation of rodent sexual maturation is not just a laboratory curiosity because wild male mice living in natural populations produce a urinary pheromone capable of accelerating puberty in females (Massey & Vandenbergh, 1981). It has been shown that wild mice respond to pheromonal stimulation of laboratory mice and conversely that laboratory mice respond to pheromonal cues of wild mice (Massey & Vandenbergh, 1980, 1981). This result not only validates the use of laboratory mice as a model to study the mechanisms sustaining puberty modulation induced by pheromones in wild mice but it also opens the potential to provide new ideas for chemosensory approaches to rodent control. Such chemosensory approaches acting at the level of the reproductive system to pest control are proving to be effective in the control of insect populations and offer the prospect of humane and ecologically-benign control of the size and distribution of various pest populations.

Finally at the clinical level, chemosignals have been suggested to stimulate LH release in humans (Preti et al., 2003; Wisocky & Preti, 2004). Diseases associated with altered hormonal state are usually treated with hormone therapy that often has negative side effects. In this context, the use of social or artificial olfactory chemosignals to overcome health deficits could be an emerging strategy which has been for example proposed in the management of cortisol replacement therapies (Wyart et al., 2007) but also in contexts that are not hormonal dependent such as the management of apneas occuring in premature newborn (Marlier et al., 2005). In more specific cases of reproductive deficits, we can also imagine to try to overcome deficits by stimulating the reproductive axis with putative pheromones, although this goal is for instance purely speculative.

CONCLUSION

In conclusion, pheromones represent promising tools to control reproductive function. However, many gaps are still to fill to better understand how and where the pheromonal information acts on the reproductive axis to stimulate reproductive function. If the physiology of both the olfactory system and the reproductive axis are quite well characterized, understanding the interplay between both systems surely represent the major challenge for the coming years.

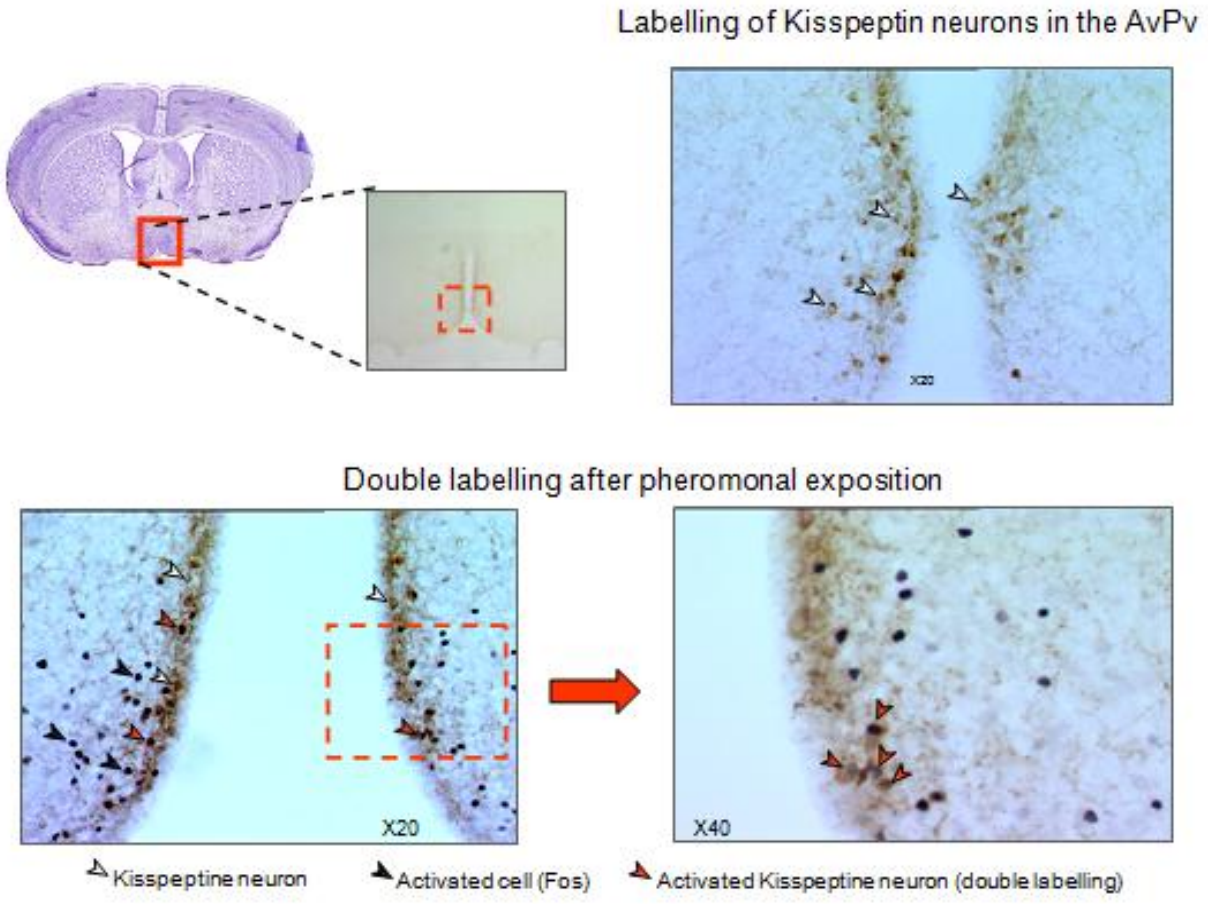

Figure 2: Activation of Kisspeptin cells in the anteroperiventricular nucleus (AvPv) after male pheromonal stimulation infemale mice.

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